An umbrella review and meta-analysis of the use of renin-angiotensin system drugs and COVID-19 outcomes: what do we know so far?

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Abstract

Aim To provide a comprehensive assessment of the effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor II blockers (ARBs) on COVID-19 related outcomes by summarising the currently available evidence. Methods This was an umbrella review of systematic reviews/meta-analysis conducted using Medline (OVID), Embase, Scopus, Cochrane library and medRxiv from inception to 1st February 2021. Systematic reviews with meta-analysis that evaluated the effect of ACEIs/ARBs on COVID-19 related clinical outcomes were eligible. Studies' quality was appraised using the AMSTAR 2 Critical Appraisal Tool. Data were analysed using the random-effects modelling including several sub-group analyses. Heterogenicity was assessed using I2 statistic. The study protocol was registered in PROSPERO (CRD42021233398). Results Overall, 47 reviews were eligible for inclusion. Out of the nine COVID-19 outcomes evaluated, there was significant associations between ACEIs/ARBs use and each of death (OR=0.80, 95%CI=0.75-0.86; I2=51.9%), death/ICU admission as composite outcome (OR=0.86, 95%CI=0.80-0.92; I2=43.9%), severe COVID-19 (OR=0.86, 95%CI=0.78-0.95; I2=68%), and hospitalisation (OR=1.23, 95%CI=1.04-1.46; I2= 76.4%). The significant reduction in death/ICU admission, however, was higher among studies which presented adjusted measure of effects (OR=0.63, 95%CI=0.47-0.84) and were of moderate quality (OR=0.74, 95%CI=0.63-0.85). There was no evidence of any significant association between ACEIs, or ARBs and COVID-19 outcomes. Conclusions Collective evidence from observational studies indicate a good quality evidence on the significant association between ACEIs/ARBs use and reduction in death and death/ICU admission, but poor-quality evidence on both reducing severe COVID-19 and increasing hospitalisation. Our findings further support the current recommendations of not discontinuing ACEIs/ARBs therapy in patients with COVID-19.

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Running title: Renin-angiotensin drugs and COVID-19

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Conclusions

Collective evidence from observational studies indicate a good quality evidence on the significant association between ACEIs/ARBs use and reduction in death and death/ICU admission, but poor-quality evidence on both reducing severe COVID-19 and increasing hospitalisation. Our findings further support the current recommendations of not discontinuing ACEIs/ARBs therapy in patients with COVID-19.

Keywords

renin-angiotensin-aldosterone system (RAAS) inhibitors; COVID-19; angiotensin-converting enzyme inhibitors (ACEIs); angiotensin receptor II blockers (ARBs)

Abbreviations and Acronyms

ACEIs: Angiotensin-Converting Enzyme Inhibitors; ACE2: Angiotensin-Converting Enzyme 2; ARBs: Angiotensin Receptor Blockers; AT_1R: Angiotensin Receptor 1; CVD: Cardiovascular Disease

Introduction

Several risk factors linked to poor COVID-19 outcomes have been identified early on, including cardiovascular diseases such as hypertension (1). Consequently, the possible impact of renin-angiotensin-aldosterone system (RAAS) inhibitors on COVID-19 related outcomes has emerged as a topic of interest (2) and their mechanisms of action– in particular, the potential upregulation of angiotensin-converting enzyme 2 (ACE2) which is associated with viral entry into bronchial cells (3). This has resulted in the rapid dissemination of numerous studies, mostly retrospective observational in nature, focusing on the risk of COVID-19 infection, disease severity, and/or disease outcomes in patients being treated with either angiotensin-converting-enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) since early 2020 (4-6).

