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REVIEW

# Effects of renin–angiotensin system blockers on outcomes from COVID-19: a systematic review and meta-analysis of randomized controlled trials

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**Background and aims** Randomized controlled trials (RCTs) have assessed the effects of renin–angiotensin system (RAS) blockers in adults with coronavirus disease 2019 (COVID-19). This meta-analysis provides estimates of the safety and efficacy of treatment with (vs. without) RAS blockers from these trials.

**Methods** PubMed, Web of Science, and ClinicalTrials.gov were searched (1 March–12 April 2023). Event/patient numbers were extracted, comparing angiotensin-converting enzyme (ACE) inhibitor/angiotensin-receptor blocker (ARB) treatment with no treatment, for the outcomes: intensive care unit (ICU) admission, mechanical ventilation, vasopressor use, acute kidney injury (AKI), renal replacement therapy (RRT), acute myocardial infarction, stroke/transient ischaemic attack, heart failure, thromboembolic events, and all-cause death. Fixed-effects meta-analysis estimates were pooled.

**Results** Sixteen RCTs including 3492 patients were analysed. Compared with discontinuation of RAS blockers, continuation was not associated with increased risk of ICU [risk ratio (RR) 0.96, 0.66–1.41], ventilation (RR 0.77, 0.55–1.09), vasopressors (RR 0.92, 0.58–1.44), AKI (RR 1.01, 0.40–2.56), RRT (RR 1.01, 0.46–2.21), or thromboembolic events (RR 1.07, 0.36–3.19). RAS blocker initiation was not associated with increased risk of ICU (RR 0.71, 0.47–1.08), ventilation (RR 1.12, 0.91–1.38), AKI (RR 1.28, 0.89–1.86), RRT (RR 1.66, 0.89–3.12), or thromboembolic events (RR 1.20, 0.06–23.70), although vasopressor use increased (RR 1.27, 1.02–1.57). The RR for all-cause death in the continuation/discontinuation trials was 1.24 (0.80–1.92), and 1.22 (0.96–1.55) in the initiation trials. In patients with severe/critical COVID-19, RAS blocker initiation increased the risk of all-cause death (RR 1.31, 1.01–1.72).

**Conclusion** ACE inhibitors and ARBs may be continued in non-severe COVID-19 infection, where indicated. Conversely, initiation of RAS blockers may be harmful in critically ill patients.
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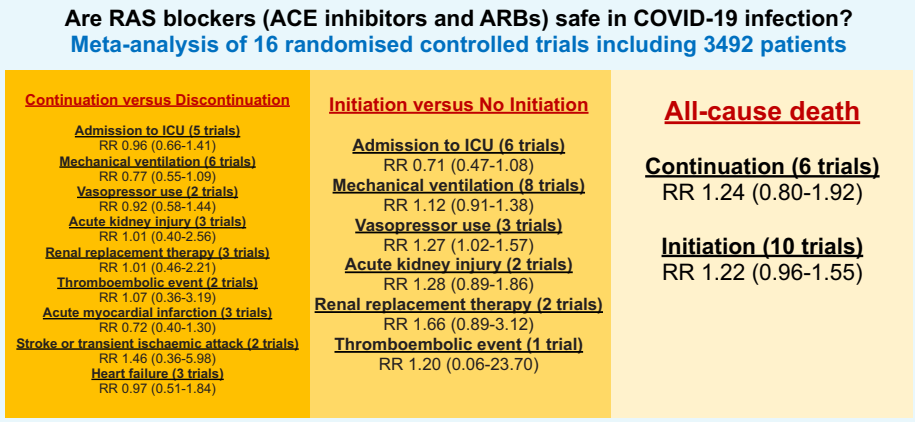
## Graphical Abstract

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**ACE**, angiotensin-converting enzyme; **ARB**, angiotensin-receptor blocker; **COVID-19**, coronavirus disease 2019; **ICU**, intensive care unit; **RAS**, renin-angiotensin system; **RR**, risk ratio (95% confidence intervals)

Are RAS blockers (ACE inhibitors and ARBs) safe in COVID-19 infection?

**Keywords** Angiotensin-converting enzyme inhibitor • Angiotensin-receptor blocker • COVID-19 • Meta-analysis • Randomized controlled trial • Renin–angiotensin system • Severe acute respiratory syndrome coronavirus 2

## Key learning points

### Key question

- For millions of patients with hypertension, diabetes, and cardiovascular and renal diseases treated with renin–angiotensin system (RAS) blockers, it is crucial to understand the safety of RAS blockers in coronavirus disease 2019 (COVID-19) infection, which is likely to remain endemic for the foreseeable future.

### Key finding

- This is the largest and most up-to-date meta-analysis, examining 10 clinical outcomes in almost 3500 patients enrolled in 16 randomized controlled trials (RCTs). Outcomes were analysed according to design (discontinuation vs. initiation), COVID-19 severity, blinding, region, and type of RAS blocker.

### Take-home message

- The meta-analysis showed that there is no benefit to initiating a RAS blocker as a treatment for COVID-19. However, it is safe to continue existing RAS blocker therapy in non-critically ill patients with a prior indication for such treatment.

## Introduction

Angiotensin-converting enzyme 2 (ACE2) is the functional receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which is responsible for the coronavirus disease 2019 (COVID-19) infection.[1] Renin–angiotensin system (RAS) blockers such as angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-receptor blockers (ARBs) may upregulate ACE2 and thus theoretically increase susceptibility to or increase severity of COVID-19. Conversely, ACE2 is responsible for the degradation of angiotensin II in a process that produces angiotensin (1-7), which acts as a physiological antagonist of angiotensin II.[1] Because SARS-CoV-2 downregulates ACE2, this may lead to an increase in angiotensin II and a decrease in angiotensin (1-7). Increased and unopposed angiotensin II appears to aggravate pulmonary injury in experimental models, and RAS inhibitors reduce lung damage and mortality in these models.[1]

Consequently, it has been uncertain whether these drugs should be continued or stopped in patients contracting this infection and whether their initiation might be beneficial or harmful in people with COVID-19. Over the last 3 years, several randomized controlled trials (RCTs) have reported safety and efficacy outcomes related to the use of RAS blockers in patients with COVID-19. However, these trials have been modest in size, with only two enrolling >700 patients (CLARITY, BRACE-CORONA) and another two enrolling >200 patients (ACEI-COVID, ALPS-IP).[2–5] Now, the latest and probably last large trial, the Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), has reported outcomes in 779 adult patients (721 critically ill) hospitalized for COVID-19.[6] Each of these trials individually was underpowered for important clinical endpoints such as all-cause death. Consequently, with the final major randomized trial now reported, we have

undertaken an updated systematic review and meta-analysis of RCTs with the aim to provide the most complete assessment of the safety and efficacy of RAS blockers: (1) in the context of COVID-19 infection (continuation vs. discontinuation trials); and (2) as a treatment for COVID-19 infection (initiation vs. no initiation trials).[2–17]

# Methods

The corresponding author had full access to all the data and takes responsibility for its integrity and the data analysis. The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42023408926 and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary material online, *Appendix S1*).

## Search strategy and selection criteria

We performed a systematic review of RCTs comparing treatment with RAS inhibitors vs. without RAS inhibitors in patients with COVID-19. Two researchers (M.M.Y.L., T.K.) with prior training and experience in meta-analysis techniques independently performed searches and reviewed articles for inclusion. Any conflicts over inclusion were resolved by consensus. Databases (PubMed and Web of Science) and registries (ClinicalTrials.gov) were searched, without language restriction, until 12 April 2023. Our search strategy (Supplementary material online, *Appendix S2*), in brief, included a combination of the following main search terms: [('severe acute respiratory syndrome*' OR 'SARS*' OR 'coronavirus*' OR 'COVID*' OR 'nCoV' OR '2019-nCoV') AND ('renin angiotensin system*' OR 'renin-angiotensin system*' OR 'angiotensin converting enzyme*' OR 'angiotensin-converting enzyme*' OR 'angiotensin*' OR 'ACE inhibitor' OR 'ARB*' OR 'RAS inhibitor' OR 'RAS blocker') AND ('trial' OR 'randomiz*' OR 'randomis*')].

