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Renin–angiotensin system inhibition and risk of infection and mortality in COVID-19: a systematic review and meta-analysis

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Key words
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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, enters human cells by binding of its viral protein to the aminopeptidase angiotensin-converting enzyme 2 (ACE2). This has led to speculation whether treatment with renin–angiotensin system (RAS) inhibitors was associated with an increased likelihood of a positive test for COVID-19 and risk of mortality.
Aims: We performed a systematic review and meta-analysis to investigate whether RAS inhibitors increased the likelihood of a positive test or death/severe illness in patients with COVID-19.
Methods: A systematic search of MEDLINE, PubMed and EMBASE was conducted for studies stratified by the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Pooled analysis was performed using a random-effects model.
Results: Seven trials of 73 122 patients were included. Overall, 16 624 (22.7%) patients had a positive COVID-19 test and 7892 (10.8%) were on a RAS inhibitor. RAS inhibitors were not associated with higher likelihood of a positive COVID-19 test result (odds ratio (OR) 0.97 (95% CI 0.97–1.05, $P = 0.48$) with low heterogeneity. This was comparable when stratifying by use of each medication class. The use of RAS inhibitors was also not associated with mortality or severe illness (OR 0.89, 95% CI 0.73–1.07, $P = 0.21$) with moderate heterogeneity.
Conclusion: Use of ACEI or ARB was not associated with a heightened susceptibility for a positive diagnosis of COVID-19. Furthermore, they were not associated with increased illness severity or mortality due to COVID-19. Randomised controlled trials are needed to address definitively the potential benefits or harms of RAS inhibitors in patients with COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, enters human cells by binding of its viral protein to the membrane-bound form of the aminopeptidase angiotensin-converting enzyme 2 (ACE2).[1] Experimental studies in normotensive rats reported that treatment with renin–angiotensin system (RAS) inhibitors including ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) can increase cardiac ACE2 expression.[2] This led to speculation that treatment with RAS inhibitors may increase both the susceptibility and the risk of mortality from COVID-19.[3,4] However, our group and consensus reports from professional societies have suggested equipoise in this matter,[5–10] especially given that until recently there was no clinical data to support the opinion that ACEI or ARB use increases the risk of COVID-19. Despite this, there have been reports recommending cessation of treatment with ACEI and ARB in patients with COVID-19.[3,4] With the release of new evidence,[11–13] we performed a

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systematic review and meta-analysis of studies to assess whether RAS inhibitors were associated with a risk of a positive test for COVID-19 as well as the likelihood of severe illness or mortality due to the disease.

Methods

A systematic review of MEDLINE, PubMed and EMBASE was performed by two authors according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines up to 7 May 2020.[14] Studies were included if they reported either the likelihood of a positive test or death/severe illness in patients with COVID-19, stratified by the use of ACEI/ARB. Keyword search was performed using medical subject heading (MeSH) terms and included in Supporting Information Table S1. Reference lists of reviewed articles were screened to identify further relevant studies. The search was limited to articles in English and non-peer reviewed articles were excluded. Severe illness was defined as hospitalised patients that required non-invasive or mechanical ventilation. Co-primary outcomes included the likelihood of a positive test for COVID-19 and the occurrence of death or severe illness. Due to the potentially differential effects of the RAS medication classes on ACE2 expression and clinical outcomes, exposures to ACEI and ARB were evaluated in separate and pooled analyses.

Methodological quality was assessed using the Newcastle-Ottawa Scale for quality assessment of observational studies in meta-analyses.[15] Assessment of quality on this instrument was judged on study group selection, study-group comparability and outcome assessment. Studies meeting >5 criteria were considered to be of high quality. We collected event counts and/or effect size data and preferentially extracted adjusted metrics. This was prespecified in order to account for a likely adverse cardiovascular risk factor profile in the RAS inhibitor cohort. Random-effects analysis was prespecified due to clinical variations in study types and populations assessed. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. To exclude the possibility that any one study was exerting excessive influence on the results, we also systematically excluded each study at a time and then reran the analysis to assess the change in effect size. Statistical heterogeneity was quantified using the I^2 statistic, where $I^2 \geq 80\%$ was considered to be significant