As was the case in most early COVID-19 related research, the evidence comprised observational studies with notably small sample sizes and short durations of follow-up. Resultantly, a number of systematic reviews were swiftly published in attempt to offer a more substantial view by aggregating findings of these small-scale studies. These meta-analyses have offered tentative insights into all three areas of interest with regards to the use of RAAS inhibitors in times of COVID-19: (i) risk of infection, usually measured as the share of positive PCR tests within a study cohort; (ii) risk of severe COVID-19, with various underlying definitions ranging from hospitalisation due to the disease to the requirement for mechanical ventilation; and (iii) the risk of mortality. While there were similarities between some of the published results – e.g. indicating, in general, no association between RAAS inhibitor use and risk of COVID-19 infection – other results were more varied and the findings are still controversial/conflicting (4-6). A logical next step, besides conducting additional systematic reviews/meta-analyses, is to perform a systematic review of systematic reviews (also known as umbrella review), thereby taking advantage of the availability of high-level evidence and providing an opportunity to contrast and compare (7). The aim of this umbrella review and meta-analysis, therefore, was to assess the effect of ACEIs/ARBs on COVID-19 related outcomes by summarising the currently available, aggregate evidence.

Methods

An umbrella literature review and subsequent meta-analysis was conducted. The protocol was informed by Joanna Briggs Reviewer's Manual for 'Development of an Umbrella review protocol' (8) and published on PROSPERO (CRD42021233398).

Eligibility criteria

Eligible studies were systematic reviews which conducted a meta-analysis to explore the effect of ACEIs/ARBs on any COVID-19 related clinical outcomes among adults ([?]18 years) with COVID-19 diagnosis.

Search strategy

The databases Medline, EMBASE, Scopus, Cochrane, and medRxiv were searched from January 2019 until February 2021. The search was limited to the English language and for systematic review articles. Search terms are listed in **Supplementary file 1** .

Article selection

Article selection was conducted using Covidence software (9); 10% of the articles' titles/abstracts and full texts were randomly selected and screened independently. The percentage of agreement was calculated for all independent validation, with >80% considered adequate (10).

Data extraction

A data extraction template in Microsoft Excel was piloted with 10% of reviews by NW and agreed for use by all authors. 10% of reviews were randomly selected and underwent independent data extraction; the percentage of agreement was calculated. Again, agreement >80% was considered adequate (10) . Data extracted from the reviews included: title; authors; year review published; study design; sample size; setting; pop-

ulation; exposure (e.g. ACEIs/ARBs, ACEIs, or ARBs); and outcomes (e.g. death, COVID-19 infection, hospitalisation).

Quality Assessment

Quality assessment was conducted independently using the AMSTAR 2 tool (11). Studies were categorised as having high, moderate, low and critically low confidence in the results based on the number of 'critical domains'. Critical domains related to each review containing: an explicit statement that the methods were established a priori within a protocol; if a satisfactory technique for assessing the risk of bias was conducted and sufficiently discussed; if the meta-analysis used appropriate methods; and if publication bias (small study bias) was conducted.

Data analysis and synthesis

The random-effects meta-analysis model was used to statistically combine the measure of effects for those outcomes that were reported by more than one study, stratified by the three level of exposure (ACEIs/ARBs, ACEIs, ARBs). We conducted several sub-group analyses based on numerous variables including: whether the reported measure of effects was crude or adjusted, the study was peer-reviewed or not, and the study's methodological quality as per the quality assessment. Furthermore, to assess the impact of ACEIs/ARBs among patients with hypertension (the most common indication for ACEIs/ARBs), we also conducted sub-group analysis based on whether the studies had included either patients with hypertension only or at least had hypertension as one of the comorbidities versus those studies which did not recorded the hypertension status of their study population. The combined pooled estimates were presented as odds ratios and 95%CI and graphically as forest plots. I^2 statistic (12) was used to assess heterogeneity between the studies with I^2 of 0% indicating lack of heterogeneity, whereas 25%, 50%, and 75% indicating low, moderate and high heterogeneity, respectively (12). Publication bias was assessed using funnel plots and Egger's asymmetry test (13) only for those outcomes where >10 studies were included in the analysis as recommended by Cochrane guidelines (14). Furthermore, we evaluated the influence of individual reviews on the summary pooled estimate for each outcome by conducting influential analyses (15) whereby the pooled meta-analysis estimates for each outcome were computed by omitting one study at a time. Data were analysed using STATA 12.