## Eligibility criteria

We included RCTs of any size from any region. We included all patients who had COVID-19 infection from all settings (hospitalized vs. outpatient), irrespective of COVID-19 severity and hypertension status. However, we excluded trials that only had data on other selected groups of patients, e.g. those with transcatheter aortic valve implantation (RASTAVI NCT03201185), to minimize the risk of confounding by indication.[18]

## Outcomes

We extracted data from trials that reported treatment (with either an ACEi or ARB or an ACEi and ARB, separately, where data were available) compared with neither of these treatments and the following outcomes: (i) intensive care unit (ICU) admission; (ii) mechanical ventilation; (iii) vasopressor use; (iv) acute kidney injury (AKI); (v) renal replacement therapy (RRT); (vi) acute myocardial infarction (MI); (vii) stroke or transient ischaemic attack (TIA); (viii) heart failure; (ix) thromboembolic events; and (x) all-cause death, where reported. If multiple AKI outcomes were available, AKI Kidney Disease Improving Global Outcomes stage 2 or higher was analysed.

## Data collection

Two researchers (M.M.Y.L., T.K.) independently extracted data. Any disagreements were resolved by consensus. Information about study design, methodology, and baseline characteristics (age, sex, and co-morbidities) was extracted. A standardized 2 × 2 table proforma was used to extract four key numbers: treated event, treated no event, control event, and control no event. Some trials have not publicly reported results but had data available from a published meta-analysis [ACEI-COVID (stroke outcome only), COVIDMED, PRAETORIAN-COVID, STAR-COVID, and SWITCH-COVID].[19] Additional data for subgroup analyses by severity of COVID-19 were extracted from a published meta-analysis.[19] Outcomes reported in REMAP-CAP were extracted for non-critically ill and critically ill patients, and analyses excluded those assigned to receive ARB + DMX-200 (10 out of 779 randomized).[6] In REMAP-CAP, data for ACEi and ARB groups were combined for analysis, to avoid double counting the control group.

## Statistical analyses

We used the statistical software ReviewManager (RevMan Web Version 4.28.1) to perform a fixed-effects model (inverse variance weighted) meta-analysis. As a sensitivity analysis, we examined a random-effects model to determine the impact of the smaller studies and found no difference in the estimates obtained. We, therefore, present the results of the fixed-effect models. We calculated risk ratios (RRs; and 95% confidence intervals), for the risk of events occurring in the group on treatment with ACEi or ARB vs. the group not on treatment with ACEi or ARB. Forest plots were generated with a risk ratio *X*-axis. Between-trial heterogeneity of treatment effect was examined using the chi-squared ($\chi^2$) test (*Q* test). $I^2$ index values ≤25% indicated low, 26–50% moderate, and >50% a high degree of heterogeneity.

## Subgroup analyses

We analysed all-cause death outcomes (as the most robust and unambiguous outcome) in patient subgroups based on severity of COVID-19, blinding (blinded vs. open-label trials), region, and type of RAS blocker. We tested treatment-by-subgroup heterogeneity of effect using the $\chi^2$ test.

## Assessment of bias

For each study, two researchers (M.M.Y.L., T.K.) independently performed a formal assessment for bias at the outcome level with the validated tool, RoB 2 ('Risk of Bias 2'), for assessing RCTs, as recommended by the Cochrane Collaboration.[20] Funnel plots were used to assess publication bias for all-cause death outcomes.

# Results

## Trials selected

We included 16 RCTs that enrolled a total of 3492 patients (up to 12 April 2023) (*Figure 1*) (Supplementary material online, *Table S1*).[2–17] Six trials assessed continuation vs. discontinuation of RAS blockers; in one of these trials (Najmeddin), the RAS blocker was replaced with amlodipine ± carvedilol. Ten trials assessed initiation vs. no initiation of RAS blockers (five losartan, three telmisartan, one valsartan, and one unspecified ACEi/ARB); the comparator was matching placebo in 5 trials, standard care in 4 trials, and amlodipine in one trial (Nouri-Vaskeh).

## Baseline characteristics

Of the 16 trials included, 3 trials enrolled >700 participants (BRACE-CORONA, CLARITY, and REMAP-CAP), another 2 trials enrolled >200 participants (ACEI-COVID, ALPS-IP), another 3 trials enrolled >100 participants (ALPS-COVID-OP, NCT04355936, REPLACE COVID), and 8 trials enrolled ≤100 participants. Of the 16 trials included, 4 were from the United States of America (USA), 2 from each of Brazil and Iran, and 1 from each of Argentina, Canada, Mexico, and the Netherlands; 4 were multinational trials. Nine trials were open label and 6 trials were blinded; one trial (CLARITY) was both double blind (India) and open label (Australia) according to the enrolling region. A total of 14 trials included only hospitalized patients, 1 trial included only outpatients (ALPS-COVID-OP), and 1 trial (ACEI-COVID) included both inpatients and outpatients. Follow-up ranged from 10 to 30 days, although 60-day data were also available in one trial (COVIDMED). Six studies only included participants with hypertension (BRACE-CORONA, Najmeddin, Nouri-Vaskeh, RAAS-COVID-19, REPLACE COVID, and SWITCH-COVID). More than half of patients in RAAS-COVID-19 and REPLACE COVID had

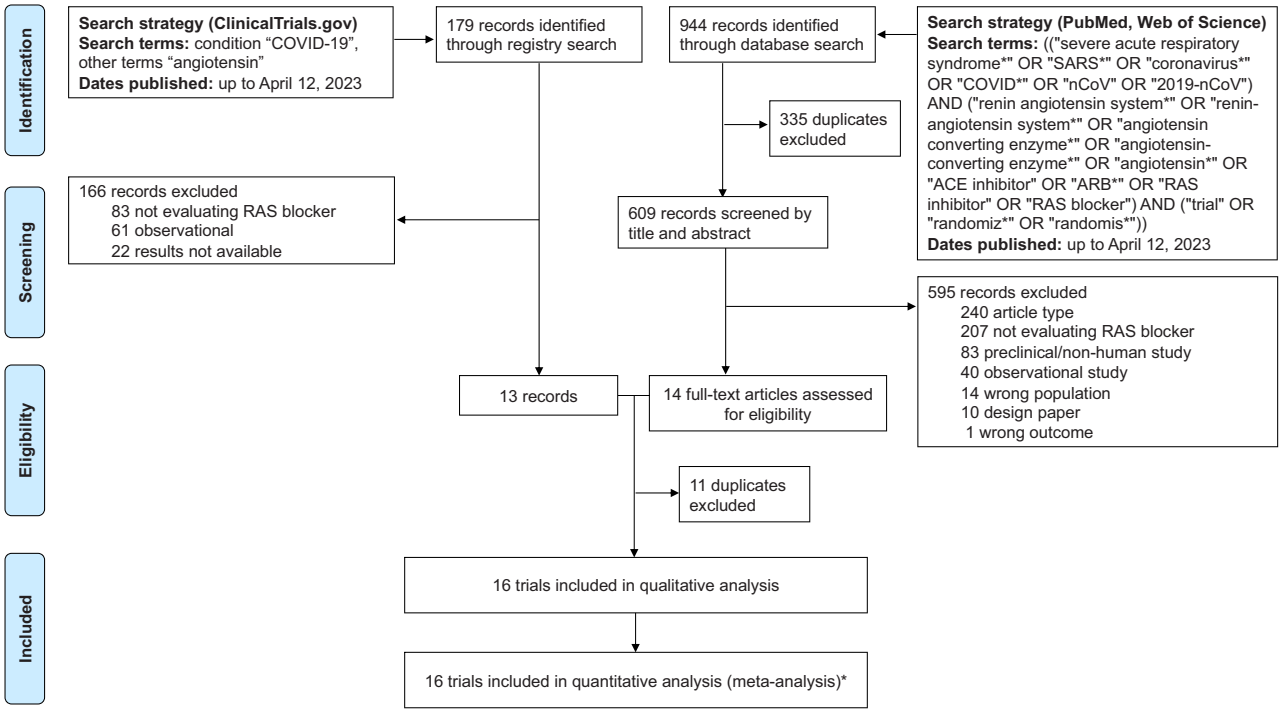


**Figure 1** Study selection (PRISMA flow diagram). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; COVID-19, coronavirus disease 2019; nCoV, novel coronavirus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAS, renin–angiotensin blocker; SARS, severe acute respiratory syndrome. *Data for five trials [ACEI-COVID (stroke outcome), COVIDMED, PRAETORIAN-COVID, STAR-COVID, and SWITCH-COVID] and subgroup analyses by severity of COVID-19 were extracted from a prior meta-analysis.[19]

mild disease (definitions in Supplementary material online, *Table S1*). In contrast, most of those analysed in REMAP-CAP were critically ill, defined as patients receiving respiratory (high-flow nasal oxygen with flow rate ≥30 L/min and fraction of inspired oxygen ≥0.4 or non-invasive or invasive mechanical ventilation) or cardiovascular (vasopressor/inotrope) organ support in an ICU unit.

