Original article

Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. CARDIOVID registry

Diego López-Otero,[a,b,c,*] Javier López-Pais,[a,b,c] Carla Eugenia Cacho-Antonio,[a] Pablo José Antúnez-Muiños,[a] Teba González-Ferrero,[a] Marta Pérez-Poza,[a] Óscar Otero-García,[a] Brais Díaz-Fernández,[a,b,c] María Bastos-Fernández,[a,b,c] Noelia Bouzas-Cruz,[a,c] Xoan Carlos Sanmartín-Pena,[a,b,c] Alfonso Varela-Román,[a,b,c] Manuel Portela-Romero,[d] Luis Valdés-Cuadrado,[e] Antonio Pose-Reino,[f] and José Ramón González-Juanatey[a,b,c]

[a] Servicio de Cardiología, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain
[b] Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares, CIBERCV, Madrid, Spain
[c] Instituto de Investigación Sanitaria Santiago de Compostela (IDICHUS), Santiago de Compostela, Spain
[d] Centro de Salud Concepción Arenal, Santiago de Compostela, A Coruña, Spain
[e] Servicio de Neumología, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain
[f] Servicio de Medicina Interna, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

A B S T R A C T

Introduction and objectives: Coronavirus disease (COVID-19) has been designated a global pandemic by the World Health Organization. It is unclear whether previous treatment with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) affects the prognosis of COVID-19 patients. The aim of this study was to evaluate the clinical implications of previous treatment with ACEI/ARB on the prognosis of patients with COVID-19 infection.

Methods: Single-center, retrospective, observational cohort study based on all the inhabitants of our health area. Analyses of main outcomes (mortality, heart failure, hospitalization, intensive care unit [ICU] admission, and major acute cardiovascular events [a composite of mortality and heart failure]) were adjusted by multivariate logistic regression and propensity score matching models.

Results: Of the total population, 447 979 inhabitants, 965 patients (0.22%) were diagnosed with COVID-19 infection, and 210 (21.8%) were under ACEI or ARB treatment at the time of diagnosis. Treatment with ACEI/ARB (combined and individually) had no effect on mortality (OR, 0.62; 95%CI, 0.17-2.26; *P* = .486), heart failure (OR, 1.37; 95%CI, 0.39-4.77; *P* = .622), hospitalization rate (OR, 0.85; 95%CI, 0.45-1.64; *P* = .638), ICU admission (OR, 0.87; 95%CI, 0.30-2.50; *P* = .798), or major acute cardiovascular events (OR, 1.06; 95%CI, 0.39-2.83; *P* = .915). This neutral effect remained in a subgroup analysis of patients requiring hospitalization.

Conclusions: Previous treatment with ACEI/ARB in patients with COVID-19 had no effect on mortality, heart failure, requirement for hospitalization, or ICU admission. Withdrawal of ACEI/ARB in patients testing positive for COVID-19 would not be justified, in line with current recommendations of scientific societies and government agencies.

© 2020 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Impacto de los inhibidores de la enzima de conversión de la angiotensina y los antagonistas del receptor de la angiotensina II en la COVID-19 en una población occidental. Registro CARDIOVID

R E S U M E N

Introducción y objetivos: La Organización Mundial de la Salud calificó la enfermedad de coronavirus (COVID-19) como una pandemia global. No está claro si el tratamiento previo con inhibidores de la enzima de conversión de la angiotensina (IECA) y antagonistas de los receptores de angiotensina (ARA-II) tiene un impacto en el pronóstico de los pacientes infectados con COVID-19. El objetivo fue evaluar la implicación clínica del tratamiento previo con IECA/ARA-II en el pronóstico de la COVID-19.

* Corresponding author: Departamento de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Rúa da Choupana s/n, 15703 Santiago de Compostela, A Coruña, Spain.
E-mail address: birihh@yahoo.es (D. López-Otero).

Métodos: Estudio observacional, retrospectivo, unicéntrico, de cohortes basado en todos los habitantes del área de salud. El análisis de los resultados principales (mortalidad, insuficiencia cardiaca, hospitalización, ingreso en la unidad de cuidados intensivos (UCI) y eventos cardiovasculares agudos mayores [un compuesto de mortalidad e insuficiencia cardiaca]), se ajustó mediante modelos de regresión logística multivariada y modelos de coincidencia de puntaje de propensión.

Resultados: De una población total, 447.979 habitantes, 965 pacientes (0,22%), fueron diagnosticados de infección por COVID-19, 210 (21,8%) estaban bajo tratamiento con IECA o ARA-II en el momento del diagnóstico. El tratamiento con IECA/ARA-II (combinado e individualmente) no tuvo efecto sobre la mortalidad (OR = 0,62; IC95%, 0,17-2,26; p = 0,486), insuficiencia cardiaca (OR = 1,37; IC95%, 0,39-4,77; p = 0,622), tasa de hospitalización (OR = 0,85; IC95%, 0,45-1,64; p = 0,638), ingreso en UCI (OR = 0,87; IC95%, 0,30-2,50; p = 0,798) y cardiopatía aguda grave eventos (OR = 1,06; IC95%, 0,39-2,83; p = 0,915). En el análisis del subgrupos de pacientes que requirieron hospitalización, el efecto se mantuvo neutral.

Conclusiones: El tratamiento previo con IECA/ARA-II en pacientes con COVID-19 no tuvo efecto sobre la mortalidad, la aparición de insuficiencia cardíaca, ni en la necesidad de hospitalización ni ingreso en UCI. La supresión de IECA/ARA-II en pacientes con COVID-19 no estaría justificada en ningún caso, de acuerdo a las recomendaciones actuales de las sociedades científicas y las agencias gubernamentales.

