

ACEIs or ARBs are safe in patients with COVID-19 results of a prospective study on a hospital based cohort.

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Abstract

Aim of the study: To explore the hypothesis that the often unfavorable outcome of COVID-19 in elderly hypertensive patients might be mediated by the treatment with Renin Angiotensin System (RAS) inhibitors because of the enhancing effect on ACE2 receptors that represent the binding site of SARS-CoV-2 virus.

Methods: Prospective study on 221 (M/F ratio=143/78, mean age 72+13) consecutive hypertensive patients with COVID-19:76 (34.4%) treated with ACEIs, 63 (28.5%) with ARBs and 82 (37.1%) with antihypertensives other than ACEIs or ARBs. They were all followed up until discharge or death. **Bad:** Outcome was defined as need of invasive mechanical ventilation or death.

Results: The three classes of medication were well balanced for confounding variables. Bad outcome was overall recorded in 63/221 (28%) patients, in 20/76 (26%) of ACEI, in 17/63 (27%) of ARB and in 26/82 (32%) of other users, with no statistically significant difference on any comparison.

Conclusion: These findings refute the hypothesis that treatment with ACEIs or ARBs may negatively affect the course of COVID-19.

Keywords: COVID-19; Angiotensin converting; Enzyme inhibitors; Angiotensin receptor inhibitors.

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Introduction

For more than 15 months COVID-19 pandemic has been devastating the entire globe, with about 145 million confirmed cases, causing more than 3 million deaths and leaving a proportion of affected people with long lasting or permanent disability [1]. After binding to ACE 2 surface receptor which is widely represented in the respiratory epithelial cells, Coronavirus 2 (SARS-CoV-2) enters the pulmonary alveoli and may evoke a complex catastrophic immune reaction, the so-called cytokine storm, in about one fifth of infected patients, which ultimately leads to the systemic involvement of multiple organs, particularly muscles, heart and kidney [2]. This heavy burden is particularly frequent in elderly patients in whom case fatality rate may exceed 20% [3,4]. Elderly patients are more often hypertensive [5] and on treatment with Renin Angiotensin System (RAS) inhibitors, namely Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Inhibitors (ARBs). These drugs may increase the expression of ACE2 receptors which in turn could promote SARS-CoV-2 entry into the cell. As a consequence, the overall increased severity of COVID-19 in older patients might derive at least in part by the use of RAS inhibitors. To address this issue we conducted a prospective study in consecutive Covid 19 patients presenting at the Emergency Department of a Community Hospital with the aim of comparing clinical outcome in hypertensive patients taking ACEIs or ARBs as compared to hypertensive patients taking other drugs.

Materials and Methods

From March 12 to April 12 2020, all consecutive hypertensive patients presenting at the Emergency Department of the Community Hospital of Gavardo, in the neighborhood of Brescia, for symptoms or signs suggestive of SARS-CoV-2 infection and with Real-Time RT-PCR in nasal or pharyngeal swab positive for SARS-CoV-2 were included. Relevant clinical and laboratory variables were recorded on the field, focusing on the type of current antihypertensive treatment, namely ACEIs, ARBs, or antihypertensives other than ACEIs or ARBs (Others). Endpoints were: Good outcome if during hospital stay the patient survived and did not need invasive mechanical ventilation and bad outcome if he/she needed invasive mechanical ventilation or died. In non-hospitalized patients a follow up telephone call was done three weeks after presentation.

Results

From the entire cohort of 431 patients who accessed the Emergency Department during the study period, 221 (51%, M/F ratio=143/78, mean age 72+13) were on ongoing treatment for hypertension, 76 (34.4%) with ACEIs, 63 (28.5%) with ARBs and 82 (37.1%) with antihypertensives OTHER than ACEIs or ARBs. Outcome was good in 158/221 (72%) patients and bad in 63/221 (28%).

Compared with patients with good outcome, those with bad outcome were significantly older (79+9 vs. 69+13, $p<0.0001$), had higher levels of CRP (160+82 vs. 89+70, $p<0.0001$) AST

(64+50 vs. 46+24, $p < 0.0001$) and creatinine (1.78+1.3 vs. 1.08+0.4, $p < 0.0001$). The impact of significant variables on outcome, expressed as Relative Risk is illustrated in Table 1.

Table 1. Characteristics of the two aspheric hydrophobic intraocular lenses.