## Assessment of bias

Most outcomes for most trials had a low or moderate risk of bias except for PRAETORIAN-COVID, STAR-COVID, and SWITCH-COVID, which had a high risk of bias. Our funnel plot for all-cause death (Supplementary material online, *Figure S1*) did not show any asymmetry, suggesting a low risk of publication bias.

## Heterogeneity

Most outcomes had little to no evidence of heterogeneity across trials, but there was moderate heterogeneity for a few individual endpoints, i.e. acute MI (continuation trials), thromboembolic events (continuation trials), and all-cause death (initiation trials) and there was high heterogeneity for one outcome (heart failure in the continuation trials).

## Admission to ICU

In five trials including 477 patients previously treated with an ACEi/ARB, 43/238 (18.1%) participants randomized to continue an ACEi/ARB were admitted to ICU, compared with 46/239 (19.2%) patients randomized to discontinue an ACEi/ARB (RR 0.96, 95% CI 0.66–1.41) (*Figure 2*).

In six trials including 1125 patients not previously treated with an ACEi/ARB, 39/562 (6.9%) participants initiating an ACEi/ARB were admitted to ICU, compared with 52/563 (9.2%) patients not starting these drugs (RR 0.71, 0.47–1.08) (*Figure 2*).

Therefore, in a total of 11 trials, including a total of 1602 patients, 82/800 (10.3%) participants treated with a RAS blocker required ICU admission, compared with 98/802 (12.2%) patients not treated with a RAS blocker (RR 0.84, 0.64–1.11).

## Mechanical ventilation

In six trials including 1136 patients previously treated with an ACEi/ARB, 51/563 (9.1%) participants continuing an ACEi/ARB received mechanical ventilation, compared with 63/573 (11.0%) patients discontinuing these drugs (RR 0.77, 0.55–1.09) (*Figure 3*).

In eight trials including 1866 patients not previously treated with an ACEi/ARB, 178/1017 (17.5%) participants starting an ACEi/ARB received mechanical ventilation, compared with 104/849 (12.2%) patients not starting these drugs (RR 1.12, 0.91–1.38) (*Figure 3*).

Therefore, in a total of 14 trials, including 3002 patients, 229/1580 (14.5%) participants treated with a RAS blocker received mechanical ventilation, compared with 167/1422 (11.7%) patients not treated with a RAS blocker (RR 1.01, 0.85–1.21).

## Vasopressor use

In two trials including 811 patients previously treated with an ACEi/ARB, 32/400 (8.0%) participants continuing an ACEi/ARB received treatment with a vasopressor, compared with 36/411 (8.8%) of those discontinuing an ACEi/ARB (RR 0.92, 0.58–1.44) (*Figure 4*).

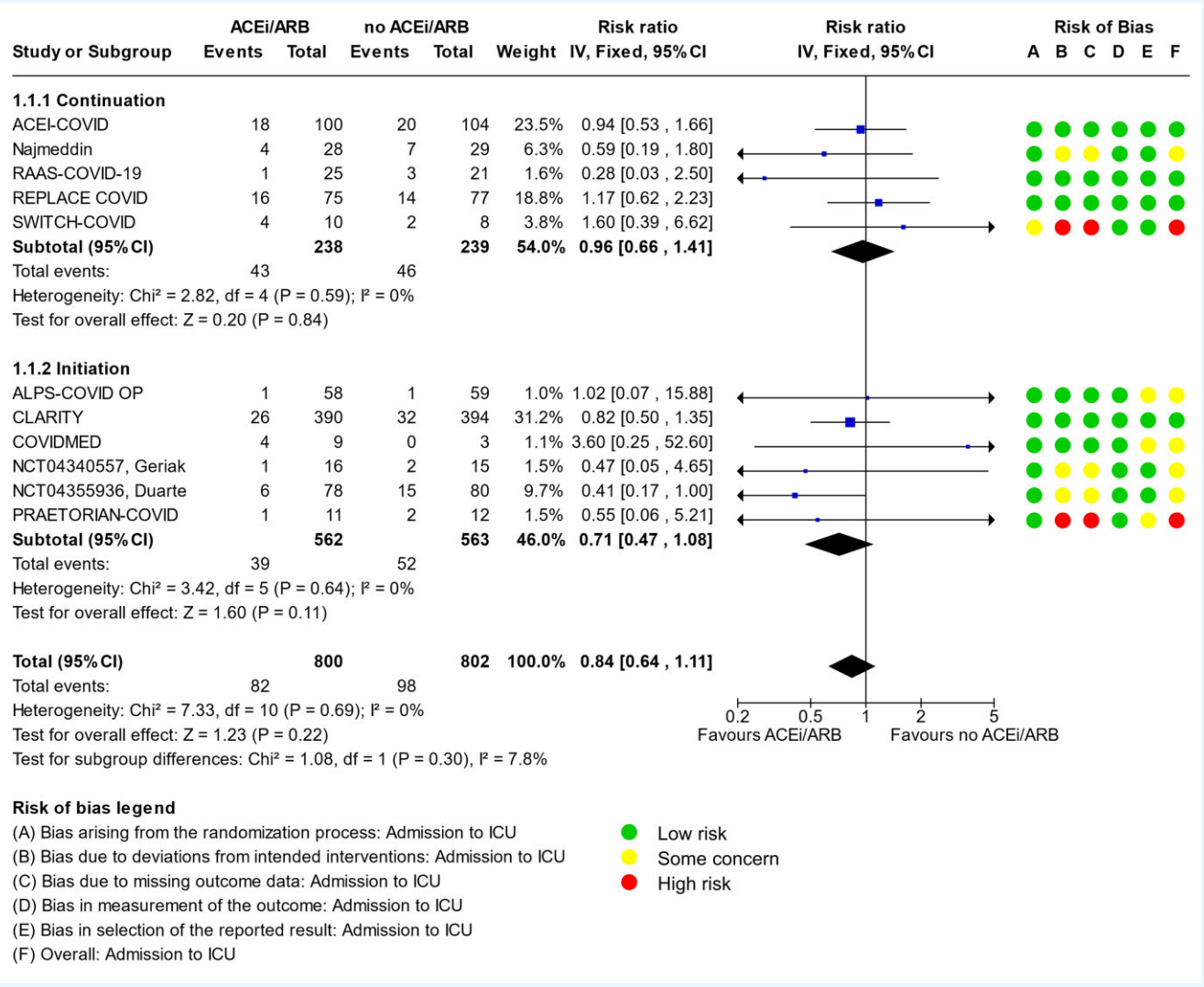


**Figure 2** ICU admission. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; and ICU, intensive care unit. Data source: Gnanenthiran *JAHA* meta-analysis (COVIDMED, PRAETORIAN-COVID, and SWITCH-COVID). Definition: RAAS-COVID-19 (transfer to ICU for invasive ventilation + transfer to ICU for other indications). Time frame: day 30 (NCT04355936).

In three trials including 1625 patients not previously treated with an ACEi/ARB, 184/907 (20.3%) participants starting an ACEi/ARB received treatment with a vasopressor, compared with 85/718 (11.8%) of patients not starting these drugs (RR 1.27, 1.02–1.57) (*Figure 4*).

Therefore, in a total of five trials, including 2436 patients, 216/1307 (16.5%) participants treated with a RAS blocker received treatment with a vasopressor, compared with 121/1129 (10.7%) patients not treated with a RAS blocker (RR 1.19, 0.98–1.45).

## Acute kidney injury

In three trials including 255 patients previously treated with an ACEi/ARB, 8/128 (6.3%) participants continuing a RAS blocker developed AKI, compared with 8/127 (6.3%) patients discontinuing these drugs (RR 1.01, 0.40–2.56) (*Figure 5*).

In two trials including 1478 patients not previously treated with an ACEi/ARB, 77/856 (9.0%) participants starting an ACEi/ARB developed AKI, compared with 42/622 (6.8%) patients not starting these drugs (RR 1.28, 0.89–1.86) (*Figure 5*).