Role of the Funding Source

None

Results

Out of an initial 157 publications, 66 systematic reviews underwent full text screening; after further exclusions based on pre-specified criteria, 47 studies were eligible for inclusion (**Figure 1**) (4-6, 16-59).

Review characteristics

Forty-six reviews (97.9%) compared COVID-19 related outcomes between ACEI/ARB users vs. non-users among patients with COVID-19 (4-6, 16-51, 53-59), one study (2.12%%) compared outcomes between ACEIs/ARBs users in patients with and without COVID-19 infection (52)), and 16 studies (34.0%) explored both (6, 18, 24-26, 39, 40, 42, 43, 47, 49, 50, 53, 55, 57, 59). Definition criteria for COVID-19 diagnosis was reported by only six (12.8%) reviews as laboratory confirmed diagnosis based on a reverse transcriptase–polymerase chain reaction, whereas the remaining 41 (87.2%) reviews did not report any criteria for COVID-19 diagnosis definition. Most of the included reviews were peer-reviewed publications (68.1%; n=32), whereas the remining 15 (31.9%) reviews were non-peer reviewed publications (i.e. were published in a pre-print database) (16-18, 20-22, 29, 31-33, 35, 45, 49, 53, 59). The time the searches were conducted ranged from April 2020 to October 2020, with 21 (44.7%) review searches conducted in the month of May 2020 (4-6, 16, 20, 22, 23, 27, 29-31, 34, 35, 39-41, 43, 45, 47, 49, 53) Pre-print articles were included in 28 (59.6%) reviews (4, 16, 18-21, 24, 25, 29, 32, 36, 40-44, 46-52, 54, 55, 58, 59), and 10 (21.3%) reviews

adjusted for retracted studies (4, 17, 30, 39, 44, 46-49, 55). Full details of the 47 reviews are presented in **Supplementary file 3** .

A total of 213 meta-analyses were conducted by the 47 reviews (**Supplementary file 4**). In terms of number of COVID-19 related outcomes reported in each review, one outcome was reported by 13 reviews (27.7%) (17, 19, 20, 22, 23, 27, 28, 37, 38, 46, 51, 52, 60), two outcomes by 15 reviews (31.9%) (4, 16, 25, 30, 31, 33-36, 39, 41, 48, 53, 54, 57), three outcomes by 11 reviews (23.4%) (6, 21, 24, 26, 32, 43-45, 49, 55, 59) and 4-9 outcomes by eight reviews (17%) (18, 29, 40, 42, 47, 50, 56, 58). Overall, the 47 eligible reviews reported data on 18 unique pooled outcome estimates including death in 36 reviews, reviews (4, 6, 16-18, 21, 23, 24, 26, 29-38, 40-48, 53-55, 57-59), ICU admission in nine reviews (26, 27, 29, 40, 42, 47, 50, 55, 58), death/ICU admission as a composite outcome in 16 reviews (4, 19, 20, 22, 25, 28, 30, 31, 39, 40, 42, 44, 50, 54, 58), risk of acquiring COVID-19 infection in 15 reviews (18, 24, 26, 39, 40, 42, 43), severe COVID-19 infection in 22 reviews (6, 16, 18, 21, 24, 29, 32-36, 40-45, 47, 58, 59), hospitalisation in nine reviews (18, 29, 40, 42, 47, 58), length of hospital stay in five reviews (18, 21, 29, 45, 58), use of mechanical ventilator in three reviews (29, 40), risk of severe acute respiratory syndrome (SARS) in two reviews (25, 58), and each of hospital discharge (29), ICU admission/mechanical ventilator use (40), risk of COVID-19 infection/hospitalisation (52), severe pneumonia (40), level of serum creatinine (56), d-dimer (56), cough (56), fever (56) and renal dialysis (58) in one review; accordingly, nine out of these 18 outcomes were included in the meta-analysis as they were reported by at least two reviews. In terms of the exposure, ACEIs and ARBs were evaluated as one class (ACEIs/ARBs) in all the eligible 47 reviews apart from three (25, 52, 56), and as separate classes in 17 (4, 6, 22, 24-26, 29, 30, 37, 39, 40, 42, 46, 49, 52, 53, 57) and 16 (4, 6, 22, 24-26, 29, 30, 37, 39, 40, 42, 49, 52, 53, 57) reviews, respectively. Majority of the reviews (66%; n=31) only evaluated one exposure, mainly ACEIs/ARBs combined as one class (n=30); whereas one third of them (29.8%; n=14) reported data for the three level of exposure (ACEIs/ARBs, ACEIs, ARBs).

