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Antiplatelet agents for the treatment of adults with COVID-19 (Review)

Fischer AL, Messer S, Riera R, Martimbianco ALC, Stegemann M, Estcourt LJ, Weibel S, Monsef I, Andreas M, Pacheco RL, Skoetz N

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Antiplatelet agents for the treatment of adults with COVID-19 (Review)

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[Intervention Review]

Antiplatelet agents for the treatment of adults with COVID-19

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ABSTRACT

Background

Severe coronavirus disease 2019 (COVID-19) can cause thrombotic events that lead to severe complications or death. Antiplatelet agents, such as acetylsalicylic acid, have been shown to effectively reduce thrombotic events in other diseases: they could influence the course of COVID-19 in general.

Objectives

To assess the efficacy and safety of antiplatelets given with standard care compared to no treatment or standard care (with/without placebo) for adults with COVID-19.

Search methods

We searched the Cochrane COVID-19 Study Register (which comprises MEDLINE (PubMed), Embase, ClinicalTrials.gov, WHO ICTRP, medRxiv, CENTRAL), Web of Science, WHO COVID-19 Global literature on coronavirus disease and the Epistemonikos COVID-19 L*OVE Platform to identify completed and ongoing studies without language restrictions to December 2022.

Selection criteria

We followed standard Cochrane methodology. We included randomised controlled trials (RCTs) evaluating antiplatelet agents for the treatment of COVID-19 in adults with COVID-19, irrespective of disease severity, gender or ethnicity.

Data collection and analysis

We followed standard Cochrane methodology.

To assess bias in included studies, we used the Cochrane risk of bias tool (RoB 2) for RCTs. We rated the certainty of evidence using the GRADE approach for the outcomes.

Main results

Antiplatelets plus standard care versus standard care (with/without placebo)

Adults with a confirmed diagnosis of moderate to severe COVID-19

We included four studies (17,541 participants) that recruited hospitalised people with a confirmed diagnosis of moderate to severe COVID-19. A total of 8964 participants were analysed in the antiplatelet arm (either with cyclooxygenase inhibitors or P2Y12 inhibitors) and 8577 participants in the control arm. Most people were older than 50 years and had comorbidities such as hypertension, lung disease or diabetes. The studies were conducted in high- to lower middle-income countries prior to wide-scale vaccination programmes.

Antiplatelets compared to standard care:

- probably result in little to no difference in 28-day mortality (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.85 to 1.05; 3 studies, 17,249 participants; moderate-certainty evidence). In absolute terms, this means that for every 177 deaths per 1000 people not receiving antiplatelets, there were 168 deaths per 1000 people who did receive the intervention (95% CI 151 to 186 per 1000 people);
- probably result in little to no difference in worsening (new need for invasive mechanical ventilation or death up to day 28) (RR 0.95, 95% CI 0.90 to 1.01; 2 studies, 15,266 participants; moderate-certainty evidence);
- probably result in little to no difference in improvement (participants discharged alive up to day 28) (RR 1.00, 95% CI 0.96 to 1.04; 2 studies, 15,454 participants; moderate-certainty evidence);
- probably result in a slight reduction of thrombotic events at longest follow-up (RR 0.90, 95% CI 0.80 to 1.02; 4 studies, 17,518 participants; moderate-certainty evidence);
- may result in a slight increase in serious adverse events at longest follow-up (Peto odds ratio (OR) 1.57, 95% CI 0.48 to 5.14; 1 study, 1815 participants; low-certainty evidence), but non-serious adverse events during study treatment were not reported;
- probably increase the occurrence of major bleeding events at longest follow-up (Peto OR 1.68, 95% CI 1.29 to 2.19; 4 studies, 17,527 participants; moderate-certainty evidence).

Adults with a confirmed diagnosis of asymptomatic SARS-CoV-2 infection or mild COVID-19

We included two RCTs allocating participants, of whom 4209 had confirmed mild COVID-19 and were not hospitalised. A total of 2109 participants were analysed in the antiplatelet arm (treated with acetylsalicylic acid) and 2100 participants in the control arm. No study included people with asymptomatic SARS-CoV-2 infection.

Antiplatelets compared to standard care:

- may result in little to no difference in all-cause mortality at day 45 (Peto OR 1.00, 95% CI 0.45 to 2.22; 2 studies, 4209 participants; low-certainty evidence);
- may slightly decrease the incidence of new thrombotic events up to day 45 (Peto OR 0.37, 95% CI 0.09 to 1.46; 2 studies, 4209 participants; low-certainty evidence);
- may make little or no difference to the incidence of serious adverse events up to day 45 (Peto OR 1.00, 95% CI 0.60 to 1.64; 1 study, 3881 participants; low-certainty evidence), but non-serious adverse events were not reported.

The evidence is very uncertain about the effect of antiplatelets on the following outcomes (compared to standard care plus placebo):

- admission to hospital or death up to day 45 (Peto OR 0.79, 95% CI 0.57 to 1.10; 2 studies, 4209 participants; very low-certainty evidence);
- major bleeding events up to longest follow-up (no event occurred in 328 participants; very low-certainty evidence).

Quality of life and adverse events during study treatment were not reported.

Authors' conclusions

In people with confirmed or suspected COVID-19 and moderate to severe disease, we found moderate-certainty evidence that antiplatelets probably result in little to no difference in 28-day mortality, clinical worsening or improvement, but probably result in a slight reduction in thrombotic events. They probably increase the occurrence of major bleeding events. Low-certainty evidence suggests that antiplatelets may result in a slight increase in serious adverse events.

In people with confirmed COVID-19 and mild symptoms, we found low-certainty evidence that antiplatelets may result in little to no difference in 45-day mortality and serious adverse events, and may slightly reduce thrombotic events. The effects on the combined outcome admission to hospital or death up to day 45 and major bleeding events are very uncertain. Quality of life was not reported.

Included studies were conducted in high- to lower middle-income settings using antiplatelets prior to vaccination roll-outs.

We identified a lack of evidence concerning quality of life assessments, adverse events and people with asymptomatic infection. The 14 ongoing and three completed, unpublished RCTs that we identified in trial registries address similar settings and research questions as in the current body of evidence. We expect to incorporate the findings of these studies in future versions of this review.

PLAIN LANGUAGE SUMMARY

Are antiplatelets an effective treatment for people with COVID-19?

Key messages

Antiplatelets are a group of different medicines that can prevent potentially fatal clot formation in the blood vessels ('thrombotic events'). For hospitalised patients with COVID-19, they probably slightly reduce thrombotic events but probably do not affect deaths, clinical worsening or improvement in COVID-19 compared with placebo or standard care.

However, antiplatelets may result in a slight increase in serious unwanted effects ('adverse events') and probably increase major bleeding.

Similarly, in non-hospitalised people, antiplatelets slightly decrease thrombotic events. They may result in little to no difference in deaths or serious unwanted effects, however the evidence on admission to hospital or death and major bleeding events is very uncertain.

There are 14 further studies that have not completed yet, and the results of three other completed studies are not yet available.

What are antiplatelets?

Antiplatelets are a group of drugs which, in different ways, stop blood from changing to a gel-like substance called a clot, which we mean by the term 'thrombotic events'. They are taken mainly by mouth, usually by people who are at high risk of developing a clot (people who have already experienced or who tend to build up a clot).

A clot could lead to a stroke, coronary heart disease, poor blood circulation in the legs, thromboses in the legs or clot obstruction ('embolism') in the lung circulation that could lead to shortness of breath, heart failure and death.

How might antiplatelets treat COVID-19?

People with COVID-19 might be at risk from blood clots. Antiplatelets prevent clots from forming in the body, and this could in turn prevent complications that lead to death and clinical deterioration.

What did we want to find out?