Therefore, in a total of 5 trials, including 1733 patients, 85/984 (8.6%) participants taking a RAS blocker had AKI, compared with 50/749 (6.7%) patients not taking a RAS blocker (RR 1.24, 0.88–1.75).

## Renal replacement therapy

In three trials including 1015 patients previously treated with an ACEi/ARB, 12/500 (2.4%) participants continuing an ACEi/ARB required RRT, compared with 12/515 (2.3%) patients discontinuing these drugs (RR 1.01, 0.46–2.21) (*Figure 6*).

In two trials including 1490 patients not previously treated with an ACEi/ARB, 40/864 (4.6%) participants starting an ACEi/ARB required RRT, compared with 13/626 (2.1%) patients not starting these drugs (RR 1.66, 0.89–3.12) (*Figure 6*).

Therefore, in a total of 5 trials, including 2505 patients, 52/1364 (3.8%) participants treated with a RAS blocker required RRT, compared with 25/1141 (2.2%) patients not treated with a RAS blocker (RR 1.37, 0.84–2.24).

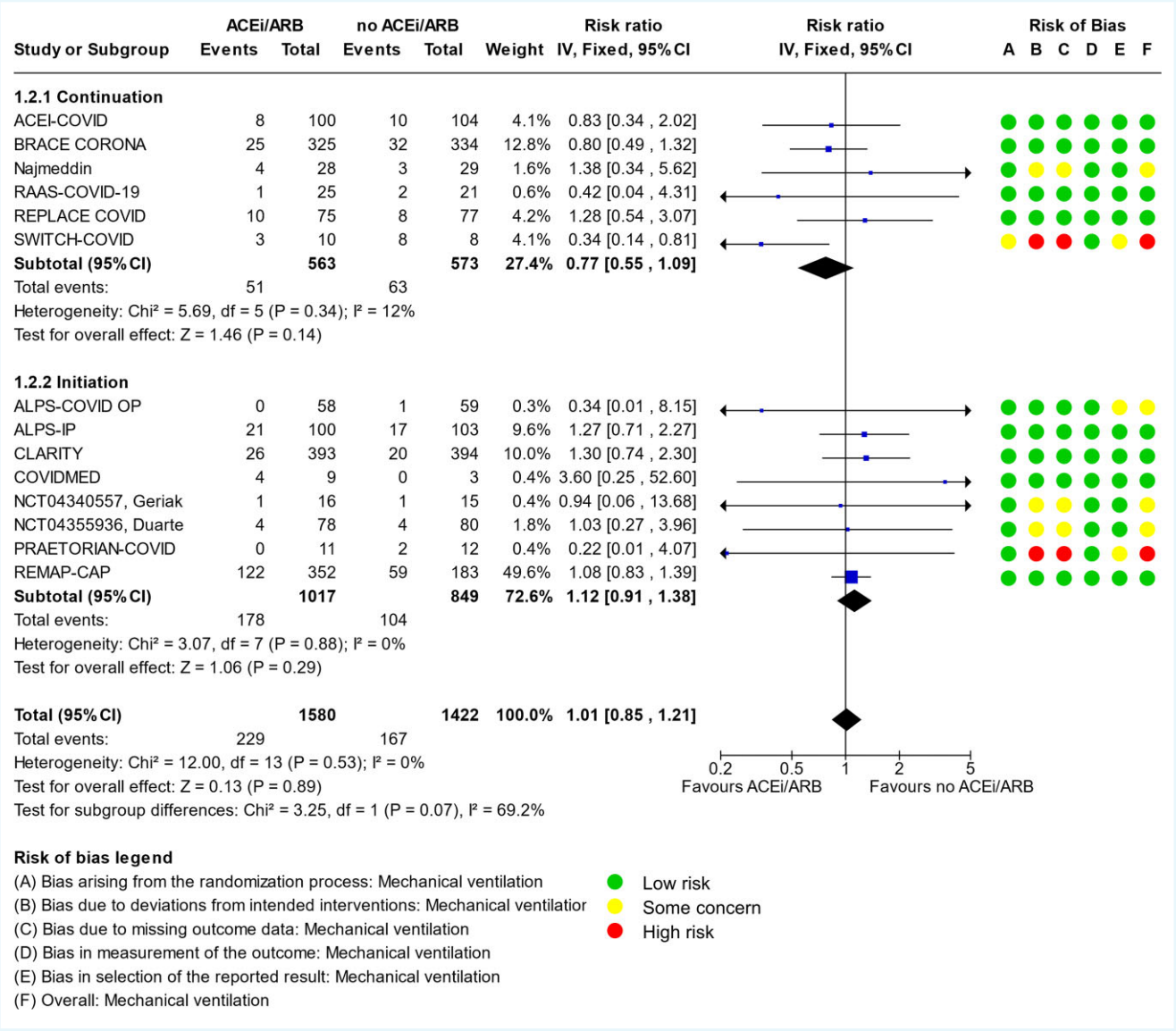


**Figure 3** Mechanical ventilation. ACEi, angiotensin-converting enzyme inhibitor and ARB, angiotensin-receptor blocker. Data source: Gnanenthiran *JAHA* meta-analysis (COVIDMED, PRAETORIAN-COVID, and SWITCH-COVID). Definition: ALPS-IP (required intubation). CLARITY (respiratory failure defined as requirement for non-invasive or invasive mechanical ventilation). Time frame: day 30 (NCT04355936). REMAP-CAP: Non-critically ill and critically ill population. Data for ACEi and ARB groups combined. The denominator corresponds to the number of patients not on ventilation support at baseline.

## Acute MI

In three trials including 857 patients previously treated with an ACEi/ARB, 19/425 (4.5%) participants continuing an ACEi/ARB had an acute MI, compared with 25/432 (5.8%) patients discontinuing an ACEi/ARB (RR 0.72, 0.40–1.30) (Supplementary material online, *Figure S2*).

## Stroke or TIA

In two trials including 863 patients previously treated with an ACEi/ARB, 5/425 (1.2%) participants continuing an ACEi/ARB had a stroke or TIA, compared to 3/438 (0.7%) patients discontinuing an ACEi/ARB (RR 1.46, 0.36–5.98) (Supplementary material online, Supplementary *Figure S3*).

## Heart failure

In three trials including 857 patients previously treated with an ACEi/ARB, 19/425 (4.5%) participants continuing an ACEi/ARB had a heart failure event, compared with 22/432 (5.1%) patients discontinuing an ACEi/ARB (RR 0.97, 0.51–1.84) (Supplementary material online, *Figure S4*).

## Thromboembolic events

In two trials including 811 patients previously treated with an ACEi/ARB, thromboembolic events occurred in 8/400 (2.0%) participants continuing an ACEi/ARB and in 7/411 (1.7%) patients discontinuing an ACEi/ARB (RR 1.07, 0.36–3.19) (*Figure 7*).

In one trial, including 12 patients not previously treated with an ACEi/ARB, 1/9 (11.1%) participants starting an ACEi/ARB had a