Quality assessment

Overall confidence in the results was 'moderate' for 10 (21.3%) reviews (18, 24, 25, 29, 36, 40-42, 55, 58), 'low' for 15 (30.6%) reviews (4, 5, 19-21, 26, 27, 30, 33, 44, 48-50, 54, 59), and 'critically low' for 22 (44.9%) reviews (6, 16, 17, 22, 23, 28, 31, 32, 34, 35, 37-39, 43, 45-47, 51-53, 56, 57) (**Supplementary file 5**). Considering the critical domains, most reviews were considered to have had a satisfactory technique for the statistical combination of results (n=45, 95.7%) (4-6, 16-21, 23-56, 58, 59) and for assessing risk of bias (n=38, 80.1%) (4-6, 16, 18-22, 24-27, 29, 30, 33-37, 39-45, 47-52, 54-56, 58, 59). Less reviews were favourably considered in terms of accounting for risk of bias when interpreting and discussing the results (n=32, 68.1%), with appropriate conduct of publication bias (n=33) (4-6, 16, 18-20, 22-26, 29-32, 36, 37, 40-44, 46, 48-50, 52, 55, 56, 58, 59), and only 15 (31.9%) reviews referred to the review methods being established a priori (18, 21, 24, 25, 27, 29, 33, 36, 40-42, 51, 54, 55, 58).

Effect of ACEIs/AEBs (as a one group) on the study outcomes

Overall, the effect of ACEIs/ARBs on nine COVID-19 related clinical outcomes were evaluated (Table 1). The combined pooled meta-analysis estimates indicated that ACEIs/ARBs used was associated with a significant reduction in three clinical outcomes including death (OR=0.80, 95%CI=0.75-0.86; I^2 = 51.9%) (**Figure 2**) death/ICU admission as composite outcome (OR=0.86, 95%CI= 0.80-0.92; I2= 43.9%) (**Figure 3**) and severe COVID-19 infection (OR=0.86, 95% CI=0.78-0.95; I2 = 68%) (**Figure 4**); on the other hand, ACEIs/ARBs was associated with a significant increase in hospitalisation (OR=1.23, 95%CI=1.04-1.46; I2= 76.4%) (**Figure 5**). However, there was insignificant association with each of ICU admission (**Figure 6**), risk of acquiring COVID-19 infection (**Figure 7**), use of mechanical ventilator (**Figure 8**), risk of SARS (**Figure 9**), and risk of severe pneumonia (**Figure 10**).

However, the sub-group analyses indicated different results for some of the outcomes (Table 2). Firstly, despite the consistent significant reduction in death in association with ACEIs/ARBs use regardless of studies' crude/adjusted measure of effects, peer-review status and hypertension use status, there was a trend toward lower protective effective of ACEIs/ARBs on death as the quality of the studies enhanced

from critically low (OR=0.75, 95%CI=0.66-0.85; I^2= 60.4%) to moderate (OR=0.85, 95%CI=0.75-0.96; I^2= 53.4%) (**Supplementary file 6A** ;Table 2). Similarly, the significant reduction in death/ICU admission associated with ACEIs/ARBs appeared to be higher among the studies which presented adjusted measure of effects (adjusted: OR=0.63, 95%CI=0.47-0.84 vs. crude: OR=0.87, 95%CI=0.81-0.93); and the pooled estimates for association ranged from insignificant association among the critically low-quality studies (OR=0.94, 95%CI=0.84-1.06; I^2 = 57.4%) to a significantly higher reduction among the moderate quality studies (OR=0.74, 95%CI=0.63-0.85; I^2 = 18.9%); (**Supplementary file 7A** ;Table 2; besides, the significant protective impact of ACEIs/ARBs on death/ICU admission was observed only among peer-reviewed studies (peer-reviewed: OR=0.85, 95%CI=0.79-0.92 vs. non-peer reviewed: OR=0.89, 95%CI=0.75-1.10) and studies included hypertension patients (OR=0.85, 95%CI=0.80-0.90) **Supplementary file 7A** ;Table 2).

