



BRIEF REPORT

Mortality in Patients with COVID-19 on Renin Angiotensin System Inhibitor Long-Term Treatment: An Observational Study Showing that Things Are Not Always as They Seem

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ABSTRACT

Introduction: At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, controversial data were reported concerning angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) that induced a number of physicians to stop using them in patients with COVID-19.

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Although large-scale studies have ruled out this concern, it is common experience that patients with COVID-19 taking ACE inhibitors or ARBs are at increased risk of death. The aim of this study was to investigate the reasons for this apparently high mortality rate.

Methods: During the first wave of the pandemic, we conducted a field study of 427 consecutive patients with COVID-19 upon their admission to the emergency department of a hospital in one of the most severely hit cities in northern Italy, and 30 days later. The disease was defined as being mild, moderate or severe on the basis of clinical, laboratory and imaging data, and a multivariate model was used to analyse the determinants of mortality.

Results: Within 30 days of admission, 31.6% of the patients treated with ACE inhibitors or ARBs and 15.2% of those not treated with these drugs had died. Multivariate analysis showed that the determinants of mortality were age ($p = 0.0001$), hypertension ($p = 0.0120$) and diabetes ($p = 0.0129$), whereas ACE inhibitors or ARBs had no effect on mortality. There was no significant difference between the patients treated with ACE inhibitors and those treated with ARBs.

Conclusion: The apparently increased mortality of patients with COVID-19 receiving long-term treatment with ACE inhibitors or ARBs is not due to the drugs themselves, but to the conditions associated with their use.

Keywords: ACE inhibitors; Angiotensin receptor blockers; COVID-19; Mortality

Key Summary Points

Why carry out this study?

Renin angiotensin system (RAS) inhibitors may upregulate ACE2, the SARS-CoV-2 receptor for entry into cells, thus theoretically RAS users could be more at risk of infection and a severe course of COVID-19.

However, observational studies and registries have demonstrated the absence of an increased risk of severe disease course or death due to COVID-19.

We sought to understand the reason for this apparent discrepancy in a field study conducted in an emergency department in a large hospital of a severely hit city during the first wave of the COVID-19 pandemic.

What was learned from the study?

RAS users had a twofold increased risk of death; however, when the conditions associated with drug consumption were taken into account (advanced age, hypertension and diabetes), it was clear that the increased mortality was due to these conditions and not to the drug use.

However, the need to act quickly should not lead us to overlook the fact that things are not always as they seem at first glance.

Our data further support the recommendations of a number of scientific societies to continue these treatments in all patients with COVID-19.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has a very broad clinical spectrum that ranges from minor signs and symptoms such as cough and mild fever to severe pneumonia with dyspnoea, tachypnoea and impaired gas exchange that lead to life-threatening manifestations in 5–20% of infected patients [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, uses angiotensin-converting enzyme (ACE) 2 as the receptor binding domain for its spike protein to infect human cells. ACE and ACE2 belong to the same family as dipeptidyl carboxydipeptidase but the two enzymes have opposite effects: the former cleaves angiotensin I into angiotensin II, the peptide that activates angiotensin II receptor 1 (AT1R) and raises blood pressure, whereas the latter cleaves angiotensin II to generate angiotensin 1–7, a heptapeptide that is a potent vasodilator [2].

Animal models have shown that the ACE inhibitor lisinopril and the angiotensin receptor blocker (ARB) losartan both increase the expression of cardiac ACE2 mRNA [3]. Increased ACE2 expression in the respiratory tract may increase the risks of SARS-CoV-2 infection and developing severe life-threatening complications [4], and another potentially detrimental effect of ACE inhibitors is that they may increase vascular permeability by increasing the levels of bradykinin, a potent vasoactive peptide that is catabolised by ACE [5].

