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Renin–angiotensin system inhibitors and mortality in patients with COVID-19

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Abstract

Association of renin–angiotensin system inhibitors with risk of death in patients with hypertension (HTN) and coronavirus disease 2019 (COVID-19) is not well characterized. The aim of this study was to evaluate the outcomes of patients with HTN and COVID-19 with respect to different chronic antihypertensive drug intake. We performed a retrospective, observational study from a large cohort of patients with HTN and with a laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection admitted to the Emergency Rooms (ER) of the Piacenza Hospital network from February 21, 2020 to March 20, 2020. There were 1050 patients admitted to the ERs of the Piacenza Hospital network with COVID-19. HTN was present in 590 patients [median age, 76.2 years (IQR 68.2–82.6)]; 399 (66.1%) patients were male. Of them, 248 patients were chronically treated with ACEi, 181 with ARBs, and 161 with other drugs (O-drugs) including beta blockers, diuretics and calcium-channel inhibitors. With respect to the antihypertensive use, there was no difference between comorbid conditions. During a follow-up of 38 days (IQR 7.0–46.0), 256 patients (43.4%) died, without any difference stratifying for antihypertensive drugs. Of them, 107 (43.1%) were in ACEi group vs 67 (37%) in ARBs group vs 82 (50.7%) in O-drugs group, (log-rank test: $p = 0.066$). In patients with HTN and COVID-19, neither ACEi nor ARBs were independently associated with mortality. After adjusting for potential confounders in risk prediction, the rate of death was similar. Our data confirm Specialty Societal recommendations, suggesting that treatment with ACEIs or ARBs should not be discontinued because of COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Renin–angiotensin system (RAS) inhibitors · Mortality · Hypertension

Abbreviations

ACE2	Angiotensin-converting enzyme 2
ACEi	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin-receptor blockers
COVID-19	Coronavirus disease 2019
ER	Emergency rooms
HTN	Hypertension
O-drugs	Other drugs
RAS	Renin–angiotensin system
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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Introduction

In late December 2019, the coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was described for the first time in Wuhan, China [1]. Quickly spreading all over the world, it was declared a pandemic infection by the World Health Organization on March 11, 2020 [2]. The clinical spectrum of COVID-19 appeared to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness and acute respiratory distress syndrome, with a high mortality rate [3, 4]. It remains unclear whether the reported mortality was related to the chronical use of renin–angiotensin system (RAS) inhibitors. Angiotensin-Converting Enzyme inhibitors (ACEi) and Angiotensin-Receptor Blockers (ARBs) are a group of pharmaceuticals that have different effects on angiotensin II, the primary substrate of the angiotensin-converting enzyme 2 (ACE2), commonly applied in the treatment of hypertension (HTN). The potential bridge between SARS-CoV-2 pathophysiology and ACEi/ARBs effects derives from evidences showing that SARS-CoV-2 uses ACE2 receptor to enter in human alveolar epithelial cells [5]. ACE2 is a homologue of ACE, widely distributed in the heart, kidneys and lungs, and it functions as a negative regulator of the RAS. Use of ACEIs and ARBs might upregulate ACE2 expression, thus increasing patient susceptibility to viral host cell entry. The purpose of the present study was to evaluate the association of ACEi and ARBs with risk of death in patients with HTN and COVID-19.

Methods

Study design and population

This was a retrospective observational study performed at Piacenza Hospital Network, including 3 Hospitals in Piacenza Province, Italy ('Guglielmo da Saliceto' Piacenza Hospital, Castel San Giovanni Hospital and Fiorenzuola d'Arda Hospital); the Hospital network is referral for 287 152 inhabitants. All consecutive patients with laboratory-confirmed COVID-19 infection admitted to the Emergency Rooms (ER) of the Piacenza Hospital network from February 21, 2020 to March 20, 2020 and HTN were enrolled in the study. Clinical investigations were conducted according to the principles of the Declaration of Helsinki. The study was approved by the Institutional Ethical Board of the "Emilia Nord Area" (Approval number 2020/0029787); written informed consent was waived by the Ethics Commission due to the emergency of the infectious disease.

Positive laboratory test for SARS-Cov-2 infection was defined as a result of real-time reverse transcription polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs [6]. The exam was implemented in a local laboratory with the adjunct of RT-PCR assays. Patients with HTN were classified based upon documented medical history with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [7].