Likewise, the protective effect of ACEIs/ARBs use on severe COVID-19 infection was observed only among: peer-reviewed studies (peer-reviewed: OR=0.89, 95%CI=0.83-0.96 vs. non-peer reviewed: OR=0.82, 95%CI=0.66-1.01), studies that did not recorded the hypertension status of their patients (OR=0.85, 95%CI=0.76-0.96) and critically low-quality studies (OR=0.69, 95%CI=0.53-0.92) and in fact the protective effect disappeared completely as the quality of the studies improved since insignificant association was observed among both low and moderate quality studies (OR=0.93, 95%CI=0.85-1.03; OR=0.89, 95%CI=0.77-1.04, respectively) (**Supplementary file 8A** ;Table 2**)** . In terms of ACEIs/ARBs' increasing impact on hospitalisation, this impact was demonstrated only among the studies which: presented adjusted measure of effects (adjusted: OR=1.33, 95%CI=1.21-1.47 vs. crude: OR=1.21, 95%CI=0.91-1.61), were not peer-reviewed (OR=1.45, 95%CI=1.10-10.20 vs. peer-reviewed: OR=1.11, 95%CI=0.90-1.31) and did not record the hypertension status of their patients (OR=1.35, 95%CI=1.15-1.58) (**Supplementary file 9A** ;Table 2).

Effect of ACEIs and AEBs (as a separate group) on the study outcomes

Overall, the effect of ACEIs and ARBs on seven COVID-19 related clinical outcomes (death, ICU admission, death/ICU admission, risk of acquiring COVID-19 infection, severe COVID-19 infection, hospitalisation, and acute SARS) were evaluated. Neither ACEIs nor ARBs had any significant impact on any of the seven studied outcomes (**Figures 2-10,**Table 1**)** except for hospitalisation whereby ACEIs use was associated with a significant increase in COVID-19 related hospitalisation (OR=1.18, 95%CI=1.04-1.35; I^2 = 6.7%) (**Figure 5** ;Table 1). These results were mostly consistent across all the sub-group analyses (**Supplementary Files 6B&C, 7B&C, 8B&C;** Table 2**)** except for the increasing effect of ACEIs on hospitalisation which was only observed among those studies which did not record the hypertension status of their patients (OR=1.23, 95%CI=1.10-1.41) (**Supplementary Files 9B&C;** Table 2**)**

Publication bias

Results from the funnel plots and Egger's asymmetry tests for the six outcomes that were reported by at least 10 studies indicated no evidence of significant publication bias in all of them except for death/ICU admission and severe COVID-19 infection (p-value=0.022 and 0.019, respectively) (**Supplementary file 10**).

Influential analyses

The results from the influential analyses indicated that none of the combined pooled meta-analysis estimates for the nine outcomes were dominated/influenced by an individual study since the omission of any of these individual studies one at a time made no difference to the pooled meta-analysis estimate because all of pooled meta-analysis estimates were overlapping (**Supplementary file 11**).

Discussion

This umbrella review for the first time combined all the available evidence so far from observational studies on the impact of ACEIs/ARBs on COVID-19 clinical outcomes (47 systematic review studies which reported 213 meta-analyses) into one pooled estimate. The collective, combined pooled estimates indicated evidence

of statistically significant reduction in mortality, death/ICU admission and severe COVID-19 infection in association with ACEIs/ARBs use, but significant increase in the risk of hospitalisation (Table 1). Interestingly, there was no evidence of any significant association between ACEIs, or ARBs and any of the nine COVID-19 related clinical outcomes analysed in our study.

