Severity of SARS-COV-2 infection and angiotensin converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis

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Abstract

Background: The mechanism of entry of SARS-CoV-2 into the human host cell is through the ACE2 receptor. During the pandemic, a hypothesis has been proposed that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) could be risk factors for the development of severe SARS-CoV-2 infection. The objective of the study was to conduct a meta-analysis of the association between ACEI or ARB use and SARS-CoV-2 infection severity or mortality.

Material and methods: We searched PubMed, EMBASE, Google scholar and the Cochrane Database of Systematic Reviews for observational studies published between December 2019 and August 4, 2020

Studies were included if they contained data on ACEI or ARB use and SARS-CoV-2 infection severity or mortality. Effect statistics were pooled using random-effects models. The quality of included studies was assessed with the Newcastle–Ottawa Scale (NOS).

Data on study design, study location, year of publication, number of participants, sex, age at baseline, outcome definition, exposure definition, effect estimates and 95% CIs were extracted.

Results: Twenty-six studies (21 cohort studies and 5 case-control studies) were identified for inclusion, combining to a total sample of 361467 participants. Mean age was 61.48 (SD 8.26) years and 51.63% were men. The mean NOS score of included studies was 7.85 (range: 7–9). Results suggested that ACEI or ARB use did not increase the risk of severe disease or mortality from SARS-CoV-2 infection (OR = 0.88, 95% CI: 0.75–1.02, p > 0.05).

Conclusions: At present, the evidence available does not support the hypothesis of increased SARS-CoV-2 risk with ACEI or ARB drugs.

Key words: SARS-CoV-2; COVID-19; angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors; renin–angiotensin system (RAS)

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Introduction

It had not been anticipated that a phenomenon such as the appearance of the new SARS-CoV-2 pandemic would affect the world in such a short time and lead to serious health and economic consequences. Scientists around the world are in a race against time in the search for effective treatment approaches. Among the many questions that need urgent clarification is that of the possible drug-disease interactions in patients taking angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). These are among the most widely used antihypertensive drug classes in the world [1].

The renin–angiotensin system (RAS) has the function of maintaining homeostasis of blood pressure, fluid and salt in the human body. The renin–angiotensin system contains two homologous enzymes belonging to the angiotensin converting enzyme (ACE) dipeptidyl carboxypeptidase family, with different functions: the angiotensin I converting enzyme 1 (ACE1) converts angiotensin I to angiotensin II; and the angiotensin I converting enzyme 2 (ACE2) decreases the level of angiotensin II and negatively regulates the RAS system. Thus, ACE2 reduces the effects of vasoconstriction, sodium retention and fibrosis. ACE2 is expressed in various organs such as the heart, kidneys and especially in alveolar epithelial cells of the lung [2]. Under normal conditions, circulating levels of soluble ACE2 are low and its function at the lung level is minimal [3].

The mechanism of entry of SARS-CoV-2 into the human host cell is through the ACE2 receptor. SARS-CoV-2 has an envelope made up of glycoproteins, called S1 (Spike) and S2, the former binding to ACE2 on the cell surface and the latter with the cell membrane [4]. While this mechanism is similar to that of another coronavirus that caused the SARS epidemic in 2002–2003 [5, 6], SARS-CoV-2 has a higher affinity for ACE2 [7]. Although their three-dimensional structure is similar, SARS-CoV and SARS-CoV-2 differ in about 28% of the amino acid sequence in the receptor binding domains; SARS-CoV-2 has a distinct loop with flexible glycyl residues replacing rigid prolyl residues, which makes its structure less rigid and may explain its greater affinity for the ACE2 receptor [7]. Angiotensin I converting enzyme 2 was involved in the pathophysiology of SARS-CoV infection [8] and it is feared that in SARS-CoV-2 infection, this effect could be of greater magnitude. In addition, prior to the pandemic it had been reported that ACEIs/ARBs could increase mRNA expression of ACE2 at the cardiac level [9]. Hence, it has been hypothesized that ACEIs and/or ARBs could be risk factors for the development of severe forms of SARS-CoV-2 infection [10, 11]. In the midst of the COVID-19 pandemic crisis, this simple hypothesis was, without clinical or research evidence to support it, widely disseminated by the media, which in turn caused great concern to patients who were taking these medications. Official statements rapidly followed recommending that these medications continue to be taken [12] in view of the absence of evidence to support the hypothesis. However, the absence of evidence does not mean evidence of absence and there is still an urgent need for clarification. In that light, we conducted a meta-analysis of the association between ACEI or ARB use and SARS-CoV-2 infection severity or mortality.