We wanted to know whether antiplatelets in addition to usual care are effective for adults with COVID-19, when compared to usual care with or without a placebo (a treatment that looks and tastes the same as the study drug but with no active ingredient), and whether they cause unwanted effects. We were particularly interested in:

- number of deaths from any cause up to 28 days after treatment, or longer if reported;
- whether people got better or worse after treatment (including unwanted effects of the disease itself, like thrombotic events);
- unwanted effects of the treatment (especially major bleeding).

What did we do?

We searched for studies that reported on people with COVID-19 who received antiplatelets together with usual care, or usual care alone (with/without placebo). We summarised the results of the studies and rated our confidence in the evidence, based on common criteria about the reliability of the evidence.

What did we find?

We identified four studies, including 17,541 people with moderate to severe COVID-19 (hospitalised). Of these, one compared acetylsalicylic acid (aspirin) with usual care, two studies compared 'P2Y12 inhibitors' (e.g. clopidogrel, prasugrel, ticagrelor) with usual care, and a fourth one compared either acetylsalicylic acid or P2Y12 inhibitors with usual care. The studies included people with a confirmed or suspected diagnosis of SARS-CoV-2 infection. Two studies compared acetylsalicylic acid to placebo in 4209 non-hospitalised people with confirmed mild COVID-19.

We also found 14 ongoing studies, two studies without published results and another that had been withdrawn after a preprint version. We found no studies that included people with COVID-19 infection but no symptoms.

Main results

Antiplatelets:

- probably make little or no difference to deaths by 28 or 180 days, worsening up to day 28 (new invasive mechanical ventilation or death) or improvement (discharged alive) up to day 28, and they probably slightly decrease thrombotic events;
- may result in a slight increase in serious unwanted effects and probably increase major bleeding events.

In people not in hospital, with mild disease, antiplatelets may result in little to no difference in death within 45 days, or in the incidence of serious adverse events, and they may slightly decrease the incidence of thrombotic events. The evidence for these participants is very uncertain about the effects on worsening (hospitalisation or death within 45 days) and on major bleeding events. Studies did not report on quality of life and general unwanted effects.

What are the limitations of the evidence?

The studies were conducted in populations from high- to middle-income countries, many of them prior to the roll-out of COVID-19 vaccination programmes and before Omicron became the most prevalent variant. We have moderate confidence in the evidence for mortality, worsening/improvement up to day 28, and major bleeding events or thrombotic events in hospitalised people. We have low confidence in the evidence for the effects on serious unwanted effects, because they occurred rarely. For non-hospitalised people, our confidence in the evidence is low for the effects on death, thrombotic events and serious adverse events, and very low for the effects on worsening and major bleeding events (those events were rare and the time period between symptom onset and treatment was long). Information about other unwanted effects and quality of life was not available.

How up-to-date is this evidence?

Our evidence is up-to-date to 22 December 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Antiplatelets in hospitalised adults with moderate to severe COVID-19

Antiplatelets (plus standard care) compared to standard care (with/without placebo) in hospitalised adults with COVID-19 (moderate to severe disease)

Patient or population: hospitalised adults with COVID-19 (moderate to severe disease)

Setting: inpatients

Intervention: antiplatelets (plus standard care)

Comparison: standard care (with/without placebo)

| Outcomes | Estimated absolute effects ^a (95% CI) | | Relative effect (95% CI) | Nº of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|--|--|--|--------------------------------|-----------------------------------|-----------------------------------|---|
| | Risk with standard care (with/without placebo) | Risk with antiplatelets (plus standard care) | | | | |
| 28-day all-cause mortality | 177 per 1000 | 168 per 1000 (151 to 186) | RR 0.95 (0.85 to 1.05) | 17,249 ^{b,c} (3 RCTs) | ⊕⊕⊕⊖ Moderated ^d | Antiplatelets probably result in little to no difference in mortality up to day 28. |
| Worsening up to day 28: participants with new need for invasive mechanical ventilation or death | 230 per 1000 | 218 per 1000 (207 to 232) | RR 0.95 (0.90 to 1.01) | 15,266 (2 RCTs) | ⊕⊕⊕⊖ Moderated ^d | Antiplatelets probably result in little to no difference in worsening up to day 28. |
| Improvement up to day 28: participants discharged alive | 743 per 1000 | 743 per 1000 (714 to 773) | RR 1.00 (0.96 to 1.04) | 15,454 (2 RCTs) | ⊕⊕⊕⊖ Moderated ^d | Antiplatelets probably result in little to no difference in improvement up to day 28. |
| Thrombotic events at longest follow-up* | 57 per 1000 | 52 per 1000 (46 to 58) | RR 0.90 (0.80 to 1.02) | 17,518 (4 RCTs) | ⊕⊕⊕⊖ Moderated ^d | Antiplatelets probably result in a slight reduction in thrombotic events. |
| Serious adverse events at longest follow-up** | 5 per 1000 | 7 per 1000 (2 to 24) | Peto OR 1.57 (0.48 to 5.14) | 1815 (1 RCT) | ⊕⊕⊕⊖ Low ^e | Antiplatelets may result in a slight increase in serious adverse events. |
| Adverse events during study treatment | Not reported | — | — | — | — | We did not identify any study reporting this outcome. |

| | | | | | | |
|--|-------------|---------------------------|--------------------------------|--------------------|--------------------------------|--|
| Major bleeding events at longest follow-up*** | 10 per 1000 | 16 per 1000 (12 to 21) | Peto OR 1.68 (1.29 to 2.19) | 17,527 (4 RCTs) | ⊕⊕⊕⊖ Moderated ^d | Antiplatelets probably increase the occurrence of major bleeding events. |
|--|-------------|---------------------------|--------------------------------|--------------------|--------------------------------|--|

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio, RCT: randomised controlled trial, RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aThe risk in the control group was assumed from the pooled effects of the control group from included studies; the intervention risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bAdditionally, there was a study with 292 participants reporting all-cause mortality at longest follow-up (RR 1.11, 95% CI 0.75 to 1.64) ([Bohula 2022 \(COVID-PACT\)](#)). We did not include this study in the meta-analysis due to an unclear duration of follow-up and high risk of bias.

^c[REMAP-CAP 2022](#) reported 180-day mortality in a second publication. Treatment with antiplatelets may result in little to no difference in 180-day mortality (RR 0.97, 95% CI 0.82 to 1.15; 1,312 participants; low-certainty evidence).

^dDowngraded one level for serious risk of bias: in [Horby 2021 \(RECOVERY\)](#), an open-label study, 10% in the intervention group did not receive acetylsalicylic acid; in the open-label study [Bohula 2022 \(COVID-PACT\)](#), where 30% in the intervention group discontinued the intervention, the co-intervention (therapeutic or prophylactic anticoagulation) showed a high level of discontinuation or cross-over.

^eDowngraded two levels for very serious imprecision: only one out of three studies contributed data, with very low event rates and a very wide CI.

*The time frames for 'the longest follow-up' were 28 days ([Berger 2022](#); [Bohula 2022 \(COVID-PACT\)](#); [Horby 2021 \(RECOVERY\)](#)) or unclear ([REMAP-CAP 2022](#)).

**The time frames for 'the longest follow-up' were reported for up to 28 days in three studies ([Berger 2022](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)).

***The time frames for 'the longest follow-up' were reported for up to 28 days in three studies ([Berger 2022](#); [Horby 2021 \(RECOVERY\)](#)). The longest follow-up in [REMAP-CAP 2022](#) for major bleeding was 14 days.