Although the magnitude of observed impact of ACEIs/ARBs use on reducing mortality was decreasing as the quality of studies improved (Table 2), the evidence were overall mostly consistent across all the sub-group analyses including a greater impact among studies that included hypertensive patients compared with studies that did not record the hypertension status of their study population (Table 2). In terms of death/ICU admission, the quality of the evidence was even better because the impact of ACEIs/ARBs use was greater and significant only among: moderate-quality studies, peer-reviewed studies and studies with hypertensive patients; however, the impact was significant regardless of whether the measure of effects was crude or adjusted, even though the impact was greater among studies with adjusted measure of effects compared those studies with crude measure of effects (Table 2). In contrast, the quality of the evidence for the impact of ACEIs/ARBs use on severe COVID-19 was low since the significant reduction was only observed among critically-low quality studies and in fact, the significant association disappeared as the quality of the studied enhanced from critically low quality to either low or moderate quality (Table 2).

In terms of the impact of ACEIs/ARBs on hospitalisation, the quality of the evidence was low because the significant association was not apparent when the data were analysed by the quality of the studies, even though the magnitude of the effect was almost consistent across the various quality of the studies; besides, the significant increase in hospitalisation was observed only among: studies that reported adjusted measure of effects, non-peer reviewed studies and studies that did not recorded the hypertensive status of their study population (Table 2).

The sub-group analyses demonstrated low-quality evidence regarding the different impact of ACEIs and ARBs (as separate groups) (Table 2). This observed difference has been suggested to be due to the increased level of angiotensin-II, which occurs following ARBs treatment but not ACEIs, which in turn imposes an increased substrate load on ACE2 enzyme requiring its upregulation (61); hence facilitates COVID-19 virus cell entry and its subsequent infectivity/pathogenicity (62). Furthermore, the increase in ACE2 activity demonstrated in patients with hypertension, either due to the pathophysiology of hypertension itself (63) or administration of ACEIs/ARBs as antihypertensive medications (64), could at least partially explain some of our study findings as why ACEIs/ARBs had significant greater impact on certain COVID-19 clinical outcomes (i.e., mortality, death/ICU admission) only among studies that included patient with hypertension.

Several hypotheses (related to the pathophysiology of COVID-19 infection and functions of ACE2) can explain the observed impact of ACEIs/ARBs in our current studies. The adverse negative effects of ACEIs/ARBs could be due to ACEIs/ARBs ability to cause upregulation of ACE2 expression (the cell entry point for COVID-19); hence facilitate and enhance COVID-19 viral binding and cell entry (64); whereas the positive protective effects could be through ACEIs/ARBs blockage of the harmful angiotensin II- AT1R axis and their effects on angiotensin II expression leading to subsequent increase in the level of the protective angiotensin 1-7 and 1-9 which have anti-inflammatory and vasodilatory effects; hence potentially attenuating the cardiac and pulmonary damages (2). Genetic ACE2 polymorphism among some individuals has been also suggested as potential factor explaining, at least partially, the harmful effects on ACEIs/ARBs on COVID-19 outcomes (65).

It is worth to highlight that our study findings are still important despite the recently published randomised clinical trial (RCT) (66) which found insignificant differences in the mean number of days alive/out of the hospital between those assigned to discontinue vs continue ACEIs or ARBs. This is because of certain points that are related to the findings from this RCT. First, this RCT was designed to evaluate the impact of continuing ACEIs or ARBs vs. their discontinuation after contracting COVID-19 rather than evaluating ACEIs/ARBs use vs. non-use of these medication which was the focus of most of the observational studies involved in our current study. Secondly, the RCT included only patients with mild or moderate COVID-19 with more than half of the participants (57%; n=376) having mild COVID-19, and evaluated only two

COVID-19 related clinical outcomes, namely days alive (mortality) and out of hospital days; hence leaving a big gap in the evidence around ACEIs/ARBs' impact on other important COVID-19 clinical outcomes as well as limiting generalisability to patients with severe COVID-19. Furthermore, although the RCT's participants were all hypertensive patients, about one-third (˜31%) and ˜1% had diabetes and heart failure, respectively, which further limits the generalisability of the RCT's findings to these conditions for which ACEIs/ARBs are commonly indicated. Moreover, the RCT's participants were all from Brazil and hence extending the findings to other races or ethnicities will be limited; this is particularly importantly because there are evidence demonstrating that there are potential genetic variants of renin, angiotensinogen, ACE, angiotensin II and ACE2 among various populations that influence the function of the renin-angiotensin aldosterone system; hence affecting someone' response to the COVID-19 infection (67).