Data collection

Clinical data are routinely collected during ER access and hospitalization in Piacenza Hospital network on a shared electronic medical record. Deaths in Piacenza Province are collected on a daily basis from the "Azienda Sanitaria Locale" (Local Health Authority) and recorded on an electronic survival record. Clinical data were extracted from the electronic medical records and merged with the survival data provided by the Azienda Sanitaria Locale by members of the research team; data were carefully reviewed and confirmed by two independent researchers to guarantee the accuracy of the data extraction procedures. Patients were followed up from the index date and until 1 of the following: outcome occurrence or end of study period (April 24, 2020). The endpoint of the study was death for any cause.

Statistical methods

Due to the retrospective nature of the study, no sample size calculation was a priori performed; sample size was equal to patients admitted to ERs of the Piacenza Hospital network. Continuous variables are expressed as mean $\pm$ standard; the independent samples t-test or Mann–Whitney U-test was used to compare normally and non-normally distributed continuous variables between survivors and non-survivors. Categorical variables are summarized as frequency and percentage, and compared using Pearson's χ^2 exact test. ANOVA and Bonferroni post hoc test for multiple comparisons were performed to estimate differences between groups stratified by the antihypertensive drug treatment. Antihypertensive drug categories included in the analysis were ACEi group, ARBs group and other drugs (O-drugs) group, and were defined as use of these drugs. O-drugs included beta blockers, calcium-channel blockers, alfa-blockers and diuretics.

Cox regression model was performed to identify risk/protective factors for death of the clinical covariates. Kaplan–Meier survival curves were used to estimate freedom from death. Log-rank test was used to compare survival times of patients stratified by the antihypertensive drug treatment. Propensity score-matched cohorts were created based on significant predictors in the previously developed Cox regression model. Patients on ACEi/ARBs/O-drugs were paired according to the propensity scores with nearest

matching and a ratio of 1:1:1. The balance of covariates was evaluated by estimating standardized differences before and after matching, and small absolute value less than 0.25 was considered successful balancing between the groups. Malignancies included active neoplasia and history of any previous neoplasia; cardiovascular disease included cardiomyopathy and heart failure. Analyses regarding different factors were based on non-missing data. Analyses were performed using SPSS statistical software version 23.0 (IBM SPSS); significance level was set at 0.05.

Results

Patients characteristics

As of February 21, 2020 to March 20, 2020, 1,050 consecutive patients with confirmed SARS-CoV2 infection were admitted to the ERs of Piacenza Hospital network. Among these patients, a total of 603 had a history of HTN. After excluding 13 patients without available key information in their medical records, we included 590 patients in the final analysis. Clinical data of patients are shown in Table 1. The median age was 76.2 years (IQR 68.2–82.6) ranging from 33.8 to 98.5 years; 399 (66.1%) were male. 90 (15.2%) were discharged from the ER and treated in the outpatient setting. 500 (84.8%) were admitted into the hospital: of these patients, 84 patients (14.2%) have had access to the intensive care unit and 133 (22.5%) were admitted in semi-intensive care units. The median time from illness onset to hospital admission was 7 days (IQR 3–10). One-third of the patients required respiratory support with invasive mechanical ventilation (76, 12.9%) or with non-invasive ventilation (119, 19.2%). Non-survivor patients were older [72.9 years old (IQR 64.1–80.2) vs 79.5 years old (IQR 73.9–84.8), $p < 0.001$] and showed more comorbidities compared to survivors. Moreover, a greater female sex prevalence was observed in survivor patients (63.5% vs 73.0%, $p = 0.01$).

Characteristics of antihypertensive drug treatment groups

248 (42.0%) patients chronically used ACEi, 181 (30.7%) ARBs, and 161 (27.3%) O-drugs; their clinical data are shown in Table 2. Users of ACEi/ARBs trended to be younger than non-users (75.6 years [IQR 66.8–81.3] vs 76.6 years [IQR 69.7–84.6] and were more often men than non-users. Underlying diseases were present in nearly half of patients, with hyperlipidemia being the most common, followed by diabetes, cardiovascular disease, chronic kidney disease and stroke. As a result, 240 (40.7%) patients had 3 or more coexisting medical conditions, without significant differences between groups.