Abbreviations

ACE: angiotensin-converting enzyme
ARB: angiotensin receptor blocker
COVID-19: coronavirus disease 2019
ICU: intensive care unit
SARS: severe acute respiratory syndrome
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

INTRODUCTION

By 1 April 1, 2020, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1–4] known as COVID-19 (coronavirus disease 2019), had spread to over 200 countries, infecting more than 1 million people, and was designated a global pandemic by the World Health Organization.[5]

Although the infection can cause severe disease in anyone, one of the largest analyses conducted to date,[6] reported more severe outcomes (intensive care unit [ICU] admission, mechanical ventilation, and death) in patients with hypertension, coronary artery disease, and diabetes.

The interaction of SARS-CoV-2 and the renin-angiotensin-aldosterone system is a cornerstone in COVID-19 infection. The virus links to membrane-bound angiotensin-converting enzyme 2 (ACE2) and is internalized in the cells by transmembrane proteases.[7,8] Angiotensin I upregulates a metalloprotease (ADAM-17) that increases the solubility of ACE2 (a form not valid for SARS-CoV-2 binding)[9,10] and also releases proinflammatory cytokines that downregulate ACE2 cell surface expression, reducing the ability of SARS-CoV-2 to cause damage.[11]

Given the possible increased susceptibility of patients taking ACEI in the COVID-19 pandemic, it has been proposed that they should discontinue this medication.[12] At this moment, the impact of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) on the clinical course of COVID-19 is controversial.[3,7,13–17] When the current study was being performed, scientific societies and government agencies were recommending continuing with this treatment, due to the lack of evidence for the hypothesis.[18,19]

There is a lack of evidence in this field, and most of the available data are based on observational studies conducted in China; none have been based on a whole population, and there is little information on how the virus affects the western population.

METHODS

Study design and participants

We performed a single-center, retrospective, observational cohort study at a university hospital covering a city and its metropolitan area, whose population has been confined during the study period under the state of alarm beginning on 14 March, 2020. We included all cases of laboratory-confirmed SARS-CoV-2 infection in the area, according to the interim guidance of the World Health Organization,[20] independently of their outcome. Diagnosis of COVID-19 was based on nasopharyngeal swab real time-polymerase chain reaction, which has high sensitivity for virus detection; however, the sensitivity can decrease if the patient's viral load is low or if there are deficiencies in sample collection. This could affect the sample size, but probably not the results, since its distribution is homogeneous in the population.

This study complied with the edicts of the 1975 Declaration of Helsinki and was approved by the Galician Medication Research Ethics Committee.

Data collection

Standardized forms were used to set up the database, including demographic information, epidemiological data, tests performed, drugs received during hospital admission and at discharge according to physician criteria, and other relevant clinical information. Clinical information was collected from electronic medical records, providing access to the entire clinical history from primary to hospital care, as well as to electronic prescriptions, to confirm treatment adherence.

Outcomes

This work was conducted to properly typify the clinical implications of previous chronic treatment with ACEI/ARB on the prognosis of COVID-19. The main outcome was the impact of previous chronic treatment with ACEI and ARB on prognosis, evaluated through mortality, heart failure, the need for hospitalization and intensive care unit (ICU) stay, and major adverse cardiovascular events (a composite of death and heart failure). Heart failure was defined following the current guidelines,[21] based on clinical, analytical, and radiological data. We also studied whether renin-angiotensin-aldosterone system inhibition maintained for more than 1 year could change the results.

Table 1
Age and sex distribution of the population affected by COVID-19

	Population	COVID-19 (% of population)	Hospitalization (% of cases)	ICU (% of cases)	Mortality (% of cases)	MACE (% of cases)
	N = 447 979	n = 965	n = 234	n = 33	n = 38	n = 35
0-14 y	53 627	15 (0.03)	1 (6.67)	0 (0.00)	0 (0.00)	0 (0.00)
Female (% of asg.)		9	1 (100.00)	-	-	-
Male (% of asg.)		6	0 (0.00)	-	-	-
15-64 y	286 951	508 (0.18)	79 (15.55)	10 (1.97)	0 (0.00)	0 (0.00)
Male (% of asg.)		221	44 (55.70)	9 (81.82)	-	-
Female (% of asg.)		287	35 (44.30)	2 (18.18)	-	-
> 64 y	107 401	442 (0.42)	154 (34.84)	23 (5.20)	38 (8.60)	29 (6.56)
Male (% of asg.)		198	93 (60.39)	15 (65.22)	30 (78.95)	17 (58.62)
Female (% of asg.)		244	61 (39.61)	8 (34.78)	8 (21.05)	12 (41.38)

Asg., age subgroup; ICU, intensive care unit; MACE, major adverse cardiovascular events (acute coronary syndrome, myocarditis, arrhythmic cardiac arrest, stroke, pulmonary emboli, heart failure, and cardiovascular mortality).
The data are expressed as No. (%).

Statistical analysis

For the comparison of patients treated and not treated with ACEI/ARB, continuous variables (expressed as mean ± standard deviation) were compared with the Student *t* test, and discrete variables (expressed as percentages) were assessed with the chi-square or Fisher's exact test, as necessary.