Strengths and limitations

This review presents the most comprehensive systematic overview on the impact of RAAS inhibitors on COVID-19 related clinical outcomes, with a wide range of sensitivity (sub-group) analyses to assess the robustness of the evidence. None of the pooled meta-analysis estimates for the nine studied outcomes was affected/dominated by an individual study. Although most of the included studies were classified as 'low' or 'critically low' quality using AMSTAR 2 tool, it is widely acknowledged that the AMSTAR 2 tool has a high standard with most reviews rated as 'critically low' (68, 69). The AMSTAR 2 tool is also prone to subjective biases (70) , and assessment results are at the discretion of the reviewers regarding what is a "comprehensive" literature search or "satisfactory" explanation of heterogeneity or risk of bias assessment (70); therefore, quality assessment was conducted fully independent in this review. Alternatives tools to AMSTAR 2 exist such as the ROBIS tool, however the measurement categories are found to be broadly similar with the AMSTAR 2 tool considered more reliable (70).

Conclusion

Collective evidence so far from observational studies indicate a good quality evidence on the significant association between ACEIs/ARBs use and reduction in death and death/ICU admission (as a composite outcome). Additionally, ACEIs/ARBs use was found to be associated with a significant reduction in severe COVID-19 but a significant increase in hospitalisation; however, the evidence for these two outcomes was of poor quality; hence, cautious interpretation of these findings is required. Interestingly, findings for some of the clinical outcomes were dependent on whether the included patients had hypertension or not. Overall, our study findings further support the current recommendations of not discontinuing ACEIs/ARBs therapy in patients with COVID-19 due to the lack of good quality evidence on their harm but rather it could be beneficial to patients.

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Conflict of interest

Nothing to declare

Author contributors

Study conception and design: all authors; data collection and management: NW, TM; data analysis and interpretation: AK; manuscript writing and drafting: all authors; manuscript reviewing and revising as well as providing constrictive criticism and final approval: all authors

Ethical approval

Not required.

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Figures captions

Figure 1 PRISMA flow diagram of the review selection process

Figure 2 Forest plot depicting pooled estimates for the association between mortality and renin-angiotensin system drugs use

Figure 3 Forest plot depicting pooled estimates for the association between death/Intensive Care Unit (as a composite outcome) and renin-angiotensin system drugs use

Figure 4 Forest plot depicting pooled estimates for the association between severe COVID-19 infection and renin-angiotensin system drugs use

Figure 5 Forest plot depicting pooled estimates for the association between hospitalisation and renin-angiotensin system drugs use

Figure 6 Forest plot depicting pooled estimates for the association between developing Intensive Care Unit admission and renin-angiotensin system drugs use

Figure 7 Forest plot depicting pooled estimates for the association between between risk of acquiring COVID-19 infection and renin-angiotensin system drugs use

Figure 8 Forest plot depicting pooled estimate for the association between use of mechanical ventilator and renin-angiotensin system drugs use

Figure 9 Forest plot depicting pooled estimates for the association between risk of severe acute respiratory syndrome (SARS)and renin-angiotensin system drugs use

Figure 10 Forest plot depicting pooled estimates for the association between severe pneumonia and renin-angiotensin system drugs use

Table captions

Table . Meta-analyses pooled estimates with 95%CI of the effects of ACEIs/ARBs on COVID-19 related clinical outcomes