The most common self-reported symptoms at onset of illness were fever and dyspnea, followed by cough, and fatigue; less common symptoms were diarrhea, sensory taste disturbances, sputum production, and headache. More than half of patients (60.7%) developed dyspnea. Symptoms were not different between groups. COVID-19 severity was classified according with the guidelines on the Diagnosis and Treatment of COVID-19 [8] and defined as severe with the presence of one of the following conditions: respiratory failure that require mechanical ventilation, shock or multi-organ dysfunction. Critical clinical conditions were not different between groups.

Outcome analysis

At the end of the study period, 228 (38.6%) patients were discharged, 16 (2.7%) patients were still hospitalized, and 256 (43.4%) patients died. All 90 patients treated in the outpatient setting were alive. The median time from illness onset to death was 12.5 days (IQR 4.5–16.0). In Cox proportional hazard modeling, age (hazard ratio: 1.059; 95% confidence interval: 1.045–1.073; $p < 0.001$) and gender (hazard ratio: 0.699; 95% confidence interval: 0.531–0.922; $p = 0.011$) were associated with death; likewise, the PaO2/FiO2, the respiratory rate, LDH and PCR serum levels were found strong mortality predictors. Chronic intake of various antihypertensive drug treatments was not associated with risk of death. None of the comorbidities was related with mortality, whereas the coexistence of 3 or more underlying diseases was a predictor of mortality (Table 3). No significant differences in mortality were found between groups (log-rank test: $p = 0.066$). Mortality was 43.1% among ACEi users, 37.0% among ARBs users, and 50.9% among patients using any other antihypertensive drug, with a hint at possible longer survival in patients on ACEi or ARBs treatment (Fig. 1). We conducted a propensity score-matched analysis to account for unbalances in the following variables: age, gender, diabetes and chronic kidney disease. 159 patients on ACEi were successfully matched with 163 patients on ARBs and 149 on O-Drugs. After matching, no significant differences in mortality were found between ACEi, ARBs, and O-drugs groups (log-rank test: $p = 0.102$). Kaplan–Meier curve for the three drug treatments after matching is shown in Fig. 2.

Discussion

In the current study, data showed that RAS inhibitors were not associated with an increased mortality of COVID-19 in patient with HTN.

As China has firstly experienced the outbreak of COVID-19, the current available epidemiological data