The two types of renin angiotensin system (RAS) inhibitors (ACE inhibitors and ARBs) are widely used to treat hypertension and heart failure throughout the world. Available data show that 162.8 million prescriptions of ACE inhibitors and 82.5 million prescriptions of ARBs were made in the USA in 2009 [6], and there were more than 24 million prescriptions of ramipril made in the UK in 2013 [7]. Although two recent large-scale studies of patients with COVID-19 treated with RAS

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inhibitors have ruled out an increased risk of SARS-CoV-2 infection [8] or developing severe life-threatening complications [9], some doubts remain because the mortality rate is apparently higher in RAS inhibitor users than in non-users [10]. It is therefore important to clarify the reasons for this apparent discrepancy by analysing the conditions that require the administration of RAS inhibitors and considering their independent contributions to mortality. For this purpose, we conducted a field study in 427 patients with COVID-19 during the first wave of the pandemic.

METHODS

Patients

The study involved 427 consecutive patients with COVID-19 who were admitted to the Emergency Department of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan between 3 March and 3 April 2020. The inclusion criteria were age over 18 years and a diagnosis of COVID-19 confirmed by a positive RT-PCR test for SARS-CoV-2 in at least one biological sample.

On the basis of the clinical, radiological and laboratory data, COVID-19 was considered to be mild in the patients who were kept under observation while receiving low-intensity care, moderate in those who required intermediate care and non-invasive ventilation, and severe in those admitted to the intensive care unit (ICU) for mechanical ventilation [11, 12]. All of the patients' demographic and clinical data were collected and stored in an anonymised database. Exposure to therapy with ACE inhibitors or ARBs was checked and, in the case of hospitalisation or death, their medical records were reviewed. The 30-day mortality rate of both hospitalised and discharged patients was recorded.

The study was approved by the hospital's ethics committee (Milano Area 2, Prot. No. 659_2020) and carried out in conformity with the 2013 revision of the Declaration of Helsinki. The need for consent to participate in the study was waived by the ethics committee because

data were obtained retrospectively from medical records and all treatments outlined were given to patients as part of standard care.

Statistical Analysis

Continuous variables are expressed as median values and interquartile ranges (IQR), and categorical variables as absolute numbers and percentages. Comparisons of qualitative variables between treatment groups were performed with Fisher's exact test, whereas the non-parametric Mann–Whitney test was used to compare quantitative variables. Logistic regression analysis was used to evaluate the effect of ACE inhibitors or ARBs on the risk of death using odds ratios with their 95% confidence intervals (CI). Univariate models of ACE inhibitor or ARB use were fitted with the following potential confounding factors: age (categorised as ≤ 55 ; 56–70; > 70), hypertension and diabetes. All of the factors that were statistically significant upon univariate analysis were then considered in a multivariate model. Two-sided *p* values less than 0.05 were considered statistically significant. All statistical analyses were made using SAS 9.4 software.

RESULTS

Of the 427 patients, 119 were receiving long-term treatment (at least 2 months) with ACE inhibitors or ARBs, and 308 were not. Table 1 shows their demographic and clinical data. The ACE inhibitor- or ARB-treated patients had a median age of 67 years (range 27–92) and 70% were male; the corresponding figures in the non-ACE inhibitor- or ARB-treated group were 58 years (range 20–95) and 62%. Ninety-four percent of the ACE inhibitor- or ARB-treated patients had hypertension and 32% diabetes mellitus; the corresponding figures in the non-ACE inhibitor- or ARB-treated were 40% and 11%. The number of dropouts during follow-up in the two groups was, respectively, 2 and 12, and the mortality rate within 30 days of admission was, respectively, 31.6% and 15.2% (Fig. 1).

Table 1 Demographic and clinical characteristics of 427 consecutive patients with COVID-19 receiving or not receiving long-term treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)

	Patients not treated with ACE inhibitors or ARBs, <i>n</i> = 308	Patients treated with ACE inhibitors or ARBs, <i>n</i> = 119	<i>p</i> value*
Age, median (IQR)	58 (48–68)	67 (57–79)	< 0.0001
Male, <i>n</i> (%)	190 (61.7)	83 (69.7)	0.1742
Hypertension, <i>n</i> (%)	123 (39.9)	112 (94.1)	< 0.0001
Diabetes mellitus, <i>n</i> (%)	35 (11.4)	38 (31.9)	< 0.0001
Acute kidney injury, <i>n</i> (%)	58 (18.8)	46 (38.7)	< 0.0001
Chronic renal failure, <i>n</i> (%)	17 (5.5)	13 (10.9)	0.0931
Chronic ischemic heart disease, <i>n</i> (%)	23 (7.5)	22 (18.5)	0.0015