Outcomes	**ACEIs/ARBs**
Death	0.80 (0.75, 0.86)
Number of studies	47
I-squared	51.9%
ICU	1.03 (0.86, 1.19)
Number of studies	10
I-squared (p-value)	58.7%
Death/ICU	0.86 (0.80, 0.92)
Number of studies	22
I-squared (p-value)	43.9%
Risk of COVID-19	0.99 (0.97, 1.02)
Number of studies	19
I-squared (p-value)	24.7%
Severe COVID-19	0.86 (0.78, 0.95)
Number of studies	28
I-squared (p-value)	68%
Severe pneumonia	0.82 (0.22, 3.05)
Number of studies	2
I-squared (p-value)	0%
Hospitalisation	1.23 (1.04, 1.46)
Number of studies	11
I-squared (p-value)	76.4%
Ventilator use	1.18 (0.84, 1.66)
Number of studies	3
I-squared (p-value)	53.9%
Acute SARS infection	0.71 (0.49, 1.02)
Number of studies	1

Outcomes	**ACEIs/ARBs**
I-squared (p-value)	NA
(Note) NA: not applicable indicating not enough studies to perform meta-analyses	(Note) NA: not applicable indicating n

Table . Sub-group meta-analyses pooled estimates with 95%CI of the effects of ACEIs/ARBs on COVID-19 related clinical outcomes

Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)
Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded

Number of studies
I-squared (p-value)

Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)

Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)

Adjusted outcome measure
Adjusted OR
Crude OR

Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)

Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)

Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies

I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)
Acute SARS (n=5)
Adjusted outcome measure
Adjusted OR
Crude OR
Number of studies
I-squared (p-value)
Peer reviewed article?
Yes
No
Number of studies
I-squared (p-value)
Study's quality
Critically low
Low
Moderate
Number of studies
I-squared (p-value)
Hypertension use status
Hypertensive patients
Not-recorded
Number of studies
I-squared (p-value)
(Note) *Indicates that the pooled estimate is the same as the overall analyses because all the studies were in one group; NA

Supplementary files' captions and legends

Supplementary file 1. Search strategy used in the database searches

Supplementary file 2. List and details of the irrelevant studies excluded at the stage of abstract and title screening

Supplementary file 3. Study characterises of the 47 eligible reviews included in the current umbrella

systematic review

Supplementary file 4. Details of all the 213 meta-analyses point estimates reported by the eligible 47 reviews and were included in the current study

Supplementary file 5. Quality assessment score of the 47 eligible reviews included in the current umbrella systematic review using AMSTAR 2 tool

Supplementary file 6. Forest plot depicting sub-group analyses pooled estimates for the association between mortality and ACEIs/ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 6A. Forest plot depicting sub-group analyses pooled estimates for the association between mortality and ACEIs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 6B. Forest plot depicting sub-group analyses pooled estimates for the association between mortality and ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 7. Forest plot depicting sub-group analyses pooled estimates for the association between death/ICU admission (as a composite outcome) and ACEIs/ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 7A. Forest plot depicting sub-group analyses pooled estimates for the association between death/ICU admission (as a composite outcome) and ACEIs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 7B. Forest plot depicting sub-group analyses pooled estimates for the association between death/ICU admission (as a composite outcome) and ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 8. Forest plot depicting sub-group analyses pooled estimates for the association between severe COVID-19 and ACEIs/ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 8A. Forest plot depicting sub-group analyses pooled estimates for the association between severe COVID-19 and ACEIs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 8B. Forest plot depicting sub-group analyses pooled estimates for the association between severe COVID-19 and ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 9. Forest plot depicting sub-group analyses pooled estimates for the association between hospitalisation and ACEIs/ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 9A. Forest plot depicting sub-group analyses pooled estimates for the association between hospitalisation and ACEIs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 9B. Forest plot depicting sub-group analyses pooled estimates for the association between hospitalisation and ARBs use sub-grouped by A) type of analyses (crude vs. adjusted); B) peer-review status; C) methodological quality; and D) hypertension status

Supplementary file 10. Publication bias funnel plot for the outcomes with >=10 studies

Supplementary file 11. Results of the influential analyses

Figure 1. PRISMA flow diagram of review selection process