Table 1 Characteristics of patients with hypertension and COVID-19

	All population n = 590	Survivors n = 334	Non survivors n = 256	p value
Age—median (IQR) (years)	76.2 (68.2–82.6)	72.9 (64.1–80.2)	79.5 (73.9–84.8)	< 0.001
Male gender no. (%)	399 (67.6)	212 (63.5)	187 (73.0)	0.014
Chronic disease				
Cardiovascular disease—no. (%)	95 (16.1)	50 (15.0)	45 (17.6)	0.393
Hyperlipidemia—no. (%)	205 (34.7)	113 (33.8)	92 (35.9)	0.595
Diabetes—no. (%)	137 (23.2)	70 (21.0)	67 (26.2)	0.137
Atrial fibrillation—no. (%)	101 (17.1)	49 (14.7)	52 (20.3)	0.071
COPD—no. (%)	121 (20.5)	69 (20.7)	52 (20.3)	0.918
CKD—no. (%)	90 (15.3)	32 (9.6)	58 (22.7)	< 0.001
Stroke—no. (%)	21 (3.6)	8 (2.4)	13 (5.1)	0.081
Malignancy—no. (%)	47 (8.0)	23 (6.9)	24 (9.4)	0.269
3 or more comorbidities—no. (%)	240 (40.7)	124 (37.1)	116 (45.3)	0.045
Respiratory support				
OTI—no. (%)	76 (12.9)	47 (14.1)	29 (11.3)	0.324
NIV—no. (%)	113 (19.2)	37 (11.1)	76 (29.7)	< 0.001
Symptoms at onset of illness				
Fever—no. (%)	450 (76.3)	231 (69.1)	219 (85.5)	0.550
Cough—no. (%)	227 (38.5)	138 (41.3)	89 (34.8)	0.001
Dyspnea—no. (%)	358 (60.7)	171 (51.2)	187 (73.0)	0.058
Diarrhea—no. (%)	37 (6.3)	26 (7.8)	11 (4.3)	0.010
Vital signs at admission				
Temperature (°C)—median (IQR)	37.5 (36.8–38.3)	37.4 (36.8–38.2)	37.5 (36.7–38.3)	0.934
SBP (mmHg)—median (IQR)	130.0 (115.0–145.0)	130.0 (120.0–147.5)	130 (113.5–145.0)	0.394
PaO2/FiO2—median (IQR)	238.1 (152.4–290.5)	263.9 (211.3–302.3)	200.0 (112.9–279.4)	< 0.001
PaO2/FiO2 < 300—no. (%)	375 (63.3)	164 (49.1)	211 (82.8)	< 0.001
Laboratory parameters—median (IQR)				
Serum creatinine (mg/dL)	1.1 (0.9–1.6)	1.0 (0.9–1.3)	1.3 (1.0–1.8)	< 0.001
LDH (U/L)	413.0 (305.0–537.0)	385.0 (297.0–486.0)	462.0 (338.0–601.5)	< 0.001
C-reactive protein (mg/dL)	11.3 (5.8–17.5)	9.9 (5.0–15.5)	12.9 (7.2–19.3)	< 0.001
Hemoglobin (g/dL)	13.4 (12.0–14.7)	13.6 (12.5–14.8)	13.1 (11.6–14.6)	0.025
White blood cell count (10^3/L)	6.9 (5.2–9.3)	6.6 (5.0–8.9)	7.2 (5.6–10.1)	0.019
Lymphocytes (%)	11.9 (6.4–17.9)	13.4 (7.8–19.3)	9.7 (5.4–16.6)	< 0.001
Pneumonia classification				
COVID severe—no. (%)	229 (38.8)	40 (12.0)	189 (73.8)	< 0.001
Curb 65 severe—no. (%)	100 (16.9)	44 (13.2)	56 (21.9)	0.005
qSOFA severe—no. (%)	59 (10.0)	39 (11.7)	20 (7.8)	0.121

IQR, interquartile range, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *OTI* orotracheal intubation, *NIV* non-invasive ventilation, *SBP* systolic blood pressure, *PaO2/FiO2* partial pressure of oxygen in arterial blood/fraction of inspired oxygen, *LDH* lactate dehydrogenase, *qSOFA* quick sequential organ failure assessment

concern the Chinese population [9]. Of interest, HTN was the most frequent coexisting condition, with an estimated prevalence of 15%; however, data from PEACE Million Persons Project showed that nearly half of Chinese adults are suffering from HTN [10]. In contrast to these findings, the prevalence of HTN in our data is significantly higher, reflecting the real rate of HTN in the general population.

Recently, uncertainties have been raised on the use anti-hypertensive drugs that modulate the RAS in patient at risk for COVID-19; it has been suggested that they could act as a potential risk factor for poor outcome in COVID-19 patients by up-regulating ACE2. The importance of RAS in the mechanisms that cause HTN and determine its prognosis is well established. Angiotensin II is the principal mediator

Table 2 Clinical characteristics of patients on treatment with ACEi, ARBs and other drugs