Logistic regression models were performed to explain the independent association between ACEI/ARB treatment and hospital admission, ICU admission, mortality, and heart failure. For the multivariate adjustment, all variables showing a significant association ($P < .05$) with events in the univariate analyses were included (see table 1 and table 2 of the supplementary data), with no selection. All selected multivariate models had good discrimination (c-statistic > 0.85 for the total population, and > 0.80 for hospitalized patients) and good calibration (*P* value for the Hosmer-Lemeshow test $> .6$ for the total population, and $> .40$ for hospitalized patients). The results are expressed as odds ratios (OR), with their 95% confidence intervals (95%CI). In all hypothesis tests, the null hypothesis was rejected with a type I error or alpha error $< .05$.

Due to the substantial differences in baseline characteristics between patients receiving and not receiving ACEI/ARB, the analysis was complemented with a propensity score matching analysis. Patients were matched according to ACEI/ARB therapy based on propensity scores. We applied a greedy 1:1 matching algorithm without replacement, with a caliper of 0.1. Propensity scores were estimated using a nonparsimonious multivariable logistic regression model, with ACEI/ARB therapy as the dependent variables and those characteristics that differed ($P < .05$) between patients treated and not treated with ACEI/ARB (table 1) as covariates. Propensity score matching was performed for all patients and was repeated only for those patients with hospital admissions. After propensity score matching, 164 paired patients were identified with balanced baseline characteristics and there were no significant differences according to ACEI/ARB therapy (standard deviation < 0.1 for all variables). In the propensity score-matched population, outcomes were compared using a stratified logistic regression model.

Similar analyses were repeated only for hospitalized patients, using both logistic regression and propensity score matching (with 58 paired patients). The statistical analysis was performed with SPSS 25.0.
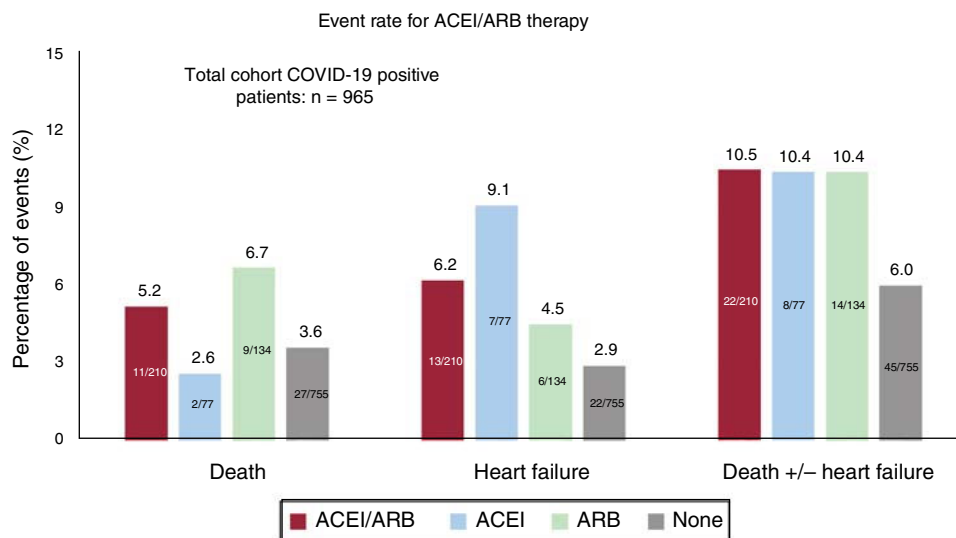

Figure 1. Events in the COVID-19 positive cohort depending on the type of treatment. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.
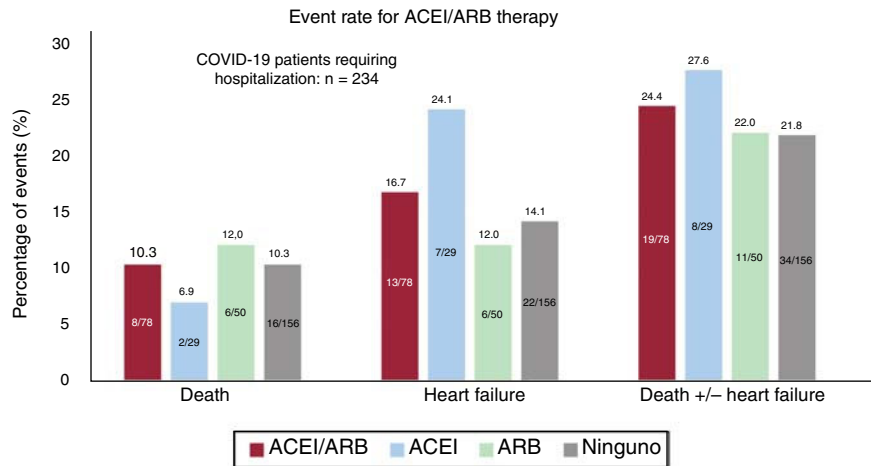
Figure 2. Events in the COVID-19 hospitalized cohort depending on the type of treatment. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

RESULTS

From 10 March to 6 April, 965 patients (0.22%) were diagnosed with COVID-19 out of the 447 979 inhabitants of the area covering the university hospital. Of COVID-19 patients, 234 (24.25%) needed hospitalization; among these patients, 33 (14.1%) required ICU admission. During the study period, 38 patients died (3.94%), of whom 35 (3.6%) had heart failure (figure 1, figure 2 and figure 3).