Material and methods

This study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13].

Search strategy

Two independent investigators performed a systematic search in PubMed, EMBASE, Google scholar and the Cochrane Database of Systematic Reviews for observational studies published between December 2019 and August 4, 2020. In addition, we conducted a secondary search based on the reference list of retrieved articles. The PubMed search strategy is detailed in Supplementary Table A.

Eligibility criteria

We searched for randomized controlled trials (RCTs) or observational studies reporting data on ACEI or ARB use and SARS-CoV-2 infection severity or mortality. We included studies in English or other languages (all ages) meeting the following criteria: a) COVID-19 patients were diagnosed according to the interim guidance of the World Health Organization [14]; b) the study presented data on hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) with confidence intervals (CIs) or offered enough data to allow these to be calculated (including via email correspondence with original authors if necessary); and c) SARS-CoV-2 infection severity criteria were described.

Quality assessment

The quality of observational studies (cohort and case-control studies) and RCTs were assessed according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [15] and the Cochrane Risk of Bias

Assessment Tool [16], respectively. Two investigators evaluated the quality of the studies independently. Conflicting results were resolved by discussion and involvement of a third reviewer if necessary.

Data extraction

The following data were extracted from each study: authors, study location, year of publication, study design, number of participants, sex, age at baseline, outcome definition, exposure definition, effect estimates and 95% CIs.

Statistical analyses

Primary analyses evaluated the association (HRs, RRs or ORs) between use of ACEI or ARB and SARS-CoV-2 infection severity or mortality. We used random effects with an inverse variance method to calculate the pooled RRs and 95% CIs according to the heterogeneity between studies [17]. The overall estimates in the pooled analysis were obtained using Meta XL (www.epigear.com) add-in for Microsoft Excel.

Results

After screening 3781 citations, 26 studies (21 cohort studies and 5 case-control studies) were included (Fig. 1) [18–44], combining to a total sample of 361467participants. The characteristics of included studies are summarized in Table 1. Thirteen studies were from China, 8 from USA and the other five being from Belgium, Italy, South Korea, Turkey and UK. Overall, mean age was 61.5 (SD 8.3) years and 51.6% were men. The mean NOS score of included studies was 7.9 (range: 7–9). The outcomes reported in the included studies are presented in Table 1.

For the meta-analysis, we used the combined outcome of severe disease and/or mortality. As shown in Figure 2, the meta-analysis suggested that ACEI or