	R.R. for Bad outcome	95% C.I.	P
Age>70	3.59	1.93-6.66	<0.0001
CVD (composite)	2.24	1.50-3.30	<0.0005
Creatinine>1	2.54	1.58-4.07	<0.0001
Lymphocyte<1100/ml	1.71	1.01-2.90	<0.05
AST>32 u/lt	2.63	1.33-5.21	<0.005

Cardio Vascular Disease (CVD); Aspartate Aminotransferase (AST)

Variables that turned significant in univariate analyses were entered a multivariate binomial logistic regression analysis with bad outcome as the dependent variable. Only age, CRP and creatinine remained independent predictors of bad outcome (Table 2).

Table 2. Logistic regression analysis with bad outcome as dependent variable.

	B	E.S.	Wald	df	Sig.	O.R.	95(%) CI for O.R.		2.63
							Lower	Upper	
Age	0.076	0.02	13.932	1	0	1.079	1.037	1.123	
AST u/lt	0.011	0.007	2.519	1	0.112	1.011	0.997	1.024	
CRP mg/lt	0.011	0.003	12.976	1	0	1.011	1.005	1.016	
Creatinine mg/dl	0.92	0.308	8.936	1	0.003	2.51	1.373	4.589	
Lymphocyte count<1000/mm	0	0	0.239	1	0.625	1	0.999	1.001	
CVD	0.624	0.417	2.237	1	0.135	1.866	0.824	4.225	
RAS inhibitors (ACEI or ARB)	0.46	0.421	1.19	1	0.275	1.584	0.693	3.618	
Costante	9.989	1.84	29.484	1	0	0			

Aspartate Aminotransferase (AST); C-Reactive Protein(CRP); Cardio Vascular Disease (CVD); Renin Angiotensin System (RAS); Angiotensin Converting Enzyme Inhibitor(ACEI); Angiotensin Receptor Inhibitor(ARB)

Bad outcome was recorded in 26% of ACEI, 27% of ARB and 32% of other users, with no statistically significant difference. In regard of age, BAD outcome was recorded in 4% of subjects younger than 60, 18% of those in the 61-70 range, 35% of those between 71 and 80 and in 48% of those older than 80. Case fatality rate was overall 23% (51/221). Among ACEI users it was 20% (15/61), among ARB 22% (14/49) and among other users 27% (22/60) with no statistically significant difference on any comparison.

Discussion

The results of the present study confirm that hypertension and age are associated with bad outcome or death in hospitalized patients [6,7]. In regard of the main aim of the study, ACEIs and ARBs each accounted for 30% of the cohort of hypertensive patients, the remaining drugs being represented for the vast majority by diuretics, beta blockers and calcium antagonists. These were put together under the heading of other, for comparison with ACEIs and ARBs. Bad outcome occurred in about one quarter of patients and was equally frequent in ACEI,

ARB and other users. The same holds for case fatality rate and ACEIs/ARBs put together were excluded by logistic regression analysis as predictors of bad outcome. Taken together, these findings refute the hypothesis that treatment with ACEIs or ARBs may negatively affect the course of COVID-19, in agreement with the results of three retrospective studies done in hospitalized patients in China [8-10]. Further support for the substantial safety of RAS inhibitors comes from two population based studies that were unable to find any association between ACEI or ARB use and the susceptibility to COVID-19 or the likelihood of a worse outcome in affected subjects. [11,12].

Conclusion

In conclusion, regardless of the study type, sample size and outcome variables, the bulk of studies published so far reject the hypothesis that taking ACEIs or ARBs adversely affects the course of COVID-19. This conclusion is confirmed by the results of the present study which is the only one, to the authors knowledge, to have assessed patients prospectively on the field from Emergency Unit to discharge or death. There is still no treatment of proven efficacy against SARS-Cov-2 and available vaccines provide a protection which is incomplete for a number of reasons; therefore, given the high infectivity of new variants, it is to be expected that in the next future a still significant amount of people will have to face COVID 19. Those at risk of worst outcome are elderly hypertensive in which RAS inhibitors represent the mainstay of cardiovascular protection. Based on the current clinical evidence their use appears safe in COVID-19. Therefore withholding ACEIs or ARBs in SARS- CoV-2 positive patients is not only unwarranted but indeed potentially at risk of enhancing severe cardiovascular complications associated with COVID-19.

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