Of the total population, 72 527 (16.19%) were under chronic treatment with ACEI (26 617 [36.7%] or ARB (48 085 [66.3%]). Of the COVID-19 patients, 210 (21.8%) were under ACEI or ARB treatment at the time of diagnosis; of these, 165 (78.57%) were taking them for more than 1 year. The age and sex distribution of the population with COVID-19 involvement are summarized in table 1.

Table 2 summarizes the baseline characteristics of COVID-19 patients and provides a comparison of the cohort under ACEI/ARB treatment and that not receiving this treatment. The cohort of patients under ACEI/ARB was older (72.1 ± 13.2 vs 56.0 ± 20.5; $P < .01$) and had more cardiovascular risk factors (hypertension, diabetes, smoking, and dyslipidemia) and cardiovascular comorbidities (coronary artery diseases and ventricular dysfunction) than the cohort without ACEI/ARB. There were fewer women in the ACEI/ARB group (43.8% vs 59.5%; $P < .01$). Renal impairment and peripheral vasculopathy were also more prevalent in patients taking ACEI/ARB.
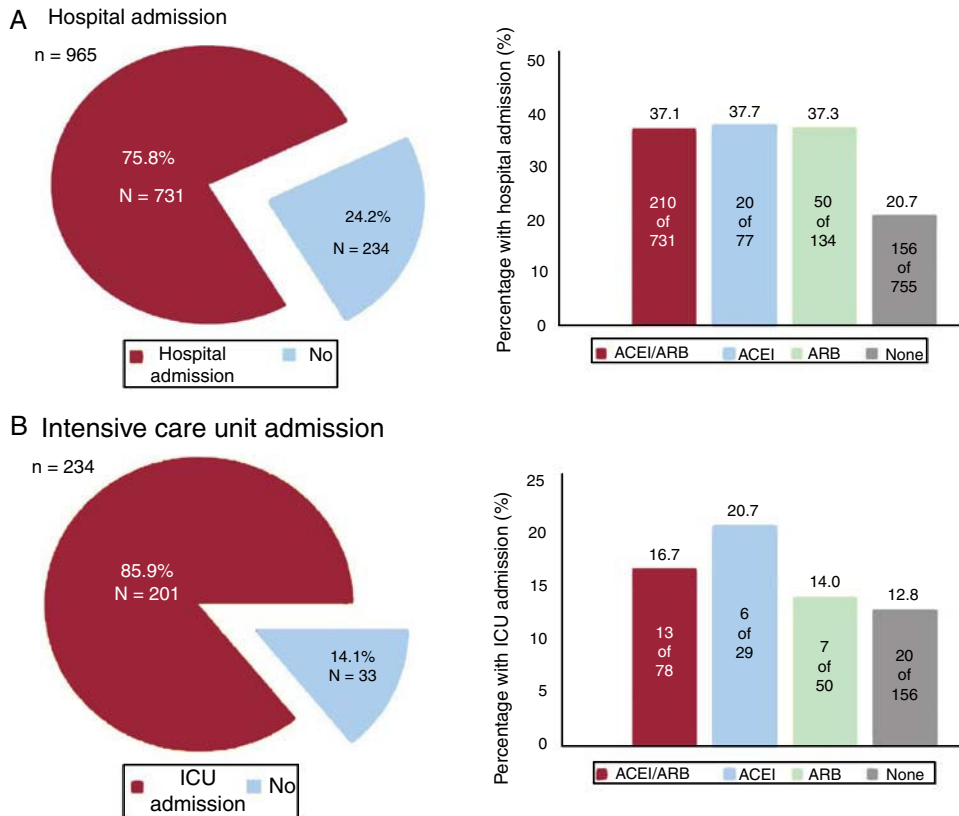

Figure 3. Hospital admissions according to type of treatment. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ICU, intensive care unit.