IQR interquartile range

*Mann–Whitney (for age) and Fisher’s exact test (for the other parameters)

Multivariate analysis of the confounding variables that were significant in the univariate analyses showed that the determinants of mortality were age ($p = 0.0001$), hypertension ($p = 0.0120$) and diabetes ($p = 0.0129$), whereas RAS inhibition had no effect on mortality (the two groups were significantly different in terms of age and the prevalence of hypertension and diabetes mellitus). There was no difference in mortality between the patients treated with ACE inhibitors and those treated with ARBs (Fig. 2), and the severity of the disease course was independent of the use of RAS inhibitors or the class of drug.

DISCUSSION

During the first wave of the COVID-19 pandemic, outcome data concerning the patients referred to the emergency department of a large hospital in Milan (one of the most severely hit cities in northern Italy) showed a twofold higher mortality rate among RAS inhibitor users than among non-users. However, when other associated conditions were taken into account, it became clear that the main determinants of

mortality were an advanced age and the presence of hypertension and diabetes mellitus (all of which are associated with the use of RAS inhibitors) rather than RAS inhibition itself.

At the beginning of the pandemic, there was a widespread suspicion that the use of ACE inhibitors and ARBs may be harmful in patients with COVID-19 because the available experimental data suggested that they could increase the expression of viral receptor ACE2 and thus lead to a higher risk of infection, severe disease, and death [13]. These suspicions induced some physicians to stop or change these antihypertensive drugs in patients with COVID-19 [14] but, given the lack of sound clinical evidence, scientific societies including the European Society of Cardiology [15] and the American Heart Association [16] recommended their continuation.

The experimental evidence that ACE inhibitors and ARBs increase the expression of ACE2 came from animal models: Ferrario et al. found the upregulation of ACE2 expression in the cardiac tissue of Lewis rats (a strain subjected to increased autoimmune and cardiovascular risk) [3], and Soler et al. found increased ACE2 expression after treatment with telmisartan in