Summary of findings 2. Antiplatelets in non-hospitalised adults with COVID-19

Antiplatelets in non-hospitalised adults with asymptomatic infection or mild COVID-19

Patient or population: non-hospitalised adults with mild COVID-19

Setting: outpatients

Intervention: antiplatelets (plus standard care)

Comparison: standard care plus placebo

| Outcomes | Estimated absolute effects ^a (95% CI) | Relative effect (95% CI) | Nº of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|----------|--|--------------------------|------------------------------|-----------------------------------|----------|
|----------|--|--------------------------|------------------------------|-----------------------------------|----------|

| | Risk with placebo (plus standard care) | Risk with antiplatelets (plus standard care) | | | | |
|--|--|--|-----------------------------|---------------|------------------------------|--|
| All-cause mortality at day 45 | 6 per 1000 | 6 per 1000 (3 to 13) | Peto OR 1.00 (0.45 to 2.22) | 4209 (2 RCTs) | ⊕⊕⊕⊕ Low ^b | Antiplatelets may result in little to no difference in all-cause mortality. |
| Admission to hospital or death up to day 45 | 39 per 1000 | 31 per 1000 (23 to 43) | Peto OR 0.79 (0.57 to 1.10) | 4209 (2 RCTs) | ⊕⊕⊕⊕ Very low ^{b,c} | The evidence is very uncertain about the effect of antiplatelets on admission to hospital or death up to day 45. |
| Quality of life up to longest follow-up* | Not reported | — | — | — | — | We did not identify any study reporting this outcome. |
| Thrombotic events up to day 45 | 3 per 1000 | 1 per 1000 (0 to 4) | Peto OR 0.37 (0.09 to 1.46) | 4209 (2 RCTs) | ⊕⊕⊕⊕ Low ^b | Antiplatelets may slightly decrease the incidence of new thrombotic events. |
| Adverse events during study treatment | Not reported | — | — | — | — | We did not identify any study reporting this outcome. |
| Serious adverse events up to day 45 | 16 per 1000 | 16 per 1000 (10 to 26) | Peto OR 1.00 (0.60 to 1.64) | 3881 (1 RCT) | ⊕⊕⊕⊕ Low ^b | Antiplatelets may make little or no difference to the incidence of serious adverse events. |
| Major bleeding events up to longest follow-up** | There was no major bleeding or clinically relevant non-major bleeding event among all participants of the study (same number of participants in each group). | | Not estimable | 328 (1 RCT) | ⊕⊕⊕⊕ Very low ^d | The evidence is very uncertain about the effect of antiplatelets on the incidence of new major bleeding events. |

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; RCT: randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aThe risk in the control group was assumed from the pooled effects of the control groups from included studies; the intervention risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bDowngraded two levels due to very serious imprecision: low number of events and wide CI.

^cDowngraded one level due to serious indirectness (one study reports death only due to cardiovascular events, the other study includes major thrombosis in this outcome definition).



^dDowngraded three levels due to extremely serious imprecision; low sample size/number of events; only one RCT reporting this outcome.

*The time frame for 'at longest follow-up' in [REMAP-CAP 2022](#) was at day 180.

**The time frame for 'at longest follow-up' in [Connors 2021 \(ACTIV-4B\)](#) and [Eikelboom 2022 \(ACTCOVID\)](#) was up to 45 days. [Connors 2021 \(ACTIV-4B\)](#) reported data after an additional 30-day safety follow-up.

BACKGROUND

This work is part of a series of Cochrane reviews investigating treatments and therapies for coronavirus disease 2019 (COVID-19). Reviews of this series share information in the background section and methodology based on the first published reviews about monoclonal antibodies ([Kreuzberger 2021](#)) and convalescent plasma ([Iannizzi 2023](#)), and are part of the German research project 'CEOsys' (COVID-19 evidence-ecosystem; [CEOsys](#)).

Description of the condition

COVID-19 is a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; [WHO2021a](#)). On 22 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Despite intensive international efforts to contain its spread, as of April 2022, COVID-19 has resulted in more than 753 million confirmed cases and over 6.8 million deaths worldwide ([WHO 2023](#)), and estimated global all-age excess mortality is much higher ([COVID-19 Excess Mortality Collaborators](#)). Several vaccines against COVID-19 have been distributed across countries and more than an additional hundred vaccine candidates are in development ([WHO 2022c](#)). As of February 2023, 13 billion vaccinations could be registered worldwide ([WHO 2023](#)).

Specific risk factors for severe disease, hospitalisation and mortality have been identified: individuals aged 65 years or older, smokers and those with certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease or diabetes mellitus are more likely to have severe courses of the disease ([Huang 2020](#); [Liang 2020](#); [WHO2021a](#); [Williamson 2020](#)). COVID-19 case fatality varies widely between countries and reporting periods (from 0.1% to more than 19%; [Johns Hopkins 2021](#)). However, these numbers may be misleading due to varying testing frequency, lag in reporting dates, incomplete capturing of all cases and variations in case definitions since the beginning of the pandemic.

The median incubation period is estimated to be between five and six days. 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure ([Lauer 2020](#)). Sore throat, cough, fever, headache, fatigue and myalgia or arthralgia are the most commonly reported symptoms ([Struyf 2020](#)). Other symptoms include dyspnoea, chills, nausea or vomiting, diarrhoea, loss of taste and smell and nasal congestion ([WHO2021a](#)). The majority of infected people have mild symptoms (approximately 80%, [Wu 2020](#)) or remain completely asymptomatic ([Buitrago-Garcia 2020](#)). A smaller proportion (approximately 14%) are affected by severe or critical disease, with intensive care unit (ICU) admittance due to respiratory failure, septic shock or multiple organ dysfunction ([Wu 2020](#)). Moreover, there is an elevated risk of thrombotic complications in hospitalised COVID-19 patients ([Cui 2020](#)) and COVID-19 patients in the ICU ([Klok 2020](#)). A meta-analysis suggests that about 2 in 10 COVID-19 patients (mostly those treated in hospital) develop pulmonary embolism ([Liao 2020](#)). Numbers for deep vein thrombosis are similarly high ([Middeldorp 2020](#)). Furthermore, the high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia is confirmed ([Al Duhailib 2022](#); [Bompard 2020](#); [Katsoularis 2022](#); [Klok 2020](#)).

Nowadays, several drugs for the treatment of COVID-19 are available, mostly for patients with severe or critical disease (e.g. corticosteroids, remdesivir, tocilizumab, baricitinib) ([Ghosh 2021](#); [Grundeis 2023](#); [Kramer 2022](#); [Wagner 2022](#)), which are recommended in clinical guidelines ([WHO living guideline 2023](#)). For patients with mild disease and risk factors for severe disease, nirmatrelvir/ritonavir is available ([Reis 2022](#)). In addition, treatment consists of supportive care with oxygen supply in moderately severe cases, and non-invasive ventilation, high-flow nasal cannula therapy or even invasive mechanical ventilation, as well as prone positioning, and sometimes extracorporeal membrane oxygenation, in very severe cases ([WHO 2021e](#)).

Description of the intervention

In the early pandemic, retrospective assessments showed a potential benefit of pre-diagnosis acetylsalicylic acid treatment on 30-day mortality ([Osborne 2021](#)). As thrombotic macroangiopathy (e.g. deep vein thrombosis, ischaemic stroke, acute myocardial infarction or lung artery emboly) and microangiopathy (microangiopathic pulmonary dysfunction) can substantially influence the course of COVID-19 ([Menter 2020](#)), preventing those events could reduce the burden on our healthcare systems, i.e. hospitalisation, clinical deterioration or death.

Antiplatelets are a group of drugs, administered via oral, rectal or intravenous routes, which inhibit platelet aggregation through different mechanisms of action ([Eikelboom 2012](#)). Based on the mechanism of action, antiplatelets can be classified as follows ([Hashemzadeh 2008](#); [Krötz 2008](#)).

- Platelet aggregation inhibitors: cyclooxygenase inhibitors as acetylsalicylic acid (brand name: Aspirin® and others) and adenosine diphosphate (ADP) receptor/P2Y12 inhibitors (clopidogrel, ticlopidine, prasugrel, cangrelor and elinogrel)
- Glycoprotein IIb/IIIa platelet inhibitors (abciximab, eptifibatide and tirofiban)
- Protease-activated receptor-1 antagonists (vorapaxar)
- Others: nucleoside transport inhibitors interfering with cyclic adenosine monophosphate (dipyridamole and cilostazol)

Antiplatelets have been used as prophylactic or therapeutic interventions for a number of conditions, such as: primary and secondary cardiovascular prevention of acute ischaemic stroke ([Sandercock 2014](#)); coronary heart disease (acute coronary syndromes or stented coronaries), initially even with dual platelet aggregation inhibition ([Khan 2020](#)); and intermittent claudication ([Wong 2011](#)), amongst others ([Minhas 2022](#)).