	ACEi $n = 248$	ARBs $n = 181$	O-drugs $n = 161$	p value
Age—median (IQR) (years)	76.3 (68.8–82.7)	75.2 (66.8–81.3)	76.6 (69.7–84.6)	0.080
Male gender no. (%)	187 (75.4)	120 (66.3)	92 (57.1)	0.001
Chronic disease				
Cardiovascular disease—no. (%)	43 (17.3)	23 (12.7)	29 (18.0)	0.323
Hyperlipidemia—no. (%)	86 (34.7)	70 (38.7)	49 (30.4)	0.279
Diabetes—no. (%)	63 (25.4)	47 (26.0)	27 (16.8)	0.075
Atrial fibrillation—no. (%)	45 (18.1)	31 (17.1)	25 (15.5)	0.790
COPD—no. (%)	40 (16.1)	47 (26.0)	34 (21.1)	0.044
CKD—no. (%)	41 (16.5)	25 (13.8)	24 (14.9)	0.734
Stroke—no. (%)	11 (4.4)	6 (3.3)	4 (2.5)	0.569
Malignancy—no. (%)	22 (8.9)	13 (7.2)	12 (7.5)	0.784
3 or more comorbidities—no. (%)	101 (40.7)	78 (43.1)	61 (37.9)	0.620
Respiratory support				
OTI—no. (%)	34 (13.7)	22 (12.2)	20 (12.4)	0.875
NIV—no. (%)	50 (20.2)	39 (21.5)	24 (14.9)	0.258
Symptoms at onset of illness				
Fever—no. (%)	188 (75.8)	137 (75.7)	125 (77.6)	0.243
Cough—no. (%)	105 (42.3)	67 (37.0)	55 (34.2)	0.105
Dyspnea—no. (%)	159 (64.1)	108 (59.7)	91 (56.5)	0.194
Diarrhea—no. (%)	17 (6.9)	9 (5.0)	11 (6.8)	0.648
Vital signs at admission				
Temperature (°C)—median (IQR)	37.7 (36.9–38.4)	37.3 (36.6–38.0)	37.5 (37.0–38.1)	0.149
SBP (mmHg)—median (IQR)	130.0 (117.5–150.0)	125.0 (114.5–138.0)	127.5 (115.0–144.0)	0.045
PaO2/FiO2—median (IQR)	223.5 (151.8–281.5)	226.4 (167.3–290.5)	257.1 (137.6–304.0)	0.258
PaO2/FiO2 < 300—no. (%)	168 (67.7)	114 (63.0)	93 (57.8)	0.120
Laboratory parameters—median (IQR)				
Serum creatinine (mg/dL)	1.1 (0.9–1.6)	1.2 (0.9–1.5)	1.1 (0.9–1.7)	0.219
LDH (U/L)	425.0 (314.5–540.0)	437.0 (326.5–574.8)	364.5 (288.8–482.0)	0.009
C-reactive protein (mg/dL)	10.9 (5.7–16.8)	12.0 (6.2–18.4)	10.9 (5.4–18.5)	0.301
Hemoglobin (g/dL)	13.4 (12.1–14.9)	13.6 (12.4–14.7)	13.2 (11.8–14.5)	0.371
White blood cell count (10^3/L)	6.7 (5.2–9.2)	7.3 (5.5–10.0)	6.7 (5.2–8.8)	0.143
Lymphocytes (%)	12.6 (5.7–18.4)	11.6 (6.7–16.7)	11.3 (6.7–17.9)	0.683
Pneumonia classification				
Covid severe—no. (%)	99 (39.9)	72 (39.8)	58 (36.0)	0.696
Curb 65 severe—no. (%)	43 (17.3)	29 16.0)	28 (17.4)	0.923
qSOFA severe—no. (%)	32 (12.9)	14 (7.7)	13 (8.1)	0.134

ACEi angiotensin-converting enzyme inhibitors, *ARBs* angiotensin-receptor blockers, *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *OTI* orotracheal intubation, *NIV* non-invasive ventilation, *SBP* systolic blood pressure, *PaO2/FiO2* partial pressure of oxygen in arterial blood/fraction of inspired oxygen, *LDH* lactate dehydrogenase, *qSOFA* quick sequential organ failure assessment

of RAS. ACEi and ARBs are the major classes of RAS inhibitors and have been proved to reduce cardiovascular mortality [11, 12]. Both classes of drugs block the actions of angiotensin II and interact with ACE2 by different mechanisms. ACE2 has been found to be protective in a number of different lung injury models and it seems reasonable that RAS inhibitors should increase ACE2 level in human lungs [13, 14]. SARS-CoV-2 interfaces with RAAS through ACE2 [15]. It has been shown that SARS-CoV-2 uses ACE2 for entry into target cells [16]. Moreover, SARS-CoV-2 spike protein binding to ACE2 downmodulates ACE2 expression, and loss of ACE2 expression results in excessive production of angiotensin. Given the dual possible role of ACE2 in COVID-19, two opposite hypotheses were formulated: the first emphasizes the ability of SARS-CoV-2 to use ACE2 for entry into target cells. On the basis of this detrimental effect,

