

Therapy With Agents Acting on the Renin-Angiotensin System and Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Roberto Gnani,¹ Moreno Demaria,¹ Roberta Picariello,¹ Marco Dalmasso,¹ Fulvio Ricceri,² and Giuseppe Costa^{1,2}

¹Epidemiology Unit, Azienda Sanitaria Locale T03, Regione Piemonte, Grugliasco, Italy, and

²Department of Clinical and Biological Sciences, University of Torino, Orbassano, Italy

Exposure to agents acting on the renin-angiotensin system was not associated with a risk increase of COVID-19 infection in 2 Italian matched case-control studies, 1 nested in hypertensive patients and the other in patients with cardiovascular diseases or diabetes.

Keywords. COVID-19; SARS-CoV-2; ACE inhibitors; angiotensin II receptor blockers; administrative data.

Angiotensin-converting enzyme 2 (ACE2) is a functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that facilitates the entry of the virus into the cells [1]. As agents inhibiting the renin-angiotensin-aldosterone system (RAAS) could increase the levels of ACE2, recent studies have raised concern over the association between these agents and both SARS-CoV-2 infection and illness severity [2–6]. Consequently, patients treated with ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), in particular those with diabetes or cardiovascular disease, should be considered at higher risk of developing severe coronavirus disease 2019 (COVID-19) infection (CVi), and of experiencing unfavorable outcomes [2, 3]. Therefore, it has been suggested that these patients should be carefully monitored or even have their therapy substituted with calcium channel blockers [3, 7].

However, the hypothesis of a link between agents inhibiting the RAAS and CVi is still under debate [7, 8], and whether patients should switch to other antihypertensive therapies is controversial. Research to clarify the role of RAAS blockade therapies and CVi is highly needed [7, 9].

In the first half of February 2020, the first cases of COVID-19 infection were recorded in Italy [10], that, at present, is one of the leading countries in the world for both the number of

diagnosed cases and for case fatality. Diabetes, hypertension, and cardiovascular diseases, conditions that are frequently treated with ACEIs or ARBs, are among the most prevalent comorbidities in these patients [11, 12].

As, to the best of our knowledge, a relationship between ACEI or ARB treatments and increased risk of CVi has never been demonstrated [8], the aim of the present study was to determine whether an association exists between therapies based on agents acting on the RAAS and CVi in 2 populations at greater risk of being diagnosed with SARS-CoV-2 infection: hypertensive patients and patients who were affected by a cardio-cerebrovascular disease.

METHODS

Study Design and Population

We conducted 2 population-based case-control studies nested in 2 cohorts built using administrative data from the Piedmont region (4 400 000 inhabitants in northwest Italy, with a high rate of CVi). The population is covered by an automated system of databases, which record, among others, all drugs dispensed from all regional pharmacies, all hospital discharges, and a regional register of persons with diabetes. From the beginning of the CVi epidemics a surveillance system was implemented to collect all cases identified by reverse-transcription polymerase chain reaction testing for SARS-CoV-2. These archives can be linked together by a unique anonymous identifier that is encrypted to protect the patient's privacy.

The 2 case-control studies have been nested in the following populations, independent of each other, of patients at increased risk of SARS-CoV-2 infection:

1. Circulatory diseases/diabetes (CDD): From the hospital discharges, we extracted all persons aged ≥ 40 years, who were discharged in the previous 5 years (2015–2019) with a diagnosis of ischemic heart disease (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 410–414 at discharge), cerebrovascular disease (ICD-9-CM code 430–438), or heart failure (ICD-9-CM code 428), and those registered in the register of persons with diabetes. Those living and resident in Piedmont on 31 October 2019 represent the population base of patients with CDD.
2. Hypertension (HY): From the drug prescription database, we extracted all persons aged ≥ 40 years who, in 2019, had at least 1 prescription of an antihypertensive drug (*Anatomical Therapeutic Chemical Classification System* [ATC] codes C02–C04 or C07–C09). All subjects included in the CDD population were excluded. Those living and resident in Piedmont on 31 October 2019 represent the population base of patients with HY, free of severe cardiac complications.

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Correspondence: R. Gnani, Epidemiology Unit, ASL T03 Regione Piemonte, Via Sabaudia 164, 10095 Grugliasco, TO, Italy (roberto.gnani@epi.piemonte.it).

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Selection of Cases

From the regional surveillance system, we obtained a random sample of 1000 confirmed cases of CVi occurring in the first month of the epidemic from 22 February 2020 (beginning of the epidemic) to 23 March 2020, who were linked to the 2 populations, to include only cases within CDD or HY.

Selection of Controls

From the same population sources, we randomly selected 5 controls for each case, matched for year of birth and sex. CVi cases were ineligible for resampling as controls.

Exposure to ACEIs or ARBs

The regional drug database was used to identify cases and controls who had been prescribed ACEIs or ARBs at any time from 1 June to 31 October 2019 (last available month), considering ATC codes C09A or C09B for ACEIs, and C09C or C09D for ARBs.

Statistical Analysis

The risks of CVi associated with drug dispensation of ACEIs or ARBs, considered both separately and together (to take into account possible switch from one medication to the other), were estimated by fitting conditional logistic regression models, expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

To take into account the dose of medication prescribed (ie, to explore for a dose-response relationship), the number of boxes prescribed was grouped into 4 classes (0, 1–6, 7–12, and > 12).