Table 2
Baseline characteristics

	Total cohort (N = 965)	ACEI/ARB (n = 213 [21.8%])	No ACEI/ARB (n = 755 [78.2%])	P
Clinical presentation				
Days with symptoms	6.1 ± 4.6	5.9 ± 4.3	6.2 ± 4.7	.418
Fever, %	59.9	59.5	60.0	.901
$SaO_2 < 95\%$, %	22.4	31.9	19.7	< .001
Demographic characteristics				
Age, y	59.5 ± 20.3	72.1 ± 13.2	56.0 ± 20.5	< .001
Female sex, %	56.1	43.8	59.5	< .001
Obesity, %	6.6	16.7	3.8	< .001
Health workers, %	13.1	4.3	15.5	< .001
Institutionalized, %	11.4	12.4	11.1	.613
Dementia, %	7.4	5.7	7.8	.302
Care dependency, %	14.1	16.7	13.4	.226
Cardiovascular risk factors				
Active smokers, %	2.4	0.0	3.0	.010
Hypertension, %	30.9	98.6	12.1	< .001
Diabetes, %	12.8	27.6	8.7	< .001
Dyslipidemia, %	28.2	60.0	19.3	< .001
Peripheral artery disease, %	2.7	2.7	1.5	< .001
Heart disease				
Coronary artery disease, %	4.4	11.4	2.4	< .001
Depressed LVEF, %	1.6	4.8	0.7	< .001
Significant valvulopathy, %	1.8	5.7	0.7	< .001
Atrial fibrillation, %	3.8	8.6	2.5	< .001
Lung disease				
Pulmonary disease, %	11.9	12.9	11.7	.635
COPD/asthma, %	8.9	7.6	9.3	.457
OSAHS, %	2.5	5.2	1.7	.004
Comorbidity				
GFR < 30 mL/min, %	3.0	6.7	2.0	.001
Stroke/TIA, %	3.1	5.7	2.4	.014
Active cancer, %	2.5	3.8	2.1	.164
Hypothyroidism, %	4.8	2.9	5.3	.142
Autoimmune disease, %	2.9	3.3	2.8	.673
Laboratory tests (admitted patients only)				
$pO_2 < 60$ mmHg, %	30.9	43.9	26.9	< .001
$pCO_2 > 45$ mmHg, %	2.2	3.8	1.8	.129
Hemoglobin, g/dL	13.2 ± 1.9	12.9 ± 2.0	13.4 ± 1.8	.071
Leukocytes, x 1000/μL	6.5 ± 3.5	6.3 ± 3.6	6.6 ± 3.4	.551
Lymphocytes, x 1000/μL	0.9 ± 0.8	0.9 ± 0.9	1.0 ± 0.8	.352
Platelets, x 1000/μL	199.4 ± 97.0	195.6 ± 88.6	201.2 ± 101.0	.658
Creatinine, mg/dL	1.2 ± 0.9	1.4 ± 1.1	1.1 ± 0.8	.019
Troponin, ng/mL	0.12 ± 0.43	0.14 ± 0.38	0.11 ± 0.46	.595
Elevated troponin levels, %	18.2	25.9	14.5	.028
D-dimer, ng/mL	2720.2 ± 10 247.8	2537.9 ± 5008.7	2809.7 ± 12 025.8	.846
Ferritin, ng/mL	914.8 ± 990.6	969.1 ± 965.8	886.3 ± 1005.5	.559
C-reactive protein, mg/dL	11.9 ± 13.3	13.6 ± 12.0	11.1 ± 13.9	.164
Interleukin-6, pg/mL	112.5 ± 407.0	110.2 ± 285.4	113.7 ± 457.9	.955
Previous treatment				
Antiplatelet therapy, %	9.9	23.8	6.1	< .001
Anticoagulation, %	5.7	13.8	3.4	< .001
Beta-blockers, %	9.1	26.2	4.4	< .001
Corticoids, %	3.7	2.4	4.1	.243

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricle ejection fraction; OSAHS, obstructive sleep apnea-hypopnea syndrome; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SaO2, arterial oxygen saturation; TIA, transient ischemic attack.
Values are expressed as No. (%) or mean ± standard deviation.

On admission, patients with previous treatment with ACEI/ARB had lower oxygenation (peripheral O_2 saturation under 95% in 31.9% vs 19.7%; $P < .01$; respiratory insufficiency in 43.9% vs 26.9%, $P < .01$) and had higher creatinine and troponin levels. Figure 1 and figure 2 show the events in all COVID-19 patients and in those who were admitted. Figure 3 shows hospital admissions according to type of treatment.

Table 3 shows that, on univariate analysis, treatment with ACEI/ARB (combined and individually) significantly increased in the risk of hospitalization, but this association disappeared both in the multivariate analysis with logistic regression and in that performed in the model created with propensity score matching to adjust for potential risk arguments. Hospitalized patients under ACEI/ARB showed more frequent need for more ICU admissions.

Previous treatment with ACEI/ARB (combined and individually) showed no impact on mortality or on heart failure, either in the multivariate analysis or in the propensity score-adjusted model. Taking the treatment for more than 1 year also had no effect (table 4). When we analyzed only the subgroup of patients requiring hospitalization, the absence of an impact on mortality and on heart failure remained both in the multivariate analysis and in the propensity score model, including in the evaluation of treatment taken for more than 1 year (table 5). The lack of effect remained when we applied the same models to the combined endpoint of mortality and heart failure (table 6).

Table 3

Association between ACEI/ARBs and hospital and ICU admissions

Events	Admissions within the whole cohort			ICU admissions within the admitted cohort		
Univariate analysis						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARBs	2.27	1.63-3.16	< .001	1.36	0.64-2.90	.427
ACEI/ARBs ≥ 1 y	2.51	1.76-3.58	< .001	1.81	0.84-3.90	.127
ACEI	2.01	1.24-3.28	.005	1.72	0.64-4.61	.281
ACEI ≥ 1 y	1.89	1.10-3.27	.022	2.57	0.93-7.14	.070
ARBs	2.09	1.42-3.08	< .001	0.99	0.40-2.43	.981
ARBs ≥ 1 y	2.54	1.67-3.87	< .001	1.19	0.48-2.96	.703
*Multivariate analysis**						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARBs	0.85	0.45-1.64	.638	0.87	0.30-2.50	.798
ACEI/ARBs ≥ 1 y	1.08	0.58-1.99	.808	1.13	0.37-3.42	.828
ACEI	0.78	0.38-1.60	.505	0.97	0.22-4.16	.962
ACEI ≥ 1 year	0.59	0.27-1.28	.182	1.23	0.27-5.60	.787
ARBs	1.10	0.59-2.04	.757	0.84	0.25-2.87	.786
ARBs ≥ 1 y	1.57	0.82-2.99	.173	1.02	0.28-3.64	.979
Propensity score matching						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARBs	1.11	0.59-2.11	.744	1.00	0.22-4.45	1.000
ACEI/ARBs ≥ 1 y	0.96	0.50-1.85	.909	1.50	0.34-6.70	.596
ACEI	1.01	0.44-2.28	.988	0.65	0.07-5.97	.651
ACEI ≥ 1 y	0.83	0.32-2.18	.709	1.05	0.01-1.06	.968
ARBs	1.22	0.62-2.41	.572	1.16	0.25-5.47	.847
ARBs ≥ 1 y	1.06	0.52-2.18	.871	1.54	0.32-7.33	.586

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ICU, intensive care unit; OR, odds ratio.
* Whole cohort: adjustment for those variables with a $P < .05$ in the univariate analysis (days with symptoms, fever, arterial oxygen saturation <95%, age, sex, health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy). ICU admitted cohort: adjustment for those variables with a $P < .05$ in the univariate analysis (arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6) (table 2 of the supplementary data).