Table 3 Cox regression analysis of factors associated with mortality

	HR	95% CI	*p* value
Age	1.059	1.045–1.073	< 0.001
Gender	0.699	0.531–0.922	0.011
Vital signs at admission			
Temperature	0.990	0.870–1.126	0.882
PaO2/FiO2	0.995	0.994–0.997	< 0.001
PaO2/FiO2 < 300	3.519	2.549–4.859	< 0.001
Laboratory parameters			
LDH	1.001	1.000–1.001	< 0.001
C-reactive protein	1.018	1.011–1.025	< 0.001
White blood cell count	1.044	1.015–1.074	0.003
Lymphocytes rate	0.971	0.956–0.985	< 0.001
Chronic diseases			
Cardiovascular disease	1.180	0.855–1.628	0.314
Hyperlipidemia	1.108	0.859–1.431	0.429
Diabetes	1.233	0.933–1.629	0.141
Atrial fibrillation	1.390	0.925–1.885	0.134
COPD	1.012	0.746–1.372	0.939
CKD	1.565	0.988–1.983	0.066
Stroke	1.721	0.985–3.008	0.056
Malignancy	1.306	0.858–1.989	0.213
3 or more comorbidities	1.322	1.034–1.692	0.026
Chronical drugs intake			
ACEi	0.993	0.775–1.273	0.956
ARBs	0.771	0.584–1.019	0.068
CCBs	0.951	0.736–1.229	0.702
Alpha blockers	1.180	0.797–1.746	0.410
Diuretics	1.466	1.003–1.882	0.063
Beta blockers	1.171	0.916–1.497	0.207

HR hazard ratio, *PaO2/FiO2* partial pressure of oxygen in arterial blood/fraction of inspired oxygen, *LDH* lactate dehydrogenase, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *ACEi* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin-receptor blockers, *CCBs* calcium-channel blockers

some experts have postulated that use of ACEi/ARBs could increase risk for or severity of COVID-19, suggesting the withdrawal of these drugs [17]. The second hypothesis highlights the protective role of ACE2 on lung injury by reducing angiotensin II level. It has been postulated that unabated angiotensin II may be in part responsible for organ injury in COVID-19 [15], suggesting potential for benefit rather than harm of pharmacological regulation of ACE2 expression. Both hypotheses are based on few data, and observational studies have not yielded compelling data on whether COVID-19 patients who take these drugs fare better or worse than otherwise similar patients. Experimental animal models and studies in humans have shown mixed findings with respect to the effects of RAS inhibition on ACE2 levels or activity in tissue. Unfortunately, data regarding the effects of RAS inhibitors on lung-specific expression of ACE2 are
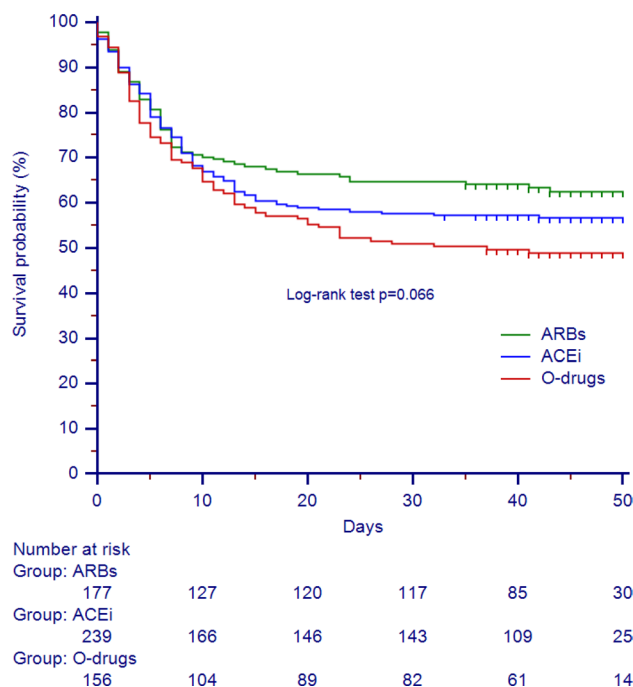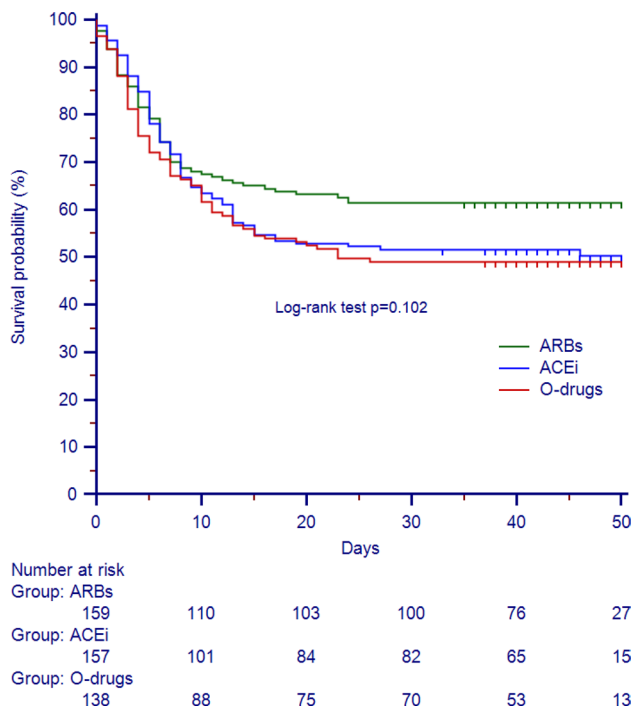