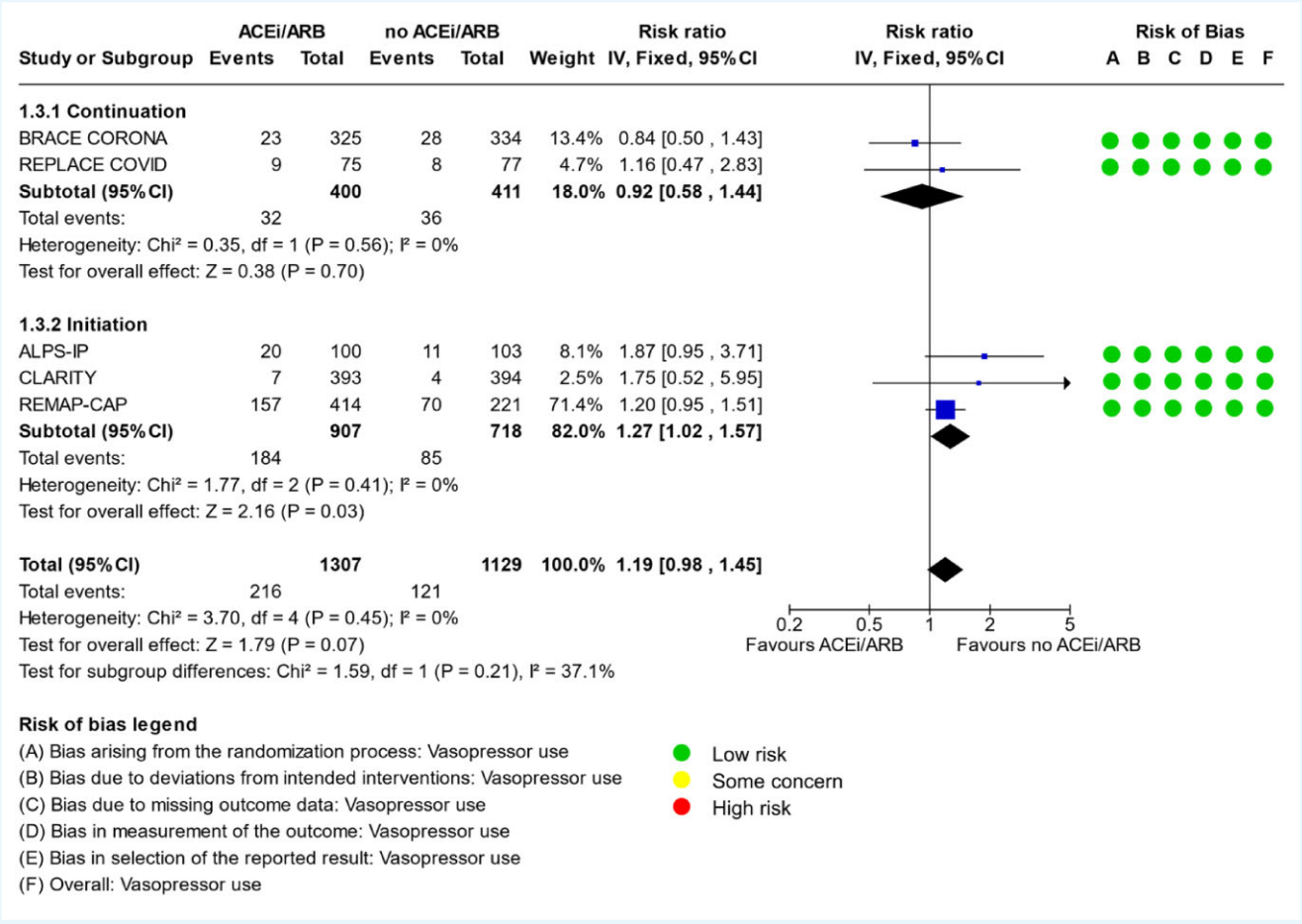


**Figure 4** Vasopressor use. ACEi, angiotensin-converting enzyme inhibitor and ARB, angiotensin-receptor blocker. Definitions: REPLACE COVID (Hypotension requiring hemodynamic support). REMAP-CAP: Non-critically ill and critically ill population. Data for ACEi and ARB groups combined. The denominator corresponds to the number of patients not on vasopressors or inotropes at baseline.

thromboembolic event, compared with 0/3 (0%) patients not starting these drugs (RR 1.20, 0.06–23.70) (*Figure 7*).

Therefore, in a total of three trials, including 823 patients, 9/409 (2.2%) participants taking a RAS blocker had a thromboembolic event, compared with 7/414 (1.7%) patients not taking a RAS blocker (RR 1.09, 0.39–3.02).

## Death from any cause

In 6 trials including 1136 patients previously treated with an ACEi/ARB, 42/563 (7.5%) participants randomized to continue an ACEi/ARB died, compared with 34/573 (5.9%) patients randomized to discontinue these drugs (RR 1.24, 0.80–1.92) (*Figure 8*).

In ten trials, including 2163 patients not previously treated with an ACEi/ARB, 170/1202 (14.1%) participants starting an ACEi/ARB died, compared with 94/961 (9.8%) patients not starting on these drugs (RR 1.22, 0.96–1.55) (*Figure 8*).

Therefore, in a total of 16 trials, including 3299 patients, 212/1765 (12.0%) participants treated with a RAS blocker died, compared with 128/1534 (8.3%) patients not treated with a RAS blocker (RR 1.23, 0.99–1.51).

## Subgroup analyses

Severity of COVID-19: In the ACEi/ARB continuation/discontinuation trials, the RR of death from any causes was 1.33, 0.44–4.00 in patients with mild disease, 1.72, 0.82–3.61 in moderate disease, and 0.83, 0.25–2.76 in severe/critical disease (*P* value for heterogeneity 0.60) (Supplementary material online, *Figure S5*). In the ACEi/ARB initiation trials, the RRs were 0.36, 0.04–3.24, 0.71, 0.30–1.67, and 1.31, 1.01–1.72, respectively (*P* value for heterogeneity 0.22) (Supplementary material online, *Figure S6*).

Blinding: In the ACEi/ARB continuation/discontinuation trials, the RR for all-cause death was 1.24, 0.78–1.97, and 1.29, 0.39–4.33 for open-label and blinded trials, respectively (*P* value for heterogeneity 0.94) (Supplementary material online, *Figure S7*). In the ACEi/ARB initiation trials, the RR (95% CI) for all-cause death was 1.24, 0.96–1.61 vs. 1.09, 0.55–2.15 in open-label and blinded trials, respectively (*P* value for heterogeneity 0.73) (Supplementary material online, *Figure S8*).

Region: The RR of all-cause death in the ACEi/ARB continuation/discontinuation trials was 0.42, 0.04–4.31 in North America, 1.25, 0.55–2.87 in South America, 1.29, 0.39–4.33 in Asia/Pacific, and 1.56, 0.67–3.66 in Europe (*P* value for heterogeneity 0.88) (Supplementary material online, *Figure S9*) and in the ACEi/ARB initiation trials the RRs were 1.21, 0.68–2.17, 0.19, 0.06–0.62, 1.09, 0.47–2.54, and 2.18, 0.23–20.84, respectively (*P* value for heterogeneity 0.04) (Supplementary material online, *Figure S10*).

Type of ACEi/ARB: None of the ACEi/ARB continuation/discontinuation trials analysed the type of ACEi/ARB separately (Supplementary material online, *Figure S11*). In the initiation trials, the RR of all-cause death for ACEi or ARB was 1.37, 1.02–1.83