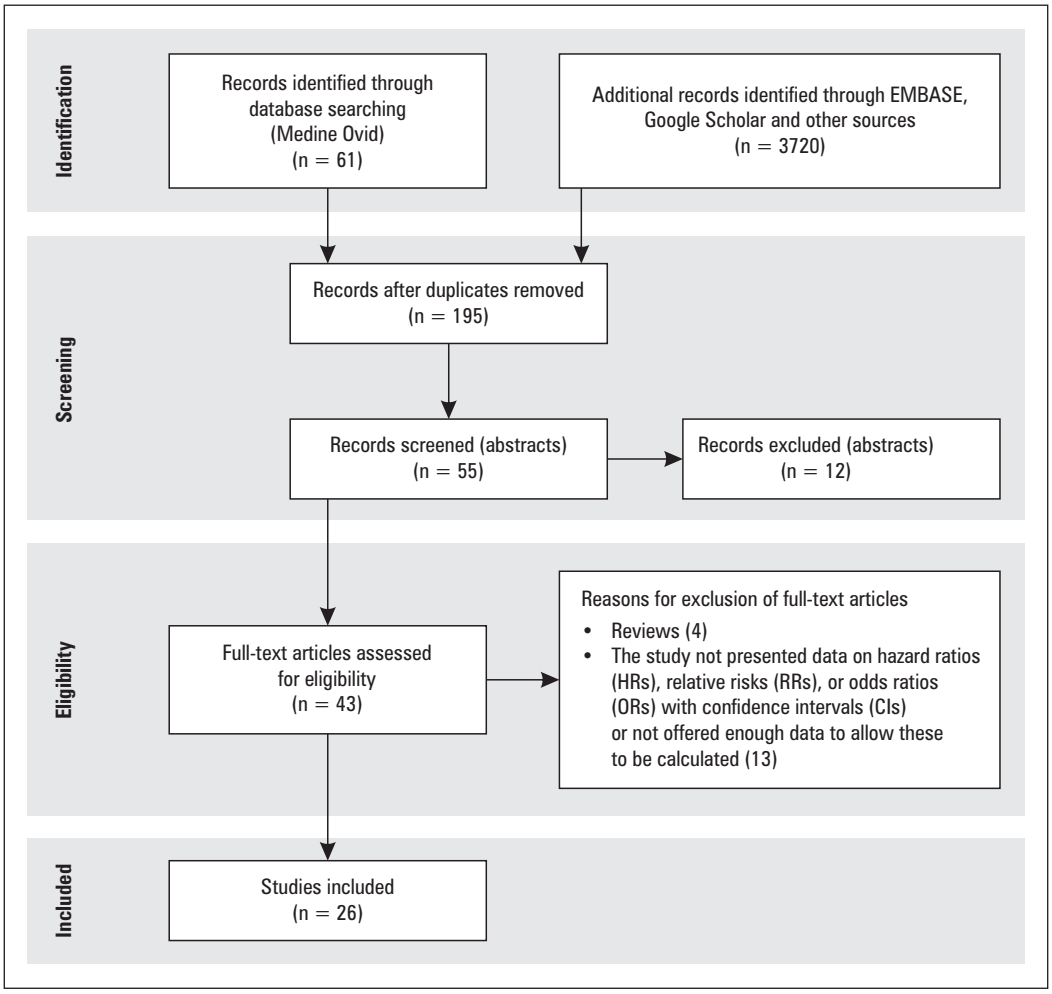

Figure 1. Flowchart of included studies

Table 1. Characteristics of the 26 studies included in the meta-analysis

Author	Country	Study design	Total sample	Mean age	Sex Male (%)	Outcome	Type of RAS inhibitor	NOS	Comorbidities
Guo T. et al. (2020)	China	Cohort	186	58.5	48.7	Mortality	ACEI/ARB	8	Hypertension (33%) Coronary heart disease (11%) Cardiomyopathy (4%) Diabetes mellitus (15%) COPD (2%) Malignant neoplasm (7%) Chronic kidney disease (3%)
Liu Y. et al. (2020)	China	Cohort	511	65	55.1	Severe disease	ACEI ARB	8	Hypertension (100%)
Peng Y. et al. (2020)	China	Cohort	112	62	47.32	Mortality	ACEI/ARB	8	Hypertension (82%) Coronary heart disease (55%) Heart failure (36%) Diabetes mellitus (21%)
Meng J. et al. (2020)	China	Cohort	417	64.5	57.1	Severe disease/ /mortality	ACEI/ARB	8	Hypertension (100%)
Bean D. et al. (2020)	UK	Cohort	205	62.95	51.7	Severe disease/ /mortality	ACEI ARB	7	Hypertension (51%) Diabetes mellitus (30%) and ischaemic heart disease or heart failure (15%)
Yang G. et al. (2020)	China	Cohort	462	67	49.4	Severe disease/ /mortality	ACEI/ARB	9	Hypertension (100%) Diabetes mellitus (30%) Respiratory disease, cardiopathy (18%) Neurological disease (8%)
Feng Y. et al. (2020)	China	Cohort	476	53	56.9	Severe disease	ACEI/ARB ARB ACEI	8	Hypertension (24%) Cardiovascular disease (8%) Diabetes mellitus (10%) Malignancy (3%) Cerebrovascular disease (4%) Immunosuppression (2%) COPD (5%)
Feng Z. et al. (2020)	China	Cohort	564	47	50.4	Severe disease	ACEI/ARB	8	Hypertension (15%) Diabetes mellitus (8%) Cardiovascular disease (4%) COPD (3%) Hepatitis B/C infection (2%) Cerebrovascular disease (1%)
Rentsch C. et al. (2020)	USA	Cohort	585	66.1	95.4	Severe disease	ACEI/ARB ARB ACEI	7	Asthma (8%) Cancer (15%) Chronic kidney disease (15%) COPD (26%) Diabetes mellitus (33%) Hypertension (65%) Liver disease (12%) Vascular disease (29%)
Zeng Z. et al. (2020)	China	Cohort	274	60	45	Mortality	ACEI/ARB	8	Hypertension (100%) COPD (6%) Chronic renal insufficiency (2%) Cardiovascular disease (11%) Diabetes mellitus (15%) Cerebrovascular disease (8%)
Zhang P. et al. (2020)	China	Cohort	1128	64	53.2	Mortality	ACEI/ARB	7	Hypertension (100%) Diabetes mellitus (23%) Coronary heart disease (15%) Chronic renal diseases (4%) Cerebrovascular diseases (3%)