Table 4

Association between ACIE/ARBs, mortality and heart failure in the whole cohort of COVID-19 positive patients

Events	Mortality			Heart failure		
Univariate analysis						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARBs	1.49	0.73-3.06	.276	2.20	1.09-4.44	.028
ACEI/ARBs ≥ 1 y	1.78	0.85-3.74	.128	2.00	0.94-4.25	.071
ACEI	0.63	0.15-2.67	.532	3.07	1.29-7.28	.011
ACEI ≥1 y	0.40	0.05-2.95	.367	3.36	1.34-8.43	.010
ARBs	1.99	0.92-4.31	.080	1.30	0.53-3.18	.571
ARBs ≥1 y	2.69	1.23-5.84	.013	1.06	0.37-3.06	.916
*Multivariate analysis**						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARBs	0.62	0.17-2.26	.468	1.37	0.39-4.77	.622
ACEI/ARBs ≥ 1 y	1.20	0.33-4.37	.787	1.10	0.33-3.66	.879
ACEI	0.14	0.01-1.57	.111	3.01	0.89-10.16	.076
ACEI ≥ 1 y	0.02	0.01-0.63	.027	3.15	0.86-11.58	.084
ARBs	1.54	0.42-5.59	.512	0.46	0.12-1.72	.248
ARBs ≥ 1 y	3.96	1.06-14.87	.041	0.36	0.08-1.57	.174
Propensity score matching						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARBs	0.47	0.14-1.64	.239	1.54	0.42-5.67	.517
ACEI/ARBs ≥ 1 y	0.47	0.12-1.81	.273	0.62	0.15-2.49	.499
ACEI	0.84	0.18-4.08	.837	1.93	0.47-7.92	.362
ACEI ≥ 1 y	0.60	0.07-4.62	.596	1.67	0.33-8.46	.532
ARBs	0.41	0.09-1.93	.259	0.92	0.22-3.70	.905
ARBs ≥ 1 y	0.52	0.11-2.49	.416	0.29	0.04-2.33	.243

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; OR, odds ratio.
* Adjustment for those variables with a $P < .05$ in the univariate analysis (fever, oxygen saturation <95%, age, sex, obesity, health personnel, dependency status, hypertension, diabetes mellitus, dyslipidemia, arterial disease, heart disease, atrial fibrillation, pneumonia, chronic renal disease, cerebrovascular disease, autoimmune disease, anticoagulation, beta-blockers) (table 1 of the supplementary data).

DISCUSSION

To our knowledge, this is one of the few studies that analyzes the impact of ACEI/ARB on COVID-19 prognosis based on a large western-world population that includes all positive cases in a health area. This is also the largest cohort of patients studied to date.

The main findings are the neutral effect of ACEI/ARB on mortality, heart failure, and the combination of mortality and heart failure. Previous treatment with ACEI/ARB in patients with COVID-19 showed no association with the need for hospitalization or ICU admission. Taking ACEI/ARB for more than 1 year also had no effect. All these findings were confirmed, both in the overall analysis of the sample and in the propensity score model. Based on these data, withdrawal of chronic treatment with ACEI/ARB in patients testing positive for COVID-19 would not be justified. The available data on the effect of ACEI/ARB on mortality in patients with COVID-19 have focused mainly on cohorts of admitted patients and especially on hypertensive patients.[22,23]

SARS-CoV-2 enters the cells through a glycoprotein of its crown, which binds to the ACE2 of the alveoli pneumocytes,[7,13] leading to its internalization after priming by the transmembrane protease, serine 2.[7,8] After the virus enters the cell, it releases its RNA and proteins, leading to the development of new viral particles. ACE2 is 2% in a soluble form—not valid for SARS-CoV-2 binding—, after cleavage by ADAM-17. Angiotensin I upregulates ADAM-17, thus

Table 5

Association between ACE/ARB and mortality and heart failure in hospitalized patients with COVID-19 infection

Events		Mortality			Heart failure	
Univariate analysis						
	OR	95%CI	P	OR	95%CI	P
ACE/ARB	1.00	0.41-2.45	1.000	1.22	0.58-2.57	.605
ACE/ARB ≥ 1 y	1.05	0.42-2.67	.912	1.02	0.46-2.26	.958
ACE	0.62	0.14-2.77	.528	2.01	0.79-5.15	.145
ACE ≥1 y	0.39	0.05-3.05	.370	2.37	0.86-6.54	.097
ARB	1.26	0.47-3.36	.647	0.73	0.28-1.87	.729
ARB ≥ 1 y	1.51	0.56-4.05	.415	0.51	0.17-1.54	.513
*Multivariate analysis**						
	OR	95%CI	P	OR	95%CI	P
ACE/ARB	1.04	0.16-6.57	.966	1.53	0.33-6.98	.583
ACE/ARB ≥ 1 y	1.13	0.15-8.53	.907	0.55	0.11-2.65	.459
ACE	0.58	0.04-9.45	.699	3.82	0.73-20.09	.114
ACE ≥ 1 y	0.02	0.00-1.95	.094	3.65	0.60-9.40	.194
ARB	1.38	0.20-9.40	.745	0.50	0.10-2.39	.385
ARB ≥ 1 y	4.75	0.49-45.68	.177	0.17	0.03-1.09	.062
Propensity score matching						
	OR	95%CI	P	OR	95%CI	P
ACE/ARB	1.00	0.23-4.45	1.000	1.30	0.31-5.44	.717
ACE/ARB ≥ 1 y	1.50	0.34-6.70	.596	1.16	0.28-4.86	.839
ACE	1.75	0.30-10.27	.535	1.46	0.26-8.38	.668
ACE ≥ 1 y	1.05	0.11-10.06	.968	0.90	0.10-8.48	.924
ARB	0.59	0.11-3.25	.547	0.94	0.21-4.24	.937
ARB ≥ 1 y	1.54	0.32-7.33	.586	1.25	0.27-5.70	.773