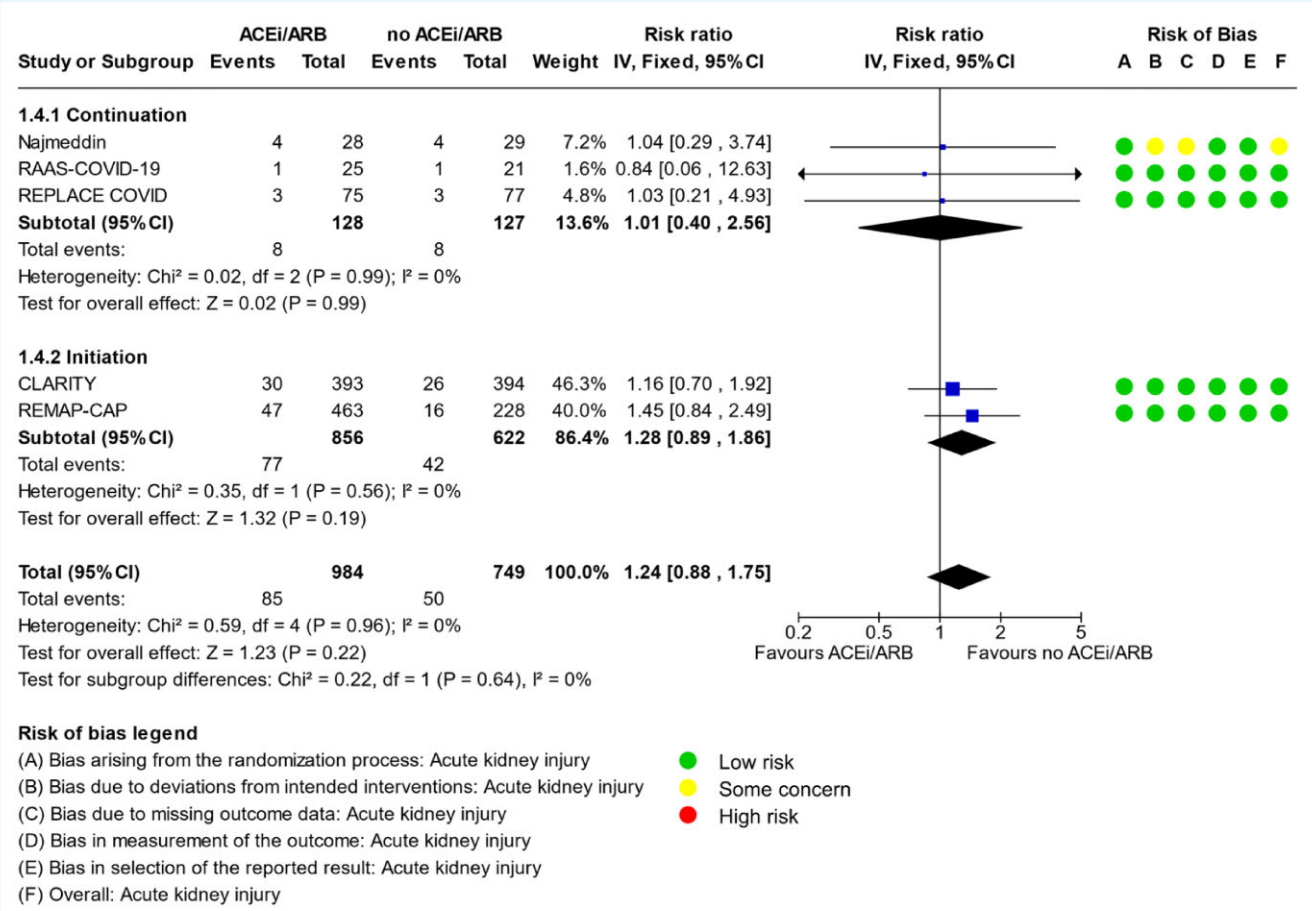


**Figure 5** Acute kidney injury. ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; and KDIGO, Kidney Disease Improving Global Outcomes. Definitions: Najmeddin (KDIGO stage 2 or higher) RAAS-COVID-19 (>40% decline in eGFR or doubling of serum creatinine), REMAP-CAP (AKI KDIGO Stage ≥2 by day 14), REPLACE COVID (>2-fold increase in creatinine). REMAP-CAP: Non-critically ill and critically ill population. Data for ACEi and ARB groups combined.

vs. 0.94, 0.61–1.45 for an ARB (*P* value for heterogeneity 0.16) (Supplementary material online, *Figure S12*).

## Discussion

In this meta-analysis of trials, including approximately 3500 patients with COVID-19, adverse clinical outcomes, overall, were not increased by treatment with a RAS blocker although there was some suggestion of worse outcomes in trials testing initiation of such treatment, compared with the trials randomizing patients to continuation vs. discontinuation of existing RAS blocker treatment, especially in participants who were critically ill.

We examined a wide range of outcomes reflecting the severity of COVID-19 and its complications, including admission to ICU, use of mechanical ventilation, treatment with vasopressors, AKI, RRT, acute myocardial infarction, stroke or transient ischaemic attack, heart failure, and thromboembolic events, none of which was increased significantly in patients assigned to a RAS blocker when all trials were combined. However, in the RAS blocker initiation trials, there was an increased use of vasopressor therapy (RR 1.27, 1.02–1.57), which contrasted with the pooled RAS blocker continuation/discontinuation trials, where there was no increase in vasopressor use (RR 0.92, 0.58–1.44). Several of the other outcomes listed also showed numerical increases in risk in the initiation trials compared to the continuation/discontinuation trials, although these differences were not statistically significant in the former, in contrast to vasopressor use.

Overall, mortality was not significantly greater among patients treated with a RAS blocker, with a total of 340 deaths from any cause, although, in patients with severe/critical COVID-19, the initiation of a RAS blocker was associated with an increased risk of death (RR 1.31, 1.01–1.72).

These findings must be interpreted in relation to both trial design and the heterogeneity of patients included. Some trials included only people with hypertension (BRACE-CORONA, Najmeddin, Nouri-Vaskeh, RAAS-COVID-19, REPLACE COVID, and SWITCH-COVID). While most trials included hospitalized patients, two trials included outpatients (ACEI-COVID, ALPS-COVID-OP). Particularly importantly, the initiation vs. discontinuation/continuation trials were likely to have included fundamentally distinct populations by design; i.e. the latter trials enrolled patients proven to tolerate this type of treatment. Furthermore, patients with a range of COVID-19 disease severity were included, e.g. more than half had mild disease in RAAS-COVID-19 and REPLACE COVID, while most analysed in REMAP-CAP were

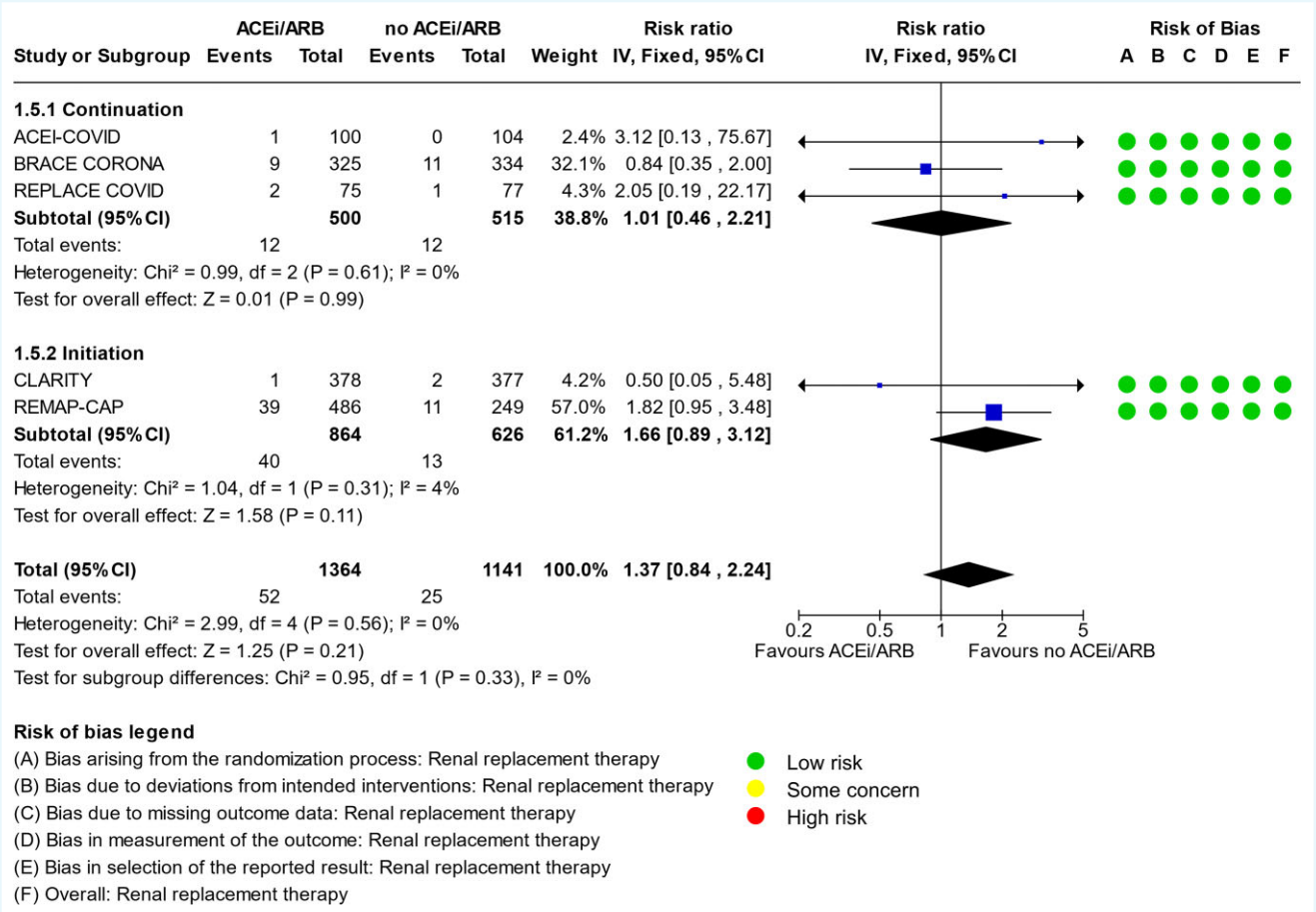


**Figure 6** Renal replacement therapy. ACEi, angiotensin-converting enzyme inhibitor and ARB, angiotensin-receptor blocker. Definitions: CLARITY (dialysis). REMAP-CAP: Non-critically ill and critically ill population. Data for ACEi and ARB groups combined.

critically ill. Because REMAP-CAP was a large treatment-initiation trial, its results strongly influenced the trend to worse outcomes in patients randomized to starting a RAS blocker. Moreover, in CLARITY, another large treatment-initiation trial, the primary outcome of COVID-19 disease severity [modified World Health Organization (WHO) Clinical Progression Scale (ordinal scale with seven categories) at day 14] was worse in patients who received ARBs compared with placebo (98% probability of worse severity scores). This was not an outcome included in the meta-analysis because it was not reported uniformly in the other trials (modified WHO 8-point scale in REMAP-CAP; WHO COVID-19 ordinal endpoint $\geq$6 in Najmeddin). By day 28, there was no clear between-group difference in this outcome.