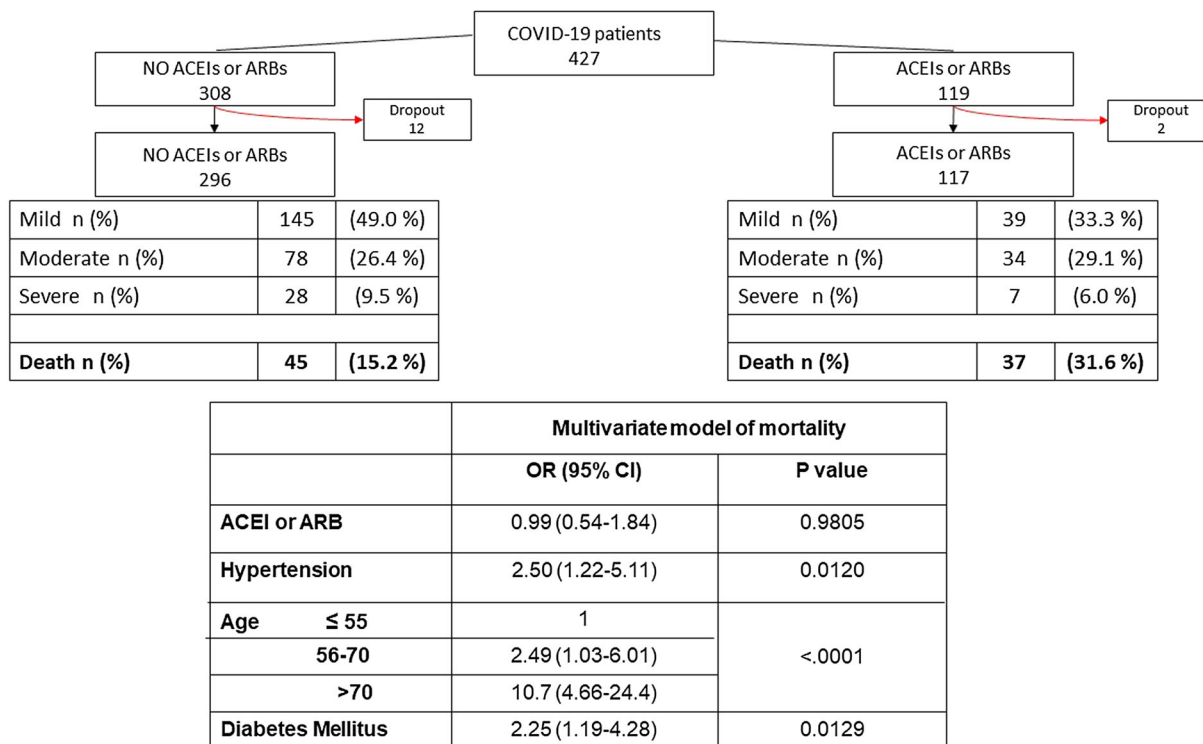


Fig. 1 Clinical course of 427 patients with coronavirus disease 2019 (COVID-19) receiving or not receiving long-term treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Multivariate analysis showed that the

determinants of mortality within 30 days of admission were age, hypertension and diabetes mellitus, and not treatment with ACEIs or ARBs

the kidney arterioles of a strain of rats susceptible to the development of diabetes and atherosclerosis [17].

However, there are conflicting data concerning the effect of RAS inhibition on ACE2 expression in humans. Vuille-dit-Bille et al. demonstrated increased intestinal levels of ACE2 mRNA after treatment with ACE inhibitors in 2015 [18], but Lee et al. have shown that there is no upregulation of ACE2 in the respiratory cilia of patients with COVID-19 receiving RAS inhibitors in comparison with non-users [19]. In particular, the finding that the expression of ciliary ACE2 was actually lower in a small subgroup of patients taking ACE inhibitors suggested that ACE inhibition potentially plays a protective role [19].

Another source of concern about the use of ACE inhibitors in patients with COVID-19 is the possibility that it may increase the levels of

bradykinin (a vasoactive peptide that is catabolised by ACE) [5], and thus contribute to the development of lung edema by increasing vascular permeability during the inflammatory phase [14, 20]. However, bradykinin binding to its receptors stimulates the endothelial production of nitric oxide (NO), prostacyclin (PGI2) and tissue-type plasminogen activator (tPA) [21, 22] and, given the pivotal role of an inflammatory cytokine storm and microthrombosis during the course of severe COVID-19, it is conceivable that the vasodilating and antithrombotic effects of bradykinin may actually improve microcirculation flow even in the presence of inflammation.

A number of observational studies and meta-analyses [8, 23–26] have shown that patients with COVID-19 treated with RAS inhibitors are not exposed to an increased risk of infection, severe disease, and death. A large case–control