Fig. 1 Kaplan–Meier event curves reported the mortality between groups stratified by the antihypertensive drug treatment. No differences between ARBs, ACEi or O-drugs treatment were found. *ARBs* angiotensin-receptor blockers, *ACEi* angiotensin converting enzyme inhibitors, *O-drugs* other drugs, including Beta-blockers, Calcium channels blockers, Alfa-blockers, and Diuretics

lacking. Recently, Zhang et al. [18] reported the outcomes of hospitalized COVID-19 patients with HTN stratified by RAS inhibitors in-hospital intake. In this retrospective inpatient study, use of ACEi/ARBs was associated with lower risk of all-cause mortality compared with ACEi/ARBs non-users. Feng Y et al. [19] found a significant difference in ACEi/ARBs usage among COVID-19 patients with different severities, according to the Chinese guidelines on diagnosis and treatment of COVID-19. Our findings were consistent with these results: the use of ACEi or ARBs was not associated with a detrimental effect on mortality, as compared with patients treated with other antihypertensive drugs.

Clinical implications

Despite the theoretical uncertainties regarding whether RAS inhibition may influence the infectivity of SARS-CoV-2, there are few available evidences about switching from a RAS inhibitor to another antihypertensive therapy in patients with known or suspected COVID-19. Moreover, a high number of HTN patients solicited therapy changes or interruption during on-going pandemic. Changes in antihypertensive drug treatment require dose titration and potentially exposes patients to the side effects related to the

Fig. 2 Kaplan–Meier event curves reported the mortality between propensity score-matched groups stratified by the antihypertensive drug treatment. No differences between groups were found. *ARBs* angiotensin-receptor blockers, *ACEi* angiotensin converting enzyme inhibitors, *O-drugs* other drugs, including Beta-blockers, Calcium channels blockers, Alfa-blockers, and Diuretics

new regimen; the risk of SARS-CoV-2 exposure related to the transient lockdown interruption for face-to-face visits should not be neglected. Accordingly, several Specialty Societies strongly recommended to continue RAS inhibitors in patients in otherwise stable condition who are at risk for, are being evaluated for, or have COVID-19. Our data confirm this statement, suggesting that treatment with ACEi or ARBs should not be discontinued because of COVID-19.

Strengths and limitations

This study was a retrospective observational analysis of data from a Hospital Network of a single Province in Italy. It is plausible that the effects of ACEi/ARBs may be different among patients in ethnically or geographically diverse populations. Moreover, we did not account for socioeconomic status. However, large sample size with absence of missing values for collected variables and long-term follow-up is a major strength. Since the study was underpowered to detect any differential effect between ACEi and ARBs, future bigger observational studies and on-going prospective randomized trials are advisable to fully elucidate possible protective effects of those drug treatments [20–23].

Conclusions

In summary, in patients with hypertension, Angiotensin-Converting Enzyme inhibitors and Angiotensin-Receptor Blockers are not associated with mortality of COVID-19. Our data confirm Specialty Societal recommendations, suggesting that treatment with renin–angiotensin system inhibitors should not be discontinued or replaced with other antihypertensive drugs because of COVID-19.

Compliance with ethical standards

Conflict of interest The authors report no conflicts.

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