The most common adverse events related to antiplatelet medications are bleeding events (upper gastrointestinal bleeding, ecchymosis, haematuria, epistaxis) acetylsalicylic acid-induced asthma, nasal polyps, thrombocytopenia ([Kalyanasundaram 2011](#)), and renal dysfunction ([Awtry 2000](#)).

How the intervention might work

Acetylsalicylic acid is the most widely used antiplatelet agent and acts by irreversibly inhibiting the activity of the cyclooxygenase enzyme (COX) during the synthesis of prostaglandin H₂, a precursor of thromboxane A₂ and prostaglandin I₂ (prostacyclin). Thromboxane A₂ induces platelet aggregation and vasoconstriction (COX-1 mediates its production),

and prostaglandin I₂ inhibits platelet aggregation and induces vasodilatation (mediated by COX-2). Acetylsalicylic acid at low doses (75 mg to 150 mg) completely or partially blocks COX-1, thus inhibiting the production of thromboxane A₂, while high doses inhibit COX-2 (Warner 2011). This could be the clue to reducing thromboembolic outcomes associated with COVID-19 (in microscopic small as well as in huge vessels) and might at the same time reduce the hyperinflammatory reaction to viral infection. It has been suggested that the SARS-CoV-2 virus uses platelets to modulate the immune responses, including the circulation of platelet-neutrophil aggregates, contributing to the hypercoagulability state observed in severe COVID-19 patients (Najm 2021). Acetylsalicylic acid, with the brand name Aspirin®, is available as both oral tablets or rectal suppository, or as an intravenously applicable medication if the patient cannot take the drug orally.

ADP receptor/P2Y₁₂ inhibitors are another group of antiplatelet drugs that includes thienopyridines (clopidogrel, ticagrelor, prasugrel and cangrelor) and cyclo-pentyltriazolo-pyrimidines (ticagrelor, cangrelor and elinogrel). They block phosphoinositide hydrolysis, thromboxane A₂ formation, protein phosphorylation and inhibit the increase in cytosolic Ca⁺⁺, which is usually the result of ADP receptor activation and a major mechanism of platelet activation (Kunapuli 2003). ADP receptor/P2Y₁₂ inhibitors bind the ADP-P2Y₁₂ receptor on the surface of platelets and inhibit activation of the glycoprotein IIb/IIIa receptor complex. This receptor complex plays an important role in platelet aggregation and thrombus formation (Al-Abdouh 2022). Other studies have shown that in addition to their antithrombotic properties, P2Y₁₂ inhibitors, particularly ticagrelor, can reduce inflammation; other beneficial effects have been reported in experimental models and in clinical inflammatory diseases, including sepsis and acute lung injury (Berger 2022).

The antithrombotic properties especially, but also the anti-inflammatory properties, of antiplatelets could be a valuable approach in the treatment of COVID-19.

Why it is important to do this review

The burden of thrombotic events in individuals with COVID-19 is high, which warrants effective treatments and prevention. There is still a lack of information regarding treatment of COVID-19. Antiplatelets are low-cost interventions that might be especially useful in low-resource settings. Therefore, the evidence from this review is needed in order to effectively decrease the burden of COVID-19.

OBJECTIVES

To assess the efficacy and safety of antiplatelets given with standard care compared to no treatment or standard care (with/without placebo) for adults with COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on the standard template of the Cochrane Haematology review group and is in line with a series of Cochrane Reviews investigating treatments and therapies

for COVID-19, mostly written under the auspices of [CEOsys](#). Specific adaptations related to the research question were made if necessary; for this review we added thrombotic and bleeding events to our core outcome set, but we did not use those outcomes to determine whether to include a trial or not. The protocol for this review was registered with the international prospective register of systematic reviews (PROSPERO) ([Piechotta 2021](#)).

To assess the effectiveness and safety of antiplatelets for the treatment of COVID-19, we included randomised controlled trials (RCTs), as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly controlled therapeutic settings. We used the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2021a](#)). We had planned to also accept cross-over RCT designs, but we would have only considered results from the first period before cross-over because COVID-19 is not a chronic condition and its exact course and long-term effects are yet to be defined.

We excluded cluster-RCTs, controlled non-randomised studies of interventions and observational studies. We also excluded animal studies, pharmacokinetic studies and in vitro studies.

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions and outcomes.

- Full-text publications
- Preprint versions
- Abstract publications
- Results published in trials registries

We included preprints and conference abstracts to have a complete overview of the ongoing research activity, especially for tracking newly emerging studies about antiplatelets in COVID-19. We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included adults with a confirmed diagnosis of COVID-19 (as described in the studies) and we did not exclude any studies based on gender, ethnicity, disease severity or setting.

We excluded studies that evaluate antiplatelets for the treatment of other coronavirus diseases such as SARS (severe acute respiratory syndrome) or MERS (Middle East respiratory syndrome), or other viral diseases, such as influenza. If studies enrolled populations with or exposed to mixed viral diseases, we had planned to only include these if trial authors provided subgroup data for SARS-CoV-2 infection. We excluded studies investigating antiplatelets for long-COVID treatment.

Types of interventions

We considered the following comparisons.

- Antiplatelets with standard care versus standard care (with/without placebo).
- Antiplatelets with standard care versus active treatment with standard care.
- Different formulations, doses, schedules of antiplatelets.

Antiplatelets, in any dose or duration of treatment, alone or in combination with other interventions, provided that it has been

possible to assess the effects of the antiplatelet agent alone (similar co-interventions in the compared groups). We allowed any co-interventions, including supportive care, anticoagulants, anti-viral drugs and corticosteroids, for example. Studies comparing different formulations, doses, schedules of antiplatelets were also included. Co-interventions were allowed, but must have been comparable between intervention groups.

We excluded studies with the following comparison.

- Antiplatelets with standard care in combination with active treatment A versus another active treatment (treatment B, e.g. monoclonal antibodies (mAbs)).

Types of outcome measures

We included studies evaluating antiplatelets for the treatment of COVID-19 independently of reported outcomes.

We evaluated core outcomes based on the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2021; Marshall 2020), and additional outcomes that have been prioritised by consumer representatives and the German guideline panel for therapy of hospitalised people with COVID-19.

We defined outcome sets for two populations. Those are: (i) hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, and (ii) ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to the WHO Clinical Progression Scale (Marshall 2020).

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Effectiveness of antiplatelets

Prioritised outcomes (included in the summary of findings tables)

- All-cause mortality up to day 28, day 60, time-to-event, and up to the longest follow-up.
- Clinical status at day 28, day 60, and up to the longest follow-up, including:
 - worsening of clinical status
 - participants with clinical deterioration (new need for invasive mechanical ventilation) or death up to day 28;
 - improvement of clinical status
 - participants discharged alive up to day 28.
- Any thrombotic event up to longest follow-up (e.g. pulmonary embolism, deep vein thrombosis, venous thromboembolism, myocardial infarction, extracorporeal membrane oxygenation (ECMO) or dialyse filter clotting).

Safety of antiplatelets

- Serious adverse events at longest follow-up available during the study period, defined as number of participants with any serious event.
- Adverse events (any grade) during study treatment during the study period, defined as number of participants with any event.
- Major bleeding up to longest follow-up defined by fulfilment of at least one of the following three criteria:
 - fatal haemorrhagic events; and/or
 - bleeding in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular,

pericardial, intramuscular with compartment syndrome); and/or

- a decrease in haemoglobin concentration of ≥ 2 g/dL, or requirement of a transfusion of two or more units of blood.