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Table 1. Characteristics of the 26 studies included in the meta-analysis

Author	Country	Study design	Total sample	Mean age	Sex Male (%)	Outcome	Type of RAS inhibitor	NOS	Comorbidities
Li J. et al. (2020)	China	Cohort	1178	55.5	46.3	Mortality	ACEI/ARB ARB ACEI	9	Hypertension (100%) Cerebrovascular disease (19%) Coronary heart disease (17%) Heart failure (3%) Diabetes mellitus (35%) Digestive disorder (22%)
Choi H. et al. (2020)	South Korea	CC	1585	63	42.7	Severe disease/ /mortality	ACEI/ARB	8	Hypertension (100%) Diabetes mellitus (47%) Major neurologic diseases (28%) Chronic lung diseases (19%)
Hu J. et al. (2020)	China	CC	149	57	59.06	Severe disease	ACEI/ARB	7	Diabetes mellitus (20%) Heart disease (5%) COPD (1%) Chronic liver disease (6%) Chronic renal disease (4%) Cancer (2%)
Zhou X. et al. (2020)	China	CC	110	57.7	54.5	Mortality	ACEI/ARB	7	Hypertension (33%) and diabetes mellitus (10%) Cardiovascular disease (9%) Chronic liver disease (4%) Malignancy (4%)
Huang Z. et al. (2020)	China	Cohort	50	52.65	54	Severe disease/ /mortality	ACEI/ARB	8	Diabetes mellitus (13%) Coronary artery disease (3%) COPD (5%) Chronic obstructive pulmonary disease (5%)
De Spiegeleer A. et al. (2020)	Belgium	Cohort	154	86	33.1	Severe disease	ACEI/ARB	8	Hypertension (25%) Diabetes (18%)
Ip A. et al. (2020)	USA	Cohort	1129	Missing	Missing	Mortality	ACEI/ARB ARB ACEI	7	Hypertension (100%)
Khera R. et al. (2020)	USA	Cohort	10196	69	45.4	Mortality	ACEI ARB	8	Hypertension (100%) Diabetes without complications (51%) Myocardial infarction (5%) Chronic heart failure (31%) Chronic pulmonary disease (39%)
Reynolds H. et al. (2020)	USA	Cohort	12594	49	41.5	Severe disease	ACEI/ARB ARB ACEI	9	Hypertension (35%) Heart failure (6%) Myocardial infarction (4%) Diabetes (18%) Chronic kidney disease (10%) Obstructive lung disease (15%)
Richardson S. et al. (2020)	USA	Cohort	5700	63	60.3	Mortality	ACEI/ARB	9	Hypertension (57%) Obesity (42%) Diabetes mellitus (32%)
Chaudhri I. et al. (2020)	USA	Cohort	300	59.1	60	Severe disease	ACEI/ARB	7	Hypertension (44%) Diabetes mellitus (25%) and/or heart failure (15%)
Dublin S. et al. (2020)	USA	Cohort	322044	51	46	Severe disease	ACEI/ARB	7	