Table 1 Baseline characteristics

	Mancia	Reynolds	Meng	Zhang	Li	Mehta
Year	2020	2020	2020	2020	2020	2020
Location	Italy	USA	China	China	China	USA
Total patients (*n*)	37 031	12 594	417	3430	1178	18 472
COVID-19 (*n*)	6272	5894	417	1128	1178	1735
ACEI (*n*)	1502	627	NR	NR	NR	116
ARB (*n*)	1394	664	NR	NR	NR	98
ACEI/ARB (*n*)	2896	1110	17	188	115	214
Study design	Case-control	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Single versus multicentre	Multicentre	Multicentre	Single centre	Multicentre	Single centre	Multicentre
Reported outcomes	Death or severe illness	Death or severe illness	Severe illness	Death	Death or severe illness	Death and severe illness
Mean age (years)	68 ± 13	64 (540–75)†	64 (56–69)	64 (55–68)‡	55.5 (38–67)	49 ± 21§
Male (%)	63.3	51.8†	57.1	53.2‡	46.3	40.0
Hypertension (%)	57.9¶	100†	12.2	100‡	30.7	40.0
Congestive heart failure (%)	5.1	16.1†	74.1	NR	2.8††	10.0
Diabetes (%)	13.7‡‡	39.7†	NR	23.4‡	35.1††	19.0
Coronary artery disease (%)	7.5	NR	NR	15.4‡	17.1††	12.0
Current smokers	NR	5.3†	NR	NR	NR	NR

Values presented as mean ± standard deviation or median (interquartile range). †Recorded demographics of patients with COVID-19 and hypertension. ‡Recorded demographics of patients with COVID-19 on an ACEI/ARB. §Recorded age of entire data set. ¶Recorded prevalence of hypertension as total number taking anti-hypertensive medications. ††Recorded demographics of patients with COVID-19 and hypertension. ‡‡Recorded prevalence of diabetes as total number anti-diabetic medications. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NR, not reported.

inter-study heterogeneity.[16] As the number of included studies was <10, we refrained from any tests on publication bias.[17] Statistical analyses were performed using Comprehensive Meta-Analysis software (version 3, Biostat, Englewood, NJ, USA). Data utilised for this study analysis are available on request.

Results

The initial search yielded 102 studies and 95 were eliminated after initial screening. Seven studies were included in the initial quantitative analysis. However, given the recent retraction of one of the studies, this has now been excluded from our quantitative analysis.[12,18] Details of the literature search and excluded studies are reported in Figure S1. Five were retrospective cohort studies[11,19–22] and one was a case–control study.[13] Populations varied across the studies with three of the studies including an all-comer patient population[11,13,21] while three specifically included only patients with hypertension.[19,20,22] Study quality was high in five of the six studies (Table S2).

Overall, 73 122 patients were included in the final analysis. In this cohort, 16 624 (22.7%) patients had a positive COVID-19 test and 7892 (10.8%) were on a RAS inhibitor. Mean age ranged from 49–64 years and 56.4% were male. Details of individual study design, baseline characteristics and cardiovascular risk factors are summarised in Table 1.

RAS inhibitors and likelihood of a positive COVID-19 test

Three studies including 68 097 patients specifically assessed the likelihood of a positive COVID-19 test based on RAS inhibitor therapy. Collectively, the use of ACEI or ARB was not associated with a higher likelihood of a