All calculations were made using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Out of 804 909 HY and 337 059 CDD subjects, we identified 316 and 171 cases, respectively, of CVi, who were matched with 1580 and 855 controls. In the HY population, 58.5% were male and the mean age was 71.4 years, whereas the mean age of the CDD population was 74.5 years and 78.4% were male. Among the HY population, 68.0% of cases and 73.0% of controls had at least 1 prescription of agents acting on the RAAS, while among the CDD population, 54.4% of cases and 55.6% of controls received at least 1 prescription. In both populations, there were no differences between cases and controls by size of the municipality of residence ([Supplementary Table](#)).

In neither of the 2 populations was the prescription associated with the risk of SARS-CoV-2 infection. In the HY population, ORs for ACEIs, ARBs, and the combination of the 2 were, respectively, 0.89 (95% CI, .70–1.15), 0.90 (95% CI, .70–1.17), and 0.78 (95% CI, .60–1.02). In the CDD population, ORs for ACEIs, ARBs, and the combination of the 2 were, respectively, 0.92 (95% CI, .64–1.32), 1.03 (95% CI, .70–1.50), and 0.95 (95%

CI, .68–1.34). There was no association with the level of exposition, thus excluding a dose-response relationship ([Table 1](#)).

As a sensitivity analysis, we considered that some controls could be unknown cases of CVi and thus a differential misclassification could have occurred. We repeated our analysis for the HY population exposed to ACEIs or ARBs (OR, 0.78) considering both 10% and 20% misclassification of controls. ORs showed a slight change only, to 0.81 and 0.89, respectively.

DISCUSSION

The question whether therapy with agents acting on the RAAS increases the susceptibility to CVi has raised concern among practitioners and citizens alike [2, 7], with conflicting opinions [8] but no sound evidence [9]. The key message of our analysis is that no association, regardless of causality, could be determined.

Our study has several strengths. We used a nested case-control design enrolling both cases and controls within 2 unselected populations of subjects at increased risk of developing CVi. The consistency of ORs in these 2 independent populations can be viewed as a confirmation of our results. The study was conducted using data retrieved from the regional surveillance system of confirmed CVi cases. All agents acting on the RAAS were included, and, as they are dispensed and reimbursed only by prescription, we are confident to have included all dispensations. Moreover, the potential confounding due to differences in access to diagnosis is probably low, given no differences in the size of municipality.

Our study also has potential limitations. Given the high prevalence of undiagnosed or unknown cases of CVi in the general population, differential misclassification of controls is likely to have occurred. However, even assuming 20% of misclassification, the ORs changed slightly, confirming the absence of association. Second, the use of a database of dispensed drugs rather than usage data might have overestimated the use ACEIs and ARBs; in addition, not considering the last 4 months closer to the onset of the disease could have slightly affected the prevalence of drug users; however, it is unlikely that these would have affected cases and controls differently. Finally, given the small sample size, an association between agents acting on the RAAS and CVi cannot be ruled out.

Despite the above limitations, at the time of this writing, our study is the first contribution to explore the question whether agents acting on RAAS increase the risk of being infected by SARS-CoV-2, and the first available evidence of safety of this class of drugs. We are aware that further epidemiological research is desirable, ideally considering larger cohort studies to confirm our first findings. However, as studies gathering a large population of confirmed cases require time and may be demanding, smaller but more timely studies can contribute to give answers to urgent public health questions. Furthermore, as our study was limited to explore whether RAAS therapy increases

Table 1. Matched Odds Ratios of Coronavirus Disease 2019 Associated With Exposure to Agents Acting on the Renin-Angiotensin System in the Hypertension and Circulatory Disease/Diabetes Populations

Population	ACEI		ARB		ACEI or ARB	
	OR (95% CI)	PValue	OR (95% CI)	PValue	OR (95% CI)	PValue
Hypertension population						
Use (any)	0.89 (.70–1.15)	.388	0.90 (.70–1.17)	.438	0.78 (.60–1.02)	.068
No. of boxes in 6 mo						
0	1		1		1	
1–6	0.89 (.66–1.21)	.463	0.89 (.67–1.19)	.424	0.78 (.58–1.03)	.080
7–12	1.01 (.69–1.47)	.967	0.89 (.57–1.39)	.967	0.84 (.60–1.18)	.319
>12	0.54 (.24–1.20)	.128	3.23 (.54–19.36)	.199	0.56 (.27–1.17)	.122
CDD population						
Use (any)	0.92 (.64–1.32)	.647	1.03 (.70–1.50)	.897	0.95 (.68–1.34)	.773
No. of boxes in 6 mo						
0	1		1		1	
1–6	0.95 (.61–1.49)	.830	0.97 (.63–1.51)	.973	0.93 (.64–1.37)	.730
7–12	0.85 (.50–1.44)	.538	1.15 (.61–2.16)	.669	0.98 (.62–1.55)	.945
>12	1.05 (.39–2.82)	.922	1.26 (.14–11.28)	.839	0.94 (.38–2.34)	.893

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CDD, circulatory disease/diabetes; CI, confidence interval; OR, odds ratio.

the risk of SARS-CoV-2 infection, the question whether RAAS therapy worsens the outcomes of CVi patients remains to be clarified.

In conclusion, on the basis of our study, as also mentioned by the major cardiology societies [13, 14], there is no reason to modify current antihypertensive therapy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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