Because this meta-analysis includes the latest and probably last major randomized trial (REMAP-CAP), the data included are likely to form the basis of future clinical decision-making regarding the use of RAS blockers in patients with COVID-19 as, to our knowledge, there will likely be no further large RCTs in this area.[6] This meta-analysis shows that there is no benefit from initiating a RAS blocker as a treatment for COVID-19. However, it is safe to continue existing RAS blocker therapy in non-critically ill patients with an indication for such treatment. There is also probably no harm in initiating RAS blockers in non-critically ill patients if there is a good indication to do so, although this is unlikely to be needed very often during active COVID-19 infection. Conversely, the results of this meta-analysis suggest that RAS blockers should not be started in patients with critical illness caused by COVID-19 because this treatment is more likely to cause harm than provide benefit. Critically ill patients are more vulnerable to hypotension and kidney dysfunction, which may be precipitated or aggravated by RAS blockers, including in the setting of COVID-19 infection. Indeed, in some healthcare systems, withdrawal of these agents is recommended in critically ill patients, although these recommendations are based on limited empirical evidence.[21] Although there are observational data suggesting worse outcomes in patients with non-COVID-19 critical illness treated with RAS blockers, some other observational studies suggest the opposite with improved outcomes with RAS blockers among patients with sepsis or pneumonia.[22–24] Therefore, our findings are unlikely to reflect harm specific to COVID-19 infection as opposed to critical illness more generally. These concerns are likely to be even greater with the new initiation of an ACEi or ARB in RAS blocker-naïve patients than with the continuation of such treatment in patients proven to tolerate it.

Overall, the data from these trials seem to disprove the hypothesis that infection with the SARS-CoV-2 virus leads to excess and unopposed angiotensin II production causing lung injury. While this is likely true, systemic administration of an ACEi or ARB may not be the best or even an adequate method of blocking local pulmonary production and activity of angiotensin II. Also, local replacement of ACE2 or angiotensin (1–7) might, theoretically, be more protective than systemic RAS blockade.[25,26] Two investigational RAS agents (TXA-127, a synthetic angiotensin (1-7), and TRV-027, a beta-arrestin

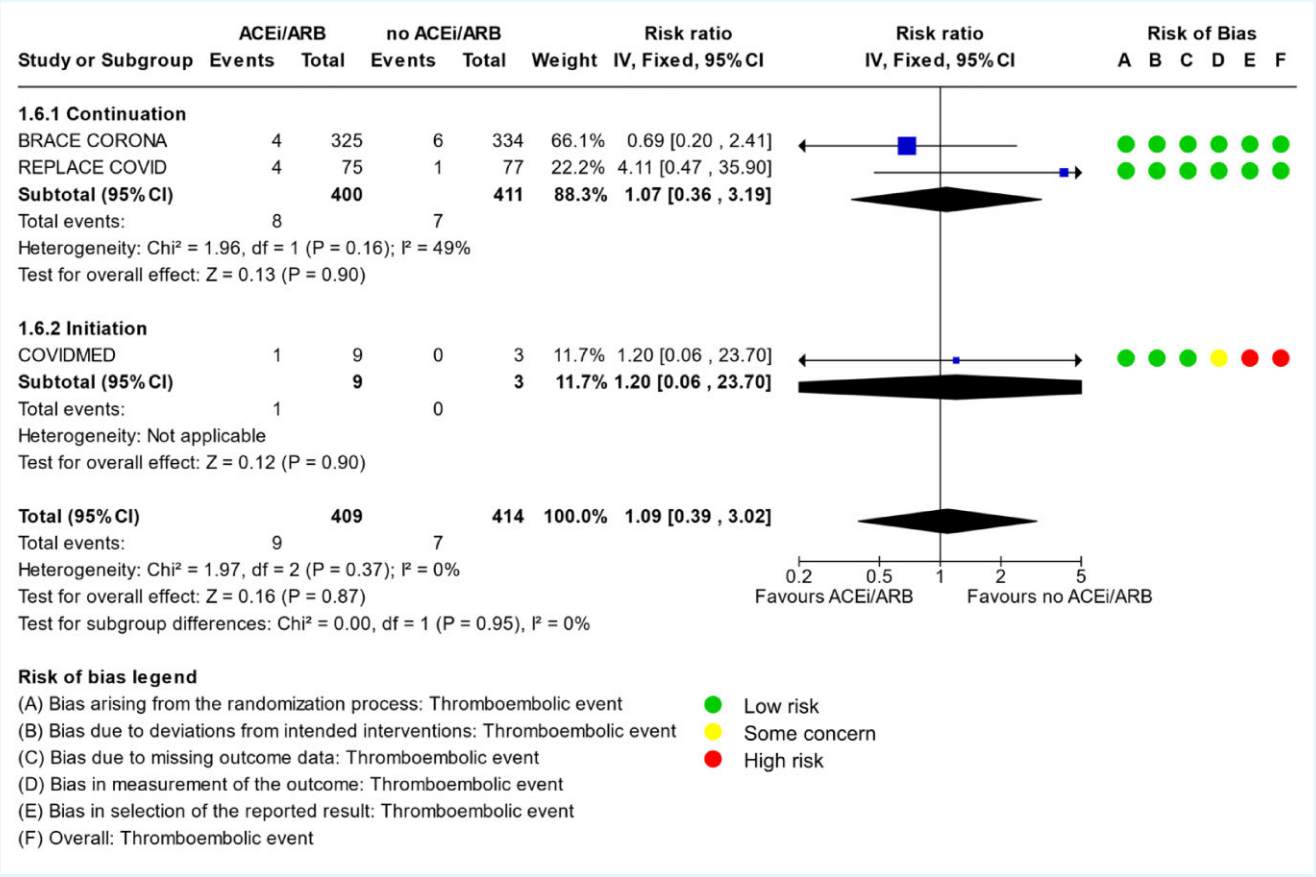


**Figure 7** Thromboembolic event. ACEi, angiotensin-converting enzyme inhibitor and ARB, angiotensin-receptor blocker. Data source: Gnanenthiran JAHA meta-analysis (COVIDMED). Definitions: REPLACE COVID (pulmonary embolism or deep vein thrombosis). Due to heterogeneity with fixed-effects model (as shown above), sensitivity analysis with random-effects model: continuation (RR 1.34, 0.24–7.30), overall (RR 1.09, 0.39–3.02).

biased ligand of the angiotensin II type 1 receptor) were tested in two trials in the ACTIV-4 programme.[27] Both trials were stopped early due to a low probability (<5%) of efficacy with a trend towards inferiority compared with placebo.

## Limitations

We did not have individual patient data and could not adjust for differences between patients treated and not treated with RAS blockers, especially in comorbidity. We did not have data on the dose of ACEi or ARB. Half of the trials (8 of 16) were small, enrolling fewer than a hundred patients. Further, overall event numbers were modest. Results were presented for patients with and without cardiovascular disease. The proportion of patients with cardiovascular disease varied in each study (Supplementary material online, *Table S1*). The threshold for ICU admission and ventilation is likely to vary between institutions and countries. We also obtained data for five trials, and for subgroup analyses by severity of COVID-19, from a prior meta-analysis.[19] Several registered trials have not reported results, although many of these have been terminated (due to futility or difficulties with recruitment or funding), and one ongoing trial (COVID-RASi NCT04591210) has significantly extended recruitment timelines by >2 years (updated estimated study completion in December 2024).[28–33] Several trials were terminated prematurely (COVIDMED, PRAETORIAN-COVID, REMAP-CAP, STAR-COVID, and SWITCH-COVID). Power to detect modest effects is limited especially in the continuation vs. discontinuation trials, with wide confidence intervals. Although moderate between-study heterogeneity was seen, i.e. 38% for all-cause death among the initiation trials, sensitivity analyses with random-effects models showed similar results. Multiplicity of data can affect the findings of our systematic review and meta-analysis, which reported 10 outcomes and 4 subgroups, although these were all pre-specified.[34]

## Conclusion

This is the largest and most up-to-date meta-analysis, examining 10 clinical outcomes in almost 3500 patients enrolled in 16 RCTs. Prior meta-analyses included non-randomized observational studies, reported fewer outcomes, included selected patients (i.e. hypertension, hospitalized), or did not analyse by design (continuation vs. discontinuation or initiation vs. no initiation).[35–38]

Our meta-analysis provides reassurance for physicians and patients that ACEis and ARBs are safe to continue in patients with non-severe COVID-19 infection where clinically indicated. This is relevant to millions of patients with hypertension, diabetes, and cardiovascular and renal diseases treated with RAS blockers worldwide since COVID-19 is likely to be endemic for the foreseeable future. On the other hand, the findings clearly do not support initiating RAS blockers for the treatment of COVID-19, *per se*, and to do so may be harmful in patients with severe COVID-19 infection.