95%CI, 95% confidence interval; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; OR, odds ratio.

* Adjusted for variables with *P* < .05 in the univariate analysis (fever, arterial oxygen saturation < 95%, age, sex, obesity, health care worker, dependency, hypertension, diabetes mellitus, dyslipidemia, peripheral artery disease, coronary artery disease, atrial fibrillation, pulmonary disease, renal impairment, stroke/ transient ischemic attack, hemoglobin, leukocytes, lymphocytes, creatinine, increased troponin, D-dimer, ferritin, ultrasensitive C-reactive protein, and interleukin-6 (table 1 of the supplementary data).

Table 6

Association between ACEI/ARB with a composite endpoint of death and heart failure

Event		Death + heart failure (whole cohort)			Death + heart failure (admitted to hospital)	
Univariate analysis						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARB	1.85	1.08-3.15	.025	1.35	0.56-3.26	.499
ACEI/ARB ≥ 1 y	2.21	1.27-3.84	.005	1.27	0.66-2.47	.477
ACEI	1.63	0.75-3.55	.219	1.16	0.61-2.19	.659
ACEI ≥ 1 y	1.86	0.81-4.27	.143	1.68	0.65-4.37	.285
ARB	1.71	0.92-3.18	.089	0.95	0.45-2.02	.902
ARB ≥ 1 y	2.11	1.11-4.01	.023	1.01	0.46-2.20	.989
*Multivariate analysis**						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARB	1.06	0.39-2.83	.915	1.07	0.25-4.64	.927
ACEI/ARB ≥ 1 y	1.57	0.58-4.26	.369	1.03	0.23-4.60	.964
ACEI	1.15	0.40-3.36	.807	1.18	0.24-5.83	.840
ACEI ≥ 1 y	1.25	0.39-4.06	.708	0.98	0.17-5.67	.976
ARB	0.94	0.36-2.47	.895	0.92	0.22-3.89	.912
ARB ≥ 1 y	1.35	0.51-3.56	.544	1.05	0.24-4.53	.945
Propensity score matching						
	OR	95%CI	P	OR	95%CI	P
ACEI/ARB	0.78	0.29-2.08	.618	1.20	0.37-3.89	.764
ACEI/ARB ≥ 1 y	0.72	0.26-2.02	.528	1.93	0.59-6.24	.279
ACEI	1.26	0.38-4.13	.704	1.29	0.29-5.77	.743
ACEI ≥ 1 y	1.34	0.35-5.06	.669	1.17	0.20-6.77	.862
ARB	0.58	0.18-1.87	.583	0.35	0.27-3.24	.913
ARB ≥ 1 y	0.51	0.14-1.86	.310	1.94	0.56-6.70	.295

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OR, odds ratio.

* Whole cohort: adjustment of variables with *P* < .05 in univariate analysis (fever, arterial oxygen saturation < 95%, age, sex, obesity, health care worker, care dependency, hypertension, diabetes, dyslipidemia, peripheral artery disease, heart disease, atrial fibrillation, lung disease, renal impairment, stroke/ transient ischemic attack). Cohort admitted to hospital: adjustment of variables with *P* < .05 in multivariate analysis (fever, arterial oxygen saturation < 95%, age, sex, obesity, health care worker, care dependency, hypertension, diabetes, dyslipidemia, peripheral artery disease, heart disease, atrial fibrillation, lung disease, renal impairment, stroke/transient ischemic attack, hemoglobin, leukocytes, lymphocytes, creatinine, elevated troponin levels, D-dimer, ferritin, C-reactive protein, interleukin-6) (table 1 of the supplementary data).

increasing soluble ACE2 levels.[9,10] Furthermore, ADAM-17 also mediates the release of membrane-bound precursors of proinflammatory cytokines (tumor necrosis factor-α, interferon-γ, and interleukin-4) into the circulation. The interaction between SARS-CoV-2 and ACE2 triggers a massive production of proinflammatory cytokines, which attracts leucocytes and hyperactive macrophages that release more cytokines, inducing the obliteration of the alveoli and developing the characteristic hyaline membranes of acute respiratory distress syndrome.[3,7,13,17] Therefore, downregulation of ACE2 cell surface expression reduces the ability of ARS-CoV-2 to cause damage.[11] ACE inhibitors and ARB are highly recommended drugs for patients with cardiovascular diseases, such as refractory hypertension, heart failure, and coronary artery disease.[18,19] Chronic treatment with these medications increases the expression of ACE.[24–26] Based on this mechanism, some authors have hypothesized that persistent downregulation of the renin-angiotensin-aldosterone system may cause harm by increasing ACE2 expression.[12,14] On the other hand, angiotensin II takes part in the immune response to acute respiratory distress syndrome, so its depuration though ACE2 may be beneficial.[15–17] When this study was being performed, scientific societies and government agencies were recommending continuing with this treatment.[18,19] This advice is supported by the results of this study, upgrading the expert-consensus recommendation to an evidence-based one according to a registry with all cases of COVID-19 infection from a western health area. An ongoing randomized clinical trial with losartan in these patients will help us to make a stronger recommendation (NCT04312009 and NCT04311177).[27]