Additional outcomes (not included in the summary of findings tables)

- Time-to-event mortality data: mortality up to longest follow-up.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-Quality of life-100 (WHOQOL-100)) at up to seven days, up to 28 days and longest follow-up available.
- Duration of hospitalisation, or time to discharge from hospital.
- Admission to the intensive care unit (ICU).
- Ventilator-free days; ventilator-free defined as WHO Clinical Progression Scale ≤ 6 for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e. WHO ≥ 7).
- Need for new dialysis (up to 28 days).

Individuals with a confirmed diagnosis of asymptomatic SARS-CoV-2 infection or mild disease

Effectiveness of antiplatelets

Prioritised outcomes (included in the summary of findings tables)

- All-cause mortality at day 28, day 60, time-to-event and up to the longest follow-up.
- Admission to hospital or death within 45 days, day 60, time-to-event and up to the longest follow-up.
- Symptom resolution:
 - All initial symptoms resolved (asymptomatic) at day 14, day 28 and up to the longest follow-up.
 - Duration to symptom resolution.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days and the longest follow-up available.
- Any thrombotic event (e.g. pulmonary embolism, deep vein thrombosis, venous thromboembolism, myocardial infarction, ECMO or dialyse filter clotting) up to the longest follow-up

Safety of antiplatelets

- Serious adverse events at longest follow-up available during the study period, defined as the number of participants with any serious event.
- Adverse events (any grade) during study treatment during the study period, defined as number of participants with any event.
- Major bleeding defined by fulfilment of at least one of the following three criteria:
 - fatal haemorrhagic events; and/or
 - bleeding in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome); and/or
 - a decrease in haemoglobin concentration of ≥ 2 g/dL, or requirement of a transfusion of two or more units of blood.

Additional outcomes (not included in the summary of findings tables)

- Time to symptom onset.
- Length of hospital stay and time to discharge, for the subgroup of participants hospitalised during the course of the disease.

- Admission to the intensive care unit (ICU).

Timing of outcome measurement

In the case of time-to-event analysis, e.g. for all-cause mortality (survival) or time to discharge from hospital, we included the outcome measure based on the longest follow-up time. We also collected information on outcomes from all other time points reported in the publications (for example, [REMAP-CAP 2022](#) also reported 90-day mortality).

We included adverse events occurring during active treatment and included long-term adverse events as well. If sufficient data were available, we grouped the measurement time points of eligible outcomes, for example, adverse events and serious adverse events, into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (up to 15 days after treatment) and longer-term outcomes (more than 30 days after treatment).

Search methods for identification of studies

Electronic searches

Our Information Specialist (IM) conducted systematic searches, which were reviewed by another Information Specialist, in the following sources from inception. Following a living systematic review approach, six searches were conducted between 28 April 2021 and 22 December 2022 (date of the last search for all databases), with no restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
 - MEDLINE (PubMed), weekly updates
 - Embase.com, weekly updates
 - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates
 - World Health Organization International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/), weekly updates
 - medRxiv (www.medrxiv.org), weekly updates
 - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates
- Web of Science Core Collection:
 - Science Citation Index Expanded (from 1945)
 - Emerging Sources Citation Index (from 2015)
- WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)
- Epistemonikos COVID-19 L*OVE Platform (app.iloveevidence.com/loves)

For detailed search strategies, see [Appendix 1](#).

Searching other resources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies, relevant systematic reviews and meta-analyses. In addition, we contacted the investigators of included studies to obtain additional information on the retrieved studies. In addition, we searched current treatment guidelines for further literature.

We searched for grey literature, which we defined as searching trials registers such as ClinicalTrials.gov and WHO ICTRP contained in

the CCSR, as well as searching preprint servers and grey literature indexes contained in the CCSR and the WHO COVID-10 Global Literature database.

Once we established our set of included studies, we searched for preprints via Europe PMC, to check if any preprints for ongoing studies were published since our database search. We also compared our identified studies with results from projects that aim to track COVID-19 intervention research, i.e. www.covid-trials.org and covid-nma.com/dataviz.

Data collection and analysis

In multi-arm studies, we extracted and analysed only the antiplatelet domain groups to avoid arbitrary omission of relevant groups and double-counting of participants. As we found no relevant differences in the outcomes between acetylsalicylic acid and P2Y12 inhibitors, and no other types of antiplatelets contributed to our outcomes, we decided to merge the antiplatelet groups.

Selection of studies

Two out of four review authors (AF, NS, MA, SM) independently screened the results of the search strategies for eligibility for this review by reading the abstracts using EndNote software ([EndNote 2013](#)). We coded the abstracts as either 'include' or 'exclude'. In the case of disagreement or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two out of three review authors (AF, NS, MA) assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted a third review author (VP) to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement ([Moher 2009](#)), and showed the total numbers of retrieved references and the numbers of included and excluded studies. We listed all studies that we excluded after full-text assessment and the reasons for their exclusion in the [Characteristics of excluded studies](#) section.

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane ([Li 2021](#)). Two out of three review authors (ALF, MA, SM) extracted data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel ([Microsoft 2018](#)). The data selection form was piloted (in other projects under the auspices of [CEOs](#)) to ensure consistency in the process of data extraction. We solved disagreements by discussion. If no agreement was obtained, a third review author was involved to solve the disagreement. We found only English-language trials, so none of them had to be translated.

Two out of three review authors (ALF, MA, SM) independently assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias. If the review authors were unable to reach a consensus, a third review author was consulted.

We extracted the following information if reported.

- General information: author, title, source, publication date, country, language, duplicate publications

- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, severity of disease, previous treatments, concurrent treatments and standard care, complementary medicine (e.g. quercetin, elderberry, zinc)
- Interventions: dose, frequency, timing, duration and route of administration, setting (e.g. hospitalised, non-hospitalised), duration of follow-up
- Control intervention: placebo, no treatment; dose, frequency, timing, duration and route of administration, setting, duration of follow-up.
- Outcomes: as specified under [Types of outcome measures](#)
- Risk of bias assessment: study design, confounding, definition of risk estimates, selection bias, attrition bias, detection bias, reporting bias

Assessment of risk of bias in included studies

We used the Risk of Bias 2 (RoB 2) tool to analyse the risk of bias of study results ([Sterne 2019](#)). Of interest for this review is the effect of the assignment to the intervention (the intention-to-treat (ITT) effect), thus we performed all assessments with RoB 2 on this effect. The outcomes that we assessed are those specified for inclusion in the summary of findings table.

Two out of five review authors (ALM, ALF, MA, RR, SM) independently assessed the risk of bias for each outcome. In case of discrepancies amongst their judgements and inability to reach consensus, we consulted a third review author to reach a final decision. We assessed the following types of bias, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2021b](#)).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias we used the signalling questions recommended in RoB 2 and made a judgement using the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- 'Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- 'Probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to allow any judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

Subsequently, we derived an overall risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result, or we judge the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (available from riskofbias.info) and stored and presented our detailed RoB 2 assessments as supplementary online material: <https://zenodo.org/record/7637454>.

We made the risk of bias assessments between November 2021 and January 2023 (November 2021: [Connors 2021 \(ACTIV-4B\)](#), [Horby 2021 \(RECOVERY\)](#); January 2022: [Berger 2022](#); March 2022: [REMAP-CAP 2022](#); January 2023: [Bohula 2022 \(COVID-PACT\)](#), [Eikelboom 2022 \(ACTCOVID\)](#), [REMAP-CAP 2022](#)).

Measures of treatment effect

For dichotomous outcomes, we recorded the number of events and total number of participants in both treatment and control groups. We reported the pooled risk ratio (RR) with a 95% confidence interval (CI) ([Higgins 2021c](#)). If the number of observed events was small (less than 5% of sample per group), and if studies had a balanced number of participants in all treatment groups, we reported the Peto odds ratio (OR) with 95% CI ([Higgins 2021c](#)).