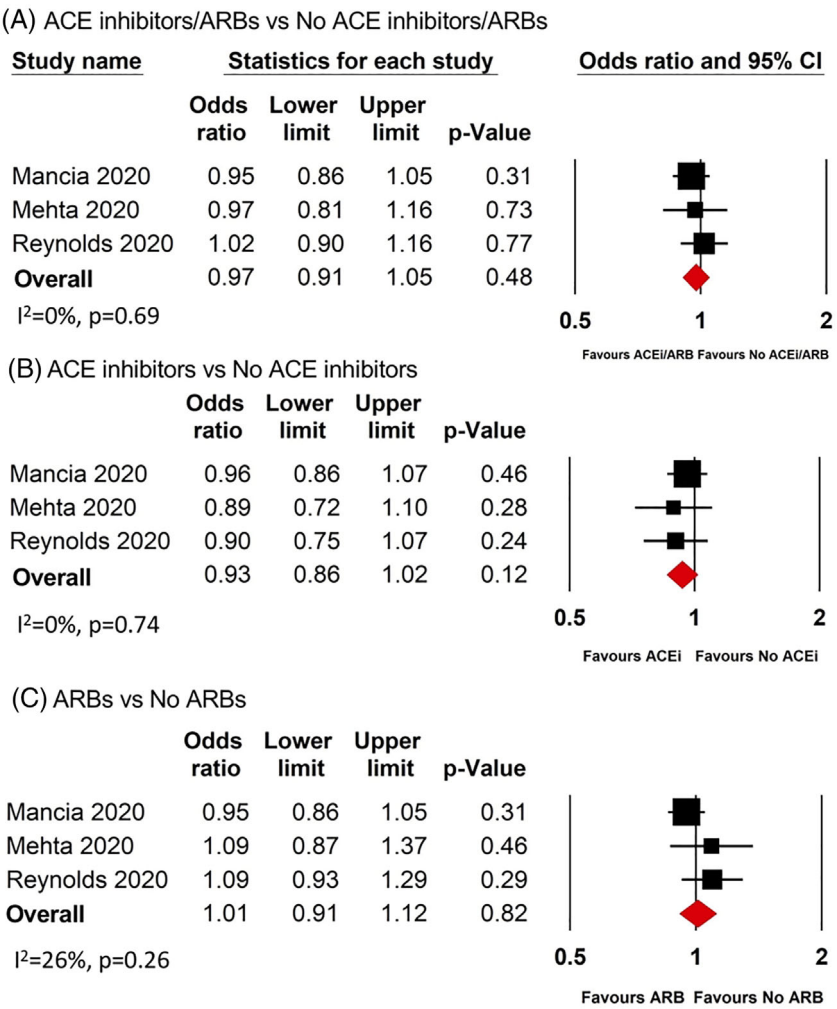

Figure 1 Renin–angiotensin system inhibitors and risk of a positive COVID-19 test.