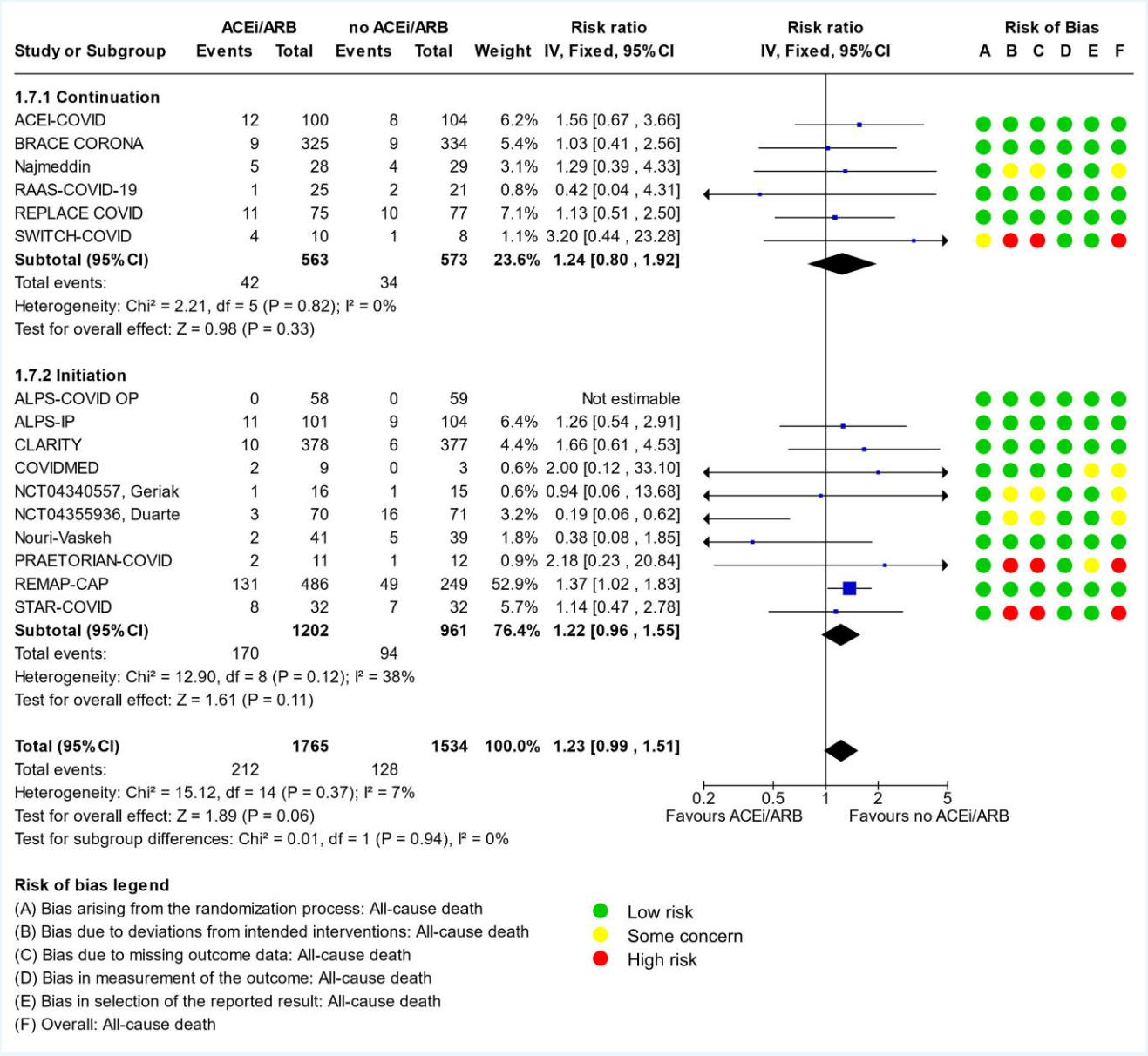


**Figure 8** All-cause death. ACEi, angiotensin-converting enzyme inhibitor and ARB, angiotensin-receptor blocker. Data source: Gnanenthiran JAHA meta-analysis (COVIDMED, PRAETORIAN-COVID, STAR-COVID). Timeframe: In-hospital (REMAP-CAP), 30 days (BRACE CORONA, NCT04355936). REMAP-CAP: Non-critically ill and critically ill population. Data for ACEi and ARB groups combined. Due to heterogeneity with fixed-effects model (as shown above), sensitivity analysis with random-effects model: initiation (RR 1.03, 0.66–1.61), overall (RR 1.18, 0.92–1.52).

# Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

## Author contributions

M.M.Y.L., MBChB, PhD (Formal analysis [Co-lead]; Writing—original draft [Co-lead]), T.K., MD, PhD (Formal analysis [Co-lead]; Writing—original draft [Co-lead]), R.T.C., PhD (Writing—review & editing [Equal]), M.C.P., MBChB (Writing—review & editing [Equal]), N.S., MD, PhD (Writing—review & editing [Equal]), S.D.S., MD (Writing—review & editing [Equal]), M.V., MD, MPH (Writing—review & editing [Equal]), P.S.J., MBChB, MSc, PhD (Writing—review & editing [Equal]), and J.J.V.M., MD (Supervision [Lead]; Writing—original draft [Co-lead]).

## Data availability

All supporting data are available within the article and its online supplementary files.

**Conflict of interest:** M.M.Y.L. reported receiving grants through his employer, the University of Glasgow, from AstraZeneca, Boehringer Ingelheim, and Roche Diagnostics, serving on a clinical endpoint committee for Bayer, and serving on a steering committee for Cytokinetics. T.K. reported receiving speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol Myers

Squibb, Boehringer Ingelheim, and Abiomed. T.K. reported receiving grants from the Uehara Memorial Foundation and the Japanese Heart Failure Society Tsuchiya Foundation for the research activities at the University of Glasgow. R.T.C. has received consultancy honoraria from Bayer and speaking honoraria from AstraZeneca. M.C.P. has received research grants or consultancy fees from SQ Innovations, AstraZeneca, Roche, Boehringer Ingelheim, Pharmacosmos, Eli Lilly, Napp Pharmaceuticals, Novartis, and Novo Nordisk and has served on committees for AbbVie, Akero, Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Resverlogix, Teikoku, New Amsterdam, and Novo Nordisk. He is a Director of Global Clinical Trial Partners. N.S. has consulted for or received lecture fees from Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi. He has received grant support from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics through his institution, the University of Glasgow. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, NeuroTronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi Sankyo, GlaxoSmithKline, Lilly, Merck, MyoKardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi Pasteur, DiNAQOR, Tremeau, CellProthera, Moderna, American Regent, and Sarepta. M.V. has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. P.S.J. reports speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals, and Intas Pharma; advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; and research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc., and Roche Diagnostics. His employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk. He is a Director Global Clinical Trial Partners. J.J.V.M. reports payments through Glasgow University from work on clinical trials, consulting, and other activities from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, KBP Biosciences, and Novartis. Personal consultancy fees from Alnylam Pharmaceuticals, Bayer, BMS, George Clinical Pty Ltd, Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, and River 2 Renal Corporation. He has received personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica health, Intas Pharma, J.B. Chemicals & Pharmaceuticals Ltd, Lupin Pharma, Medscape/Heart.Org, and ProAdWise. He has received honoraria for communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, and Translational Medicine Academy. He is a Director of Global Clinical Trial Partners Ltd.

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