We extracted hazard ratios (HRs) for time-to-event outcomes (e.g. time to death). If HRs were not available, we made every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney ([Parmar 1998](#); [Tierney 2007](#)). If sufficient studies provided HRs, we used HRs rather than RRs or mean differences (MDs) in a meta-analysis, as they provide more information. As only [REMAP-CAP 2022](#) reported the 90-day-mortality data, we decided to present mortality data as a dichotomous outcome for day 28, to use a common mortality outcome parameter and to report time-to-event data narratively.

For continuous outcomes, we recorded the mean, standard deviation and total number of participants in both treatment and control groups. Where continuous outcomes used the same scale, we would have performed analyses using the MD with 95% CIs. For continuous outcomes measured with different scales, we had planned to perform analyses using the standardised mean difference (SMD). To interpret SMDs, we would have re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale ([Marshall 2020](#))).

Unit of analysis issues

The aim of this review is to summarise trials that analyse data at the level of the individual participant. We collated multiple reports of one study so that the study, and not the report, is the unit of analysis. As COVID-19 is an acute condition, in case of cross-over trials, we would have included only data from the first period to avoid double counting of participants or events. However, we did not identify cross-over trials.

We analysed the time points as reported in the section [Types of outcome measures](#).

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021d), for studies with multiple treatment groups of the same intervention (i.e. different agent, dose, route of administration), we evaluated arms separately and compared with the common comparator. For pair-wise meta-analysis, we split the 'shared' group into two or more groups with smaller sample sizes, and included two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants was divided, and for continuous outcomes, the total number of participants would have been divided with unchanged means and SDs.

Dealing with missing data

Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we took into account: at study level, at outcome level and at summary data level (Higgins 2021c). At all levels, it is important to differentiate between data 'missing at random', which may often be unbiased, and 'not missing at random', which may bias study and thus review results.

If data were missing, we requested these data from the principal investigators (i.e. we contacted Bohula 2022 (COVID-PACT); Horby 2021 (RECOVERY); NCT04363840; NCT04483960; NCT04808895; REMAP-CAP 2022). We received responses from Dr Peto regarding the Horby 2021 (RECOVERY) trial, from Dr Baird-zars regarding the Bohula 2022 (COVID-PACT) trial and from Dr Lau regarding the NCT04363840 trial. If, after this, data were still missing, we had to make explicit assumptions of any methods the included studies used.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials by visual inspection of our forest plots and using a Chi² test with a significance level at $P < 0.1$. We used the I^2 statistic and visual examination to assess possible heterogeneity (I^2 statistic 30% to 75% taken to signify moderate heterogeneity, I^2 statistic $> 75\%$ taken to signify considerable heterogeneity; Higgins 2021c). If heterogeneity was suspected to be high, we had planned to explore potential causes through sensitivity and subgroup analyses. If we could not find a reason for heterogeneity, we would not have performed a meta-analysis, but planned to comment on results from all studies and present these in tables.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed trials that have not been published elsewhere, to minimise or determine publication bias. We intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019), but we found fewer than 10 trials and therefore could not perform this test. We would have considered $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analysis. We performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c). We analysed trials including different severities of disease separately, grouping them into mild (non-hospitalised), and moderate to severely ill (hospitalised), as these are different populations in different settings, resulting in differing outcomes (see [Types of outcome measures](#)). We treated placebo and no treatment as the same intervention, as well as standard care at different institutions and time points.

We used the Review Manager Web (RevMan Web) software for analyses (RevMan Web 2022). One out of three review authors (VP, ALF, SM) entered the data into the software, and a second review author (AM, SM, ALF) checked the data for accuracy. We used the random-effects model for the analyses as we anticipated that true effects are related, but are not the same for included studies. We used a fixed-effect model for the Peto OR. If we could not perform a meta-analysis we commented on the results, with the results from all studies presented in tables or narratively. If meta-analysis was possible, we assessed the effects of potential biases in sensitivity analyses (see [Sensitivity analysis](#)). By using the Mantel-Haenszel method for binary outcomes, we were able to calculate an estimate of the amount of variation between the studies we analysed.

We had planned to use the inverse variance method for continuous outcomes, or outcomes where HRs were available. We had planned to explore heterogeneity above 80% with subgroup analyses. If we had not found a cause for the heterogeneity, we had planned not to perform a meta-analysis, but to comment on the results narratively and present them in tables if studies were not homogenous enough.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses of 28-day mortality using the following characteristics.

- Different antiplatelets, as they have different mechanisms of action and pathways, and could therefore have different effects on the outcome.
- Additional anticoagulation versus no additional anticoagulation.

Additionally, we had planned to perform subgroup analyses of the following characteristics, but had insufficient data.

- Age of participants (divided into applicable age groups, e.g. children, 18 to 65 years, 65 years and older), suggesting that

older participants may benefit more from treatment with antiplatelets, as they are at higher risk for thrombotic events.

- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression), suggesting that participants with some diseases that increase thrombotic risk may benefit more.
- Timing of first dose administration with illness onset, suggesting that an earlier treatment may prevent deterioration.

We used the tests for interaction to test for differences between subgroup results and considered $P < 0.01$ as statistically significant for all subgroup analyses.

Sensitivity analysis

We performed sensitivity analysis of the following characteristics for mortality at 28 days.

- Fixed-effect versus random-effects model
- Risk of bias assessment components (excluding studies with a high risk of bias)

Additionally, we had planned to perform sensitivity analyses of the following characteristics, but did not find sufficient data to perform them.

- Comparison of preprints of COVID-19 interventions versus peer-reviewed articles
- Comparison of studies with premature termination versus completed studies

Summary of findings and assessment of the certainty of the evidence

Summary of findings

We used the MAGICapp software to create summary of findings tables (MAGICapp). For time-to-event outcomes, we had planned to calculate absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020), but we have not reported HR in our summary of findings tables.

According to Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions*, the “most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes” should be included in the summary of findings table(s) (Higgins 2021e). We included outcomes prioritised according to the Core Outcome Set for intervention studies (COMET 2021) and patient relevance, as follows.

Hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- 28-day all-cause mortality
- Worsening of clinical status up to day 28
 - Participants with clinical deterioration (new need for invasive mechanical ventilation) or death
- Improvement of clinical status up to day 28
 - Participants discharged alive
- Thrombotic events (at longest follow-up)
- Serious adverse events (at longest follow-up)
- Adverse events (at longest follow-up)
- Major bleeding events (at longest follow-up)

Antiplatelets in non-hospitalised individuals with asymptomatic infection or mild COVID-19

- All-cause mortality at day 45
- Worsening of clinical status up to day 45
 - Admission to hospital or death
- Quality of life up to longest follow-up
- Thrombotic events up to day 45
- Adverse events up to day 45
- Serious adverse events up to day 45
- Major bleeding events up to longest follow-up

Assessment of the certainty of the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence for the outcomes listed in the previous section.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty in the body of evidence for each prioritised outcome.

We downgraded our certainty of evidence as follows.

- Serious (-1) or very serious (-2) risk of bias
- Serious (-1) or very serious (-2) inconsistency
- Serious (-1) or very serious (-2) uncertainty about directness
- Serious (-1) or very serious (-2) or extremely (-3) imprecise or sparse data
- Serious (-1) or very serious (-2) probability of reporting bias

The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 14 (Higgins 2021e).

We used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We phrased the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

RESULTS

Description of studies

Results of the search

We searched all databases and screened the resulting records up to 22 December 2022.