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Table 1. Characteristics of the 26 studies included in the meta-analysis

Author	Country	Study design	Total sample	Mean age	Sex Male (%)	Outcome	Type of RAS inhibitor	NOS	Comorbidities
Felice et al. (2020)	Italy	CC	133	73.1	28	Mortality	ACEI/ARB ARB ACEI	8	Hypertension (100%) Chronic heart failure (18%) Diabetes mellitus (26%) Cancer (16%) Chronic obstructive pulmonary disease (11%)
Lam K. el al. (2020)	USA	CC	614	68	56.4	Mortality	ACEI/ARB	8	Hypertension (100%) Diabetes (41%) Asthma (5%) Coronary heart disease (24%) COPD (13%) Heart failure (13%) Cancer (12%) Chronic kidney disease (16%)
Senkal N. et al. (2020)	Turkey	Cohort	611	63	53.2	Severe disease	ACEI ARB	8	Diabetes mellitus (41%) COPD/asthma (14%) Coronary artery disease history (26%) Congestive heart failure (9%)

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker; SD — standard deviation; CI — confidence interval; RAS — renin–angiotensin system; NOS — Newcastle-Ottawa Scale; CC — case control; COPD — chronic obstructive pulmonary disease

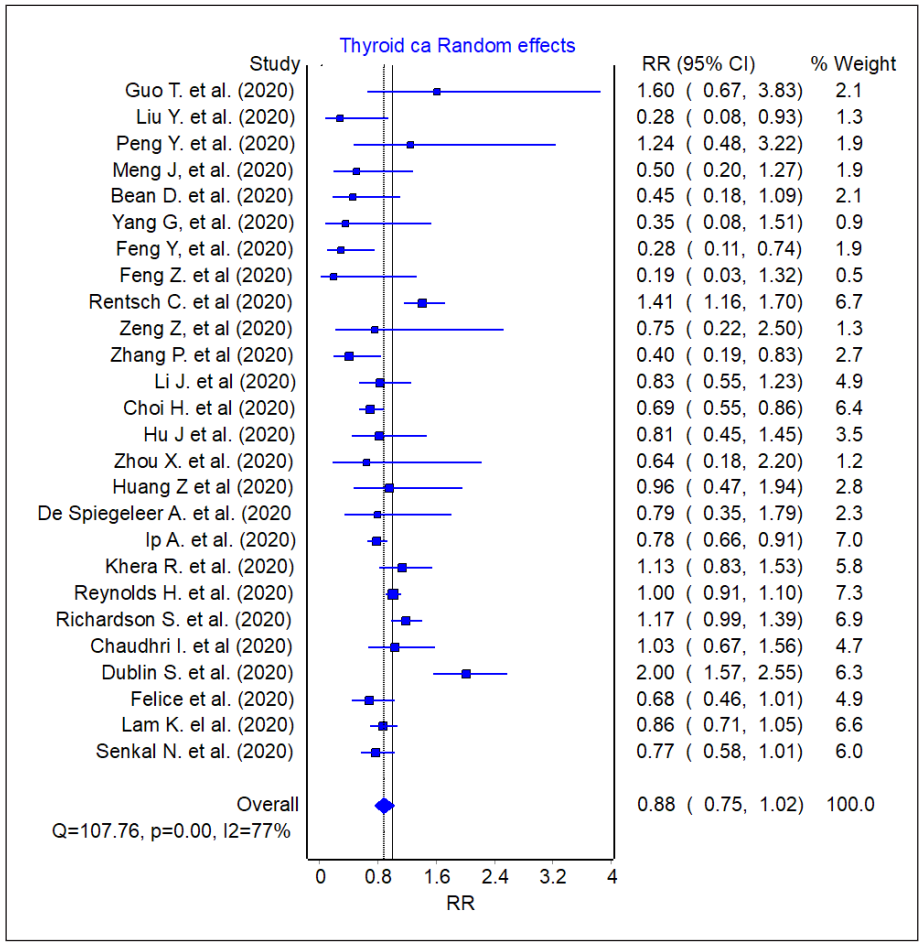

Figure 2. Forest plot of the meta-analysis of the association between angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) use and SARS-CoV-2 infection severity or mortality. Analysis model: random effect. OR — odds ratio; CI — confidence interval