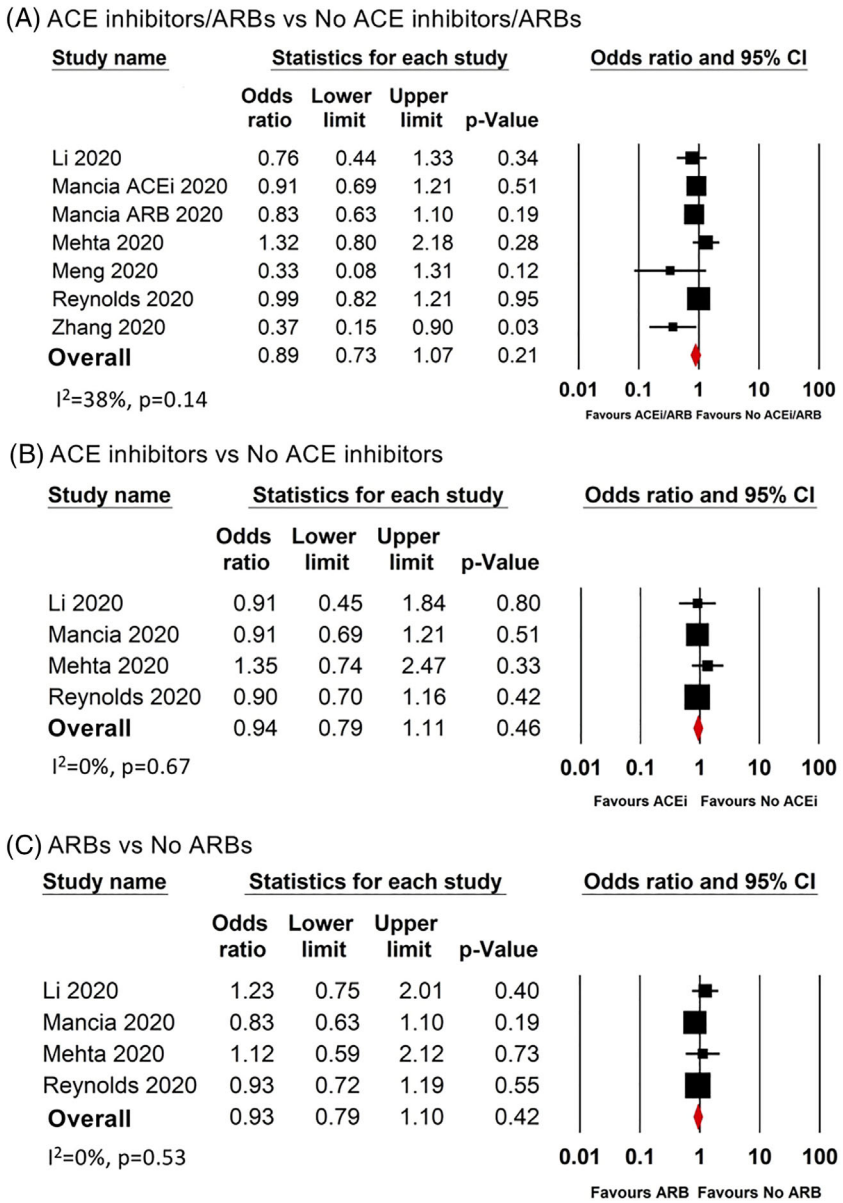

Figure 2 Renin–angiotensin system inhibitors and risk of severe illness/mortality.

positive COVID-19 test result OR 0.97 (95% CI 0.97–1.05, $P = 0.48$) with low heterogeneity ($I^2 = 0\%$, $P = 0.69$). This was comparable when stratifying by use of each medication class (ACEI 0.93, 95% CI 0.86–1.02 ($P = 0.12$); ARB 1.01, 95% CI 0.91–1.12 ($P = 0.82$)) (Fig. 1).

RAS inhibitors and risk of mortality or severe illness with COVID-19

The use of RAS inhibitors was not associated with mortality or severe illness (OR 0.89, 95% CI 0.73–1.07, $P = 0.21$). There was only moderate heterogeneity in this analysis ($I^2 = 38\%$, $P = 0.14$; Fig. 2). We also analysed the effects of ACEI and ARB separately. However, data in this stratified analysis were not mutually exclusive due to data presentation in the studies whereby patients in the no ACEI group also included ARB and vice versa. This was also noted on comparing outcomes stratified by ACEI (OR 0.94, 95% CI 0.79–1.11, $P = 0.46$) and ARB (OR 0.93, 95% CI 0.79–1.10, $P = 0.42$) both with low heterogeneity ($I^2 = 0\%$). Consistent effect sizes were observed with single-study exclusion analysis (Fig. 3) with a weak trend to lower mortality/severe illness in patients taking RAS inhibitors with removal of data from the study by Mehta *et al.*[21]

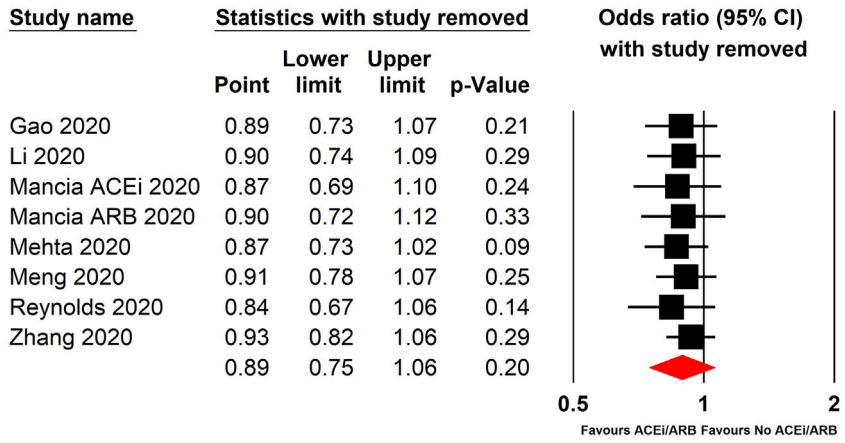

Figure 3 Pooled odds ratios with systematic exclusion of individual studies.