Our searches retrieved 806 records for the specific database searches. After removing 52 duplicates, we screened 754 records

based on their titles and abstracts. We excluded 719 records that did not meet the prespecified inclusion criteria. After screening, we identified 35 full texts that could meet our inclusion criteria. Three (five records) of these 35 studies are awaiting classification, so we could not include them in our analyses. We had to exclude two studies (two records) because they did not meet the inclusion criteria. Fourteen studies (15 records) were still ongoing, so we also could not include them. In the end, we were able to include six RCTs (13 records) that met our inclusion criteria. Details of our electronic searches can be found in the corresponding PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram

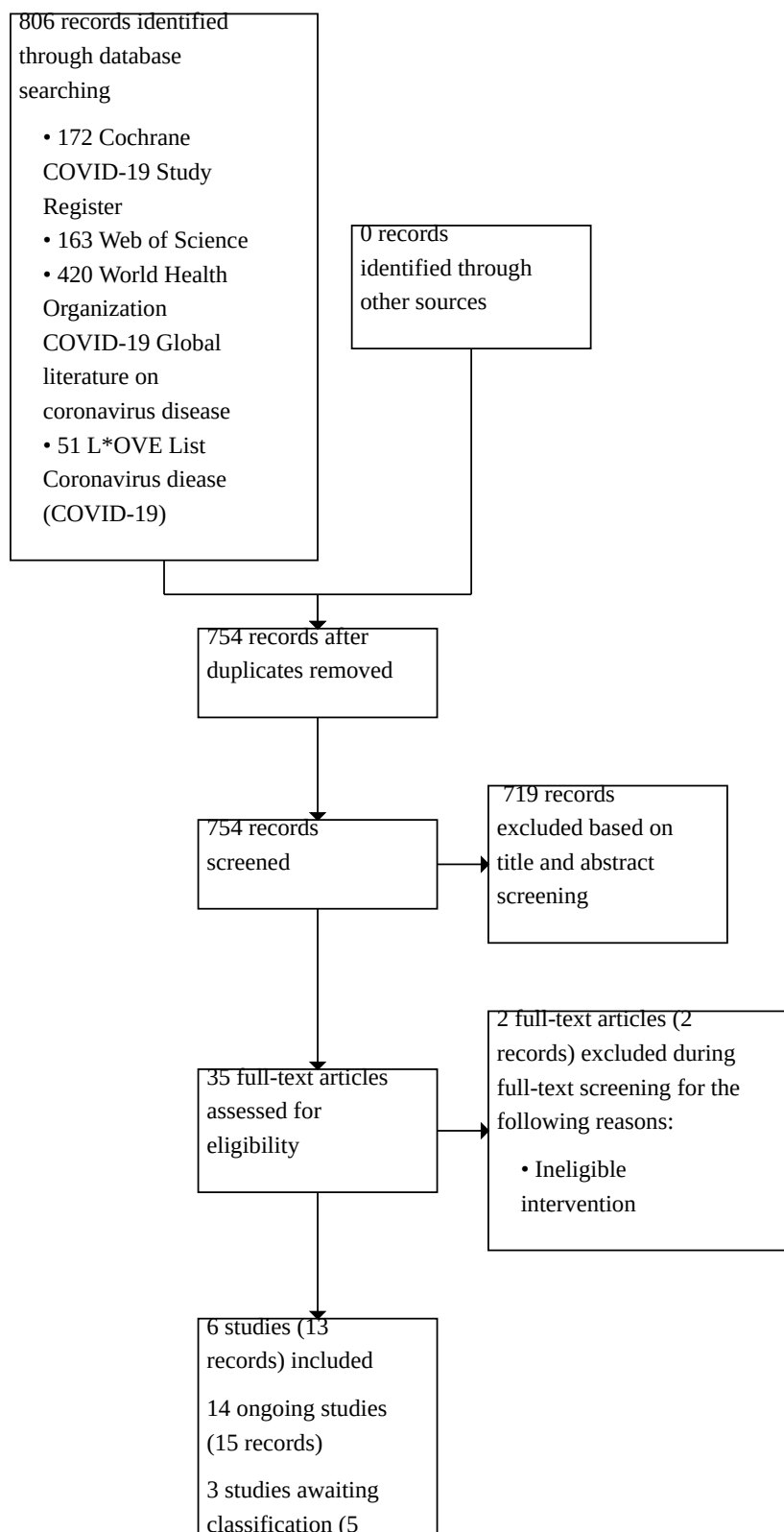
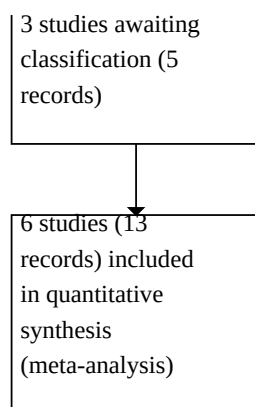


Figure 1. (Continued)



- Six RCTs are included in this review (Berger 2022; Bohula 2022 (COVID-PACT); Connors 2021 (ACTIV-4B); Eikelboom 2022 (ACTCOVID); Horby 2021 (RECOVERY); REMAP-CAP 2022), of which four RCTs included participants with moderate to severe COVID-19 (Berger 2022; Bohula 2022 (COVID-PACT); Horby 2021 (RECOVERY); REMAP-CAP 2022), and two included participants with mild disease (Connors 2021 (ACTIV-4B); Eikelboom 2022 (ACTCOVID)).
- 14 RCTs are currently ongoing (NCT05073718; NCT04808895; Bohula 2022 (COVID-PACT); CTRI/2020/08/027503; CTRI/2021/03/032059; CTRI/2021/06/034254; IRCT20180205038626N7; NCT04768179; NCT04363840; NCT04937088; NCT04445623; NCT04703608; NCT04365309; Sharma 2021).
- Three RCTs are awaiting classification (NCT04391179; NCT04659109; RESIST 2021).
- Two RCTs were excluded (Eikelboom 2022 (ACTCOVID19 hospitalised); NCT04483960), because Eikelboom 2022 (ACTCOVID19 hospitalised) used a combined intervention of a platelet inhibitor plus rivaroxaban and NCT04483960 did not use antiplatelets.

Details on the interventions planned in the ongoing trials can be found in Table 1 (Characteristics of ongoing studies).

Included studies

Design and sample size

We included six randomised controlled trials (RCTs) according to our inclusion criteria, involving 21,750 participants (17,541 moderate to severe COVID-19; 4209 asymptomatic SARS-CoV-2 infection or mild COVID-19;) (Berger 2022; Bohula 2022 (COVID-PACT); Connors 2021 (ACTIV-4B); Eikelboom 2022 (ACTCOVID); Horby 2021 (RECOVERY); REMAP-CAP 2022). All studies were published in journals.

Two of the studies are still recruiting to other drugs (not antiplatelets) as they are adaptive platform trials (Horby 2021 (RECOVERY); REMAP-CAP 2022), and one study has results but was terminated because the event rates were lower than anticipated (Connors 2021 (ACTIV-4B)). The estimated study completion dates ranged from December 2022 to December 2023. One study stopped

randomisation early due to a decrease in ICU patients with COVID-19 (Bohula 2022 (COVID-PACT)).

Berger 2022 is a Bayesian, adaptive randomised clinical trial, with completion planned in November 2023 and an estimated number of 3000 participants. Connors 2021 (ACTIV-4B) is a multicentre adaptive, randomised, double-blind, placebo-controlled platform trial, which was terminated with an actual enrolment of 657 participants, of whom 328 contributed data to our analyses as the remaining participants were randomised to either prophylactic or therapeutic doses of apixaban (an antithrombotic drug not inhibiting platelet aggregation). The completion date of this study was 5 August 2021. Horby 2021 (RECOVERY) is an open-label, randomised clinical adaptive multicentric trial, currently recruiting as of July 2023 with completion planned in November 2023 with 50,000 participants. Similarly, REMAP-CAP 2022 is a Bayesian, adaptive, open-label randomised platform trial evaluating multiple interventions in multiple domains. The estimated completion date is December 2023 with 10,000 participants. Bohula 2022 (COVID-PACT) is a multicentre, 2 x 2 factorial, open-label, randomised trial whose results were published in August 2022. This trial randomised 390 participants. Eikelboom 2022 (ACTCOVID) is an open-label, parallel-group, factorial, randomised controlled trial with 3917 participants. The estimated completion date of this study is June 2023.