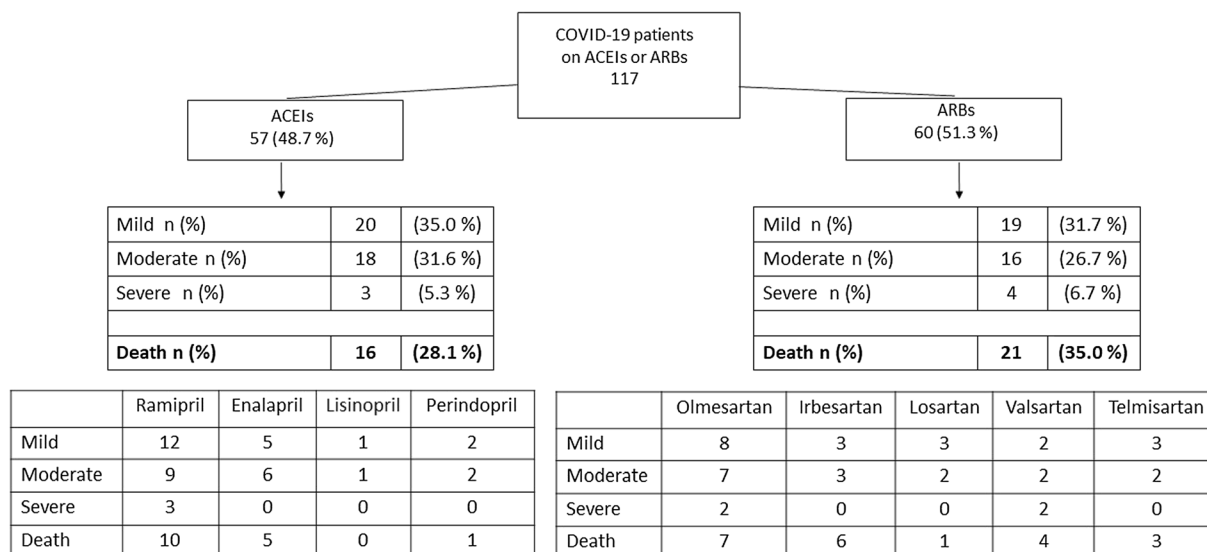


Fig. 2 Clinical course of 117 patients with coronavirus disease 2019 (COVID-19), of whom 57 were treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Deaths were recorded within 30 days of admission. The association of

the single drugs with severity of COVID-19 is reported in the lower panels

study of patients with COVID-19 using the Lombardy Epidemiological Observatory Registry has demonstrated that neither ACE inhibitors nor ARBs are associated with the risk of SARS-CoV-2 infection or severe or fatal illness [8]. A multicentre study by Reynolds et al. found that there is no association between any single medication class (ACE inhibitors, ARBs or other antihypertensive drugs) and an increased likelihood of SARS-CoV-2 infection or severe illness [23]. A Spanish case-population study of patients with COVID-19 by de Abajo et al. found that ACE inhibitors or ARBs did not affect the risk of hospitalisation, including the fatal and critical cases admitted to an ICU [9], and a Danish study has found that the previous use of ACE inhibitors or ARBs is not significantly associated with all-cause mortality or a more severe disease course in patients with COVID-19 [24]. Finally, a prospective randomised open-label trial, the REPLACE COVID study, demonstrates that RAS inhibitors can be safely continued in patients with COVID-19 [27].

The main limitations of our study are its observational nature, and the lack of collection of data on other factors that may have affected

the outcome, like diseases such as dyslipidaemia [28] or drugs such as metformin [29].

The outbreak of the COVID-19 pandemic has dramatically changed healthcare organisation, and physicians have made every effort to reduce the impact of such a historical and human challenge. However, the need to act quickly should not lead us to overlook the fact that things are not always as they seem at first glance [30] and that medical actions should always be driven by an evidence-based approach. Although ours was a single-centre study, the sample size was sufficient to ensure a reliable statistical power and alpha error, and its findings clearly show that the apparently higher mortality rate among RAS inhibitor users is not due to the drugs themselves, but to the condition for which they are prescribed (such as hypertension or diabetes mellitus) or advanced age.

CONCLUSIONS

The findings of this field study conducted during the first wave of the COVID-19 pandemic

confirm that there is no association between COVID-19 severity or mortality and treatment with ACE inhibitors or ARBs, and shows that the apparently higher mortality rate among RAS inhibitor users is not due to the drugs themselves, but to the conditions associated with their use. Our data further support the recommendations of a number of scientific societies to continue these treatments in all patients with COVID-19.

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Authors' Contributions. MC, GCa and RG designed the study; FT, GG and AT collected the data; GCo, NM and FP were responsible for the clinical management of patients; GCa performed the statistical analysis; MC drafted the manuscript; RG contributed to writing; all authors contributed to the interpretation of the results and critically reviewed the manuscript.

Disclosures. Massimo Cugno, Roberta Gualtierotti, Giovanni Casazza, Francesco Tafuri, Gabriele Ghigliazza, Adriana Torri, Giorgio Costantino, Nicola Montano, Flora Peyvandi have nothing to disclose in relation to the study.

Compliance with Ethics Guidelines. The study was approved by the hospital's ethics committee (Milano Area 2, Prot. No. 659_2020) and carried out in conformity with the 2013 revision of the Declaration of Helsinki. The need for consent to participate in the study was

waived by the ethics committee because data were obtained retrospectively from medical records and all treatments outlined were given to patients as part of standard care.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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