To obtain an overall picture of the relevance of these results, we highlight that in the area where the study was conducted, 72 527 (16.19%) of the inhabitants were under chronic treatment with ACEI or ARB. Out of the COVID-19 patients, 210 (21.8%) were under ACEI or ARB at the time of diagnosis. According to the latest estimates, it is likely that by the end of the year, up to 70% of the Spanish population will have been infected by this new coronavirus,[28] hence the importance of identifying the effects of these widely used drugs on the prognosis of this new disease.

Study limitations

Because of its observational nature, unmeasured confounders could have constrained causal inference in the present study. False negatives in the polymerase chain reaction test could have affected the sample size, underestimating the number of individuals infected by the virus.

CONCLUSIONS

Withdrawal of chronic treatment with ACEI/ARB in patients testing positive for COVID-19 would not be justified. In line with the recommendations of scientific societies and government agencies, this study supports continuation of this treatment.

WHAT IS KNOWN ABOUT THE TOPIC?

It is unclear whether previous treatment with ACEI and ARB affects the prognosis of COVID-19 patients. Chronic treatment with these medications increases ACE expression. Based on this mechanism, there is a hypothesis postulating that persistent downregulation of the renin-angiotensin-aldosterone system may be harmful because it increases ACE2 expression.

WHAT DOES THIS STUDY ADD?

Our data suggest that chronic administration of ACEI and ARB is safe in COVID-19 patients and therefore its withdrawal should not be recommended.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2020.05.018

REFERENCES

1. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wu han China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med.* 2020;382:1199–1207.
2. Huang C, Wang Y, Li X, et al. Articles Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China Lancet.* 2020;395:497–506.
3. Zhang N, He C, Wang L, et al. Recent advances in the detection of respiratory virus infection in humans. *J Med Virol.* 2020;92:408–417.
4. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV) December 2019 to January 2020. *Euro Surveill.* 2020.. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.4.2000058. Accessed 18 May 2020
5. World Health Organization. *WHO announces COVID-19 outbreak a pandemic.* 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Accessed 25 May 2020
6. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382:1708–1720.
7. Zhou P, Yang X, Wang X, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579:270–273.
8. 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;181:271–280e8.
9. Ferrario CM, Chappell MC, Tallant EA, Brosnihan KB, Diz DI. Counterregulatory actions of angiotensin-(1-7). *Hypertension.* 1997;30:535–541.
10. Jan DAH, Murray E, Daniel B. Renin-Angiotensin System Blockers and the COVID-19 Pandemic. *Hypertension.* 2020;75:1382–1385.
11. Wang K, Gheblawi M, Oudit GY. Angiotensin Converting Enzyme 2: A Double-Edged Sword. *Circulation.* 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.047049
12. Sommerstein R, Kochen MM, Messerli FH, Gräni C. Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Have a Biphasic Effect? *J Am Heart Assoc.* 2020. https://doi.org/10.1161/JAHA.120.016509
13. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science.* 2020;367:1444–1448.
14. Díaz JH, Sciences OH, Orleans N, Diaz JH, Sciences OH. Hypothesis?: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe. *J Travel Med.* 2020.;382:1653–1659https://doi.org/10.1093/jtm/taaa041
15. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med.* 2020;382:e92.
16. Liu Y, Huang F, Xu J, et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. *Med R.* 2020. https://doi.org/10.1101/2020.03.20.20039586
17. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect.* 2020;9:757–760.
18. De Simone G. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. *European Society of Cardiology.* 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 18 May 2020
19. Agencia Española de Medicamentos y Productos Sanitarios. *Medicamentos anti-hipertensivos que actúan sobre el sistema renina angiotensina e infección por COVID-19.* 2020. Available at: https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2020-seguridad-1/medicamentos-antihipertensivos-que-actuan-sobre-el-sistema-renina-angiotensina-e-infeccion-por-covid-19/. Accessed 25 May 2020
20. World Health Organization. *Clinical management of severe acute respiratory infection when COVID-19 is suspected.* 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 25 May 2020
21. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37:2129–2200.
22. Peng Z, LiHua Z, Jingjing C, 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. https://doi.org/10.1161/CIRCRESAHA.120.317134
23. Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan. *China JAMA Cardiol.* 2020. http://dx.doi.org/10.1001/jamacardio.2020.1624.
24. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus – induced lung injury. *Nat Med.* 2005;11:875–879.
25. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J.* 2019;41:407–477.
26. FC M, Jewell J, CM.F C.. et al. Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor Blockers on Cardiac Angiotensin-Converting Enzyme 2. *Circulation.* 2005;111:2605–2610.
27. U.S. National Library of Medicine. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04312009. Accessed 2020.
28. CoronaTracker Community Group; Hamzah FAB, Lau CH, Nazri H, et al. Corona-Tracker: World-wide COVID-19 Outbreak Data Analysis and Prediction. 2020 Available at: https://www.who.int/bulletin/online_first/20-255695.pdf. Accessed 25 May 2020.