Discussion

Discovery of the mechanism of SARS-CoV-2 entry into cells has fuelled speculation about the safety of ACEI and ARB during the COVID-19 pandemic. This study, which summarises the totality of published data in 73 122 patients, demonstrates no association between RAS inhibitor use and a positive test for COVID-19. Furthermore, the use of ACEI and ARB was not associated with severe illness or mortality in these patients. These findings provide important clinical evidence supporting current guidance statements from several international societies which recommend continuation of ACEI/ARB in patients with COVID-19.[9,10]

The COVID-19 pandemic has affected both the presentation and management of patients with cardiovascular disease.[23–28] During this period, the use of ACEI/ARB has remained a contentious issue. ACE2 is a cellular receptor that is required in order to facilitate SARS-CoV-2 entry and propagation in host cells.[1] Concern that ACEI or ARB exposure could possibly increase risk comes from studies in some animal models demonstrating increased ACE2, and promoting expert but unfounded opinions that these drugs would increase susceptibility to SARS-CoV-2 and disease severity in COVID-19.[2–4,29] However, these reports failed to acknowledge other studies including those from our group that reported no change in ACE2 during treatment with an ACEI or ARB in animal models of disease[30–32] or in humans with renal or cardiac disease.[33,34] This unfounded hypothesis coupled with early reports indicating higher unadjusted rates of severe illness and mortality in patients with hypertension and cardiovascular disease fuelled speculation that the use of RAS inhibitors may be harmful in the current era.[4,29,35] Our findings that quantitatively summarise all contemporary data to date indicate no association between the use of RAS inhibitors and either susceptibility to or harm in patients with COVID-19. This was confirmed on analysis stratified by the use of ACEI or ARB.

Pooling results of all the studies evaluating the risk of severe illness or mortality, we observed a weak trend towards benefit in patients on RAS inhibitors. While these findings should be interpreted with caution given the degree of heterogeneity, it highlights the importance of conducting randomised controlled trials to examine the efficacy and safety of RAS inhibition in patients with COVID-19. We await the results of the REPLACECOVID (NCT04338009), ACEI-COVID19 (NCT04353596), Controlled evaLuation of Angiotensin Receptor Blockers for COVID-19 respIraTorY Disease (CLARITY) (NCT04394117) and losartan randomised trials (NCT04312009) to guide further clinical decision-making.

Joint statements by professional societies recommend continuation of ACEI or ARB among patients with co-existing hypertension and COVID-19.[9,10] This was based on the lack of any clinical evidence demonstrating risk of harm in patients on ACEI or ARB. There are abundant data with the highest level of evidence supporting the use of these medications in the treatment of hypertension, heart failure and kidney disease.[36–38] Furthermore, ACEI, ARB and mineralocorticoid receptor antagonists all have demonstrated a significant mortality reduction in patients following acute myocardial infarction with benefit demonstrated with early initiation of these drugs.[39] Discontinuation of these essential therapies in a vulnerable patient population can precipitate deterioration in cardiac function and increase the risk of mortality. Our findings can help allay concerns of patients and providers regarding the continued use of these therapies during the COVID-19 pandemic.

Strengths of this study include the large sample size, study quality and the inclusion of studies representing a multinational patient cohort from China, Italy and the United States. However, limitations of this study include the heterogeneity in patient populations and the observational nature of the studies. Although a trend to lower mortality was observed in the RAS inhibitor cohort, it is important not to infer causality due to the risk of residual confounding.

Conclusion

Use of ACEI or ARB was not associated with a heightened susceptibility for a positive diagnosis of COVID-19. Furthermore, these drug classes were not associated with increased illness severity or mortality due to COVID-19. Randomised controlled trials are needed to address definitively the potential benefits or harms of RAS inhibitor therapy in patients with COVID-19.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. MeSH terms used for the EMBASE/MEDLINE/PubMed search.
Table S2. Newcastle-Ottawa scale for non-randomized study quality assessment.
Figure S1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.