Table 2. Association between the use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) and SARS-CoV-2 infection severity or mortality: summary of subgroup analyses

Subgroup	Studies (n)	Adjusted OR (95% CI)	p
Mean age (years)			
< 60	10	0.96 (0.71–1.30)	> 0.05
≥ 60	16	0.82 (0.67–1.0)	> 0.05
Male sex (%)			
< 55	18	0.84 (0.67–1.04)	> 0.05
≥ 55	8	0.88 (0.69–1.12)	> 0.05
Type of RAS inhibitors			
ARB	12	0.90 (0.76–1.06)	> 0.05
ACEI	11	0.90 (0.74–1.08)	> 0.05

RAS — renin–angiotensin system; OR — odds ratio; CI — confidence interval

ARB use did not increase the risk of severe disease or mortality from SARS-CoV-2 infection (OR = 0.88, 95% CI: 0.75–1.02, p > 0.05). Subgroup analyses were conducted to assess ACEI and ARB effects separately (Tab. 2) but no significant associations were found. Subgroup analyses were also negative for the effects of age (< 60 *vs*. 60+) or sex (Tab. 2).

Discussion

Our study found no evidence to support the hypothesis of increased SARS-CoV-2 risk with ACEI or ARB drugs. This would seem at odds with a previous finding that chronic use of ACEIs and ARBs was high among intensive care unit patients with non-COVID-19 sepsis [45]. However, it is possible that ACEIs/ARBs could be a marker of underlying comorbidities rather than being causal in SARS-CoV-2 severity or mortality.

Prior to the SARS-CoV-2 pandemic, Shinohara et al. published a meta-analytic study where they found a decreased risk of post-stroke pneumonia in patients treated with ACEIs compared to other antihypertensive drugs (RR: 0.61, 95% CI: 0.51–0.75; p < 0.001) [46]. In another meta-analysis, Liu et al. found that ARBs were associated with a decreased risk of pneumonia morbidity (OR = 0.55, 95% CI: 0.43–0.70, p < 0.01) and mortality (OR = 0.55, 95% CI: 0.44–0.69, p < 0.01) [19]. These findings could however be seen from the perspective that the prescription of ACEIs/ARBs may be a marker of good general medical care, given the well-evidenced preventative role of these medications in many cardiovascular and metabolic diseases.

The basis for the hypothesis of a probable ACEI/ARB-induced increase in ACE2 expression has been recently revised, evaluating the results of 12 animal and 11 human studies [47]. In animal studies, no significant changes in ACE2 expression were found, and in those where it was evidenced, it was when models of acute injury were used or at higher doses than those used in humans; furthermore, no increase in ACE2 expression induced by ACEIs/ARBs was evidenced in human studies [47].

It has been proposed that ARBs may have protective effects on severity and mortality in SARS-CoV-2 infection through increasing the production of angiotensin 1–7, reducing angiotensin II and contributing towards lung protection [48]. Recently, Liu et al. found that angiotensin II levels in the plasma of COVID-19 infected patients was markedly elevated and linearly associated to viral load and lung injury [49]. However, this may be a marker of general physiological stress during severe acute illness and not have specific drug-disease implications.

Our study is limited in that it only relies on observational studies and not RCTs and includes a relatively small number of participants. It would be important that future, more powered studies, re-evaluate the possible relevance of age (young *vs*. old), sex, and possible different roles of ACEI and ARB drugs. It would also be important to assess the risk of specific comorbidities (e.g. diabetes, hypertension, cerebrovascular disease, ischaemic heart disease) in the absence of ACEI/ARB drugs. For example, Feng et al. showed that hypertension without ACEI/ARB therapy was an independent risk factor for developing severe pneumonia irrespective of age [42].

In conclusion, the evidence available at present does not support the hypothesis of increased SARS-CoV-2 risk with ACEI or ARB drugs. However, more evidence needs to accumulate before this controversy can be resolved; in the meantime, clinicians may adopt a tailored, pragmatic approach that is supported by official recommendations [12, 50].

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Conflict of interest

None.

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