Setting and participants

All studies were multicentre trials. The Berger 2022 study was conducted in different centres in the USA, Brazil, Italy and Spain. Connors 2021 (ACTIV-4B) took place at different sites in the USA. Horby 2021 (RECOVERY) was conducted at different global sites in the United Kingdom, Indonesia and Nepal. REMAP-CAP 2022 acquired data in eight countries, including Canada, France, Germany, India, Italy, Nepal, the Netherlands or the United Kingdom. The Eikelboom 2022 (ACTCOVID) trial was conducted at 48 clinical sites in different countries, including Brazil, Canada, Colombia, Ecuador, Egypt, India, Nepal, Pakistan, Philippines, Russian Federation, South Africa and the United Arab Emirates. Bohula 2022 (COVID-PACT) was also a multicentre trial that took place in 34 centres in the United States.

Except for two studies ([Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#)), all studies examined participants with moderate to severe COVID-19 who were hospitalised.

In all studies, a SARS-CoV-2 infection was necessary for inclusion. [Connors 2021 \(ACTIV-4B\)](#) included symptomatic but clinically stable participants with mild COVID-19 who were diagnosed with a SARS-CoV-2 infection in the last 14 days. [Horby 2021 \(RECOVERY\)](#) included hospitalised participants with suspected or test-confirmed SARS-CoV-2 infection; 97% of the participants in both groups had a positive test, 1% per strata tested negative. [Berger 2022](#) explored hospitalised participants with a laboratory-confirmed SARS-CoV-2 infection without the need for intensive care (non-critically ill cohort). [REMAP-CAP 2022](#) included participants who were admitted to hospital with acute illness due to a suspected or proven COVID-19 infection, and 97% of included participants had a positive PCR result. [Bohula 2022 \(COVID-PACT\)](#) included participants with an acute SARS-CoV-2 infection admitted to an ICU. [Eikelboom 2022 \(ACTCOVID\)](#) included participants with a symptomatic and laboratory-confirmed diagnosis of COVID-19 within seven days of diagnosis.

The median age of the participants in [Berger 2022](#) was 52.7 years, and 41.5% were female. Additional reported diagnoses included cardiovascular diseases for 43.7% in the intervention group and 55.8% in the standard care group. Other additional diseases were chronic conditions such as diabetes, chronic kidney diseases, liver diseases or respiratory diseases (asthma or COPD). Previous treatments were largely balanced in both groups. Additional treatments were glucocorticoids (65.5% versus 62.5%), remdesivir (56.0% versus 47.6%), acetylsalicylic acid (15.0% versus 13.4%), anticoagulant therapy (10.6% versus 14.5%) and interleukin-6 (IL-6) inhibitors (2.7% versus 3.9%). Concerning respiratory support at randomisation, there were participants without oxygen application (12.2% versus 10.9%), on low flow oxygen (77.8% versus 78.4%) or on high-flow nasal cannula (0.8% versus 0.4%).

In [Connors 2021 \(ACTIV-4B\)](#), the median age was 54 years and 59.1% of the participants were female. Additional reported diagnoses were hypertension for 33.5% in the acetylsalicylic acid group and 54% in the placebo group, and diabetes (17.7% versus 14.6%). There were no reported previous treatments at baseline.

In [Horby 2021 \(RECOVERY\)](#), the median age in the intervention group was 59.2 years (62% female) and in the control group 59.3 years (61% female). There were several additional diagnoses reported: 22% of both groups reported diabetes, 11% (intervention group) and 10% (standard care group) had heart diseases, 19% in each group reported chronic lung diseases and 43% of both groups indicated any of the above. 94% of both groups received corticosteroids as a concomitant therapy. The trial included participants with no respiratory support or simple oxygen (67% in both strata), but also on non-invasive ventilation (28% for both) and invasive mechanical ventilation (5% for both).

In [REMAP-CAP 2022](#), the median age in the intervention groups (acetylsalicylic acid and P2Y12 inhibitor groups) was 57.0 years, and in the control group it was 57 years. In the intervention groups, 35.2% (acetylsalicylic acid) and 30.5% (P2Y12 inhibitor) were female, and in the control group 34.6% were female. The participants were divided into a critically ill group and a non-critically ill group. Additional diagnoses were diabetes (21.9%), respiratory diseases (18.8%), kidney diseases (3.5%),

severe cardiovascular diseases (4.0%) and any immunosuppressive condition (4.0%). Previous treatments within 48 hours of recruitment that were reported were steroids (97.0%), remdesivir (21.9%), tocilizumab (38.7%), sarilumab (9.3%), low-molecular-weight heparin or unfractionated heparin in different doses or direct oral anticoagulants. This study reported two groups of participants separately: the severely ill population, with around 36% of participants invasively mechanically ventilated (IMV), and the remaining participants, mostly on noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC). In the moderately ill population most participants needed no respiratory support or only oxygen (87%) and only a small number of participants needed NIV, HFNC or IMV at baseline.

In [Bohula 2022 \(COVID-PACT\)](#), the median age in the intervention group (IG) was 59 years (38 % female) and 62 years in the control group (CG) (43% female). There were several additional diagnosis reported: hypertension (56% IG versus 62% CG), diabetes (38% IG versus 26% CG), atherosclerotic cardiovascular disease (15% IG versus 13% CG), active cancer (5.2% IG versus 3.7% CG), chronic kidney disease (11% IG versus 11% CG) and pulmonary disease (22% IG versus 19% CG). All participants in both groups needed some form of oxygen therapy: 1.6% versus 0.5% needed oxygen by mask or nasal cannula, 79% versus 88% needed NIV or HFNC, and 19% versus 12% needed invasive ventilation.

In [Eikelboom 2022 \(ACTCOVID\)](#), the median age in the intervention group was 45.2 years (38.6% female) and in the control group it was 44.8 years (40.3% female). They reported five additional diagnoses: diabetes (12.7% versus 14.1%), hypertension (22.6% versus 21.5%), dyslipidaemia (8.9% versus 8.1%), cardiovascular disease (5.1% versus 4.5%) and chronic lung disease (7.1% versus 8.3%). There were no reported previous treatments at baseline.

Interventions and comparators

In [Berger 2022](#), the intervention group received a therapeutic dose of anticoagulants and P2Y12 inhibitor (heparin was standard care with an added P2Y12 inhibitor). 63.2% of the included participants received ticagrelor and 36.8% received clopidogrel for 14 days or until hospital discharge, whichever occurred first ([Berger 2022](#)). The control group of this study received a therapeutic dose of anticoagulation for 14 days or until hospital discharge (whichever occurred first).

Two RCTs compared acetylsalicylic acid to standard care with placebo ([Connors 2021 \(ACTIV-4B\)](#)) or without placebo ([Horby 2021 \(RECOVERY\)](#)).

[Connors 2021 \(ACTIV-4B\)](#) investigated the effect of acetylsalicylic acid compared with a matching placebo once a day. The application form was oral. The day's dosage was 81 mg for 45 days. In this trial, two additional intervention groups were treated with either prophylactic or therapeutic doses of anticoagulants (apixaban twice daily 2.5 or 5 mg), but those groups did not meet our inclusion criteria and data were therefore not extracted. We found no information about additional anticoagulant medication in the groups included in our meta-analysis.

In [Horby 2021 \(RECOVERY\)](#), 150 mg acetylsalicylic acid once daily until discharge was compared to standard care, which was defined as usual hospital care. Only 6587 participants (90%) in the intervention group received at least one dose of acetylsalicylic acid

and 210 participants (3%) in the control group received at least one dose of acetylsalicylic acid ([Horby 2021 \(RECOVERY\)](#)), resulting in unplanned treatment switching.

In [REMAP-CAP 2022](#), the control group received standard care, possibly with other interventions of the trial. The intervention group was divided into two arms (acetylsalicylic acid or a P2Y12 inhibitor). Participants in the acetylsalicylic acid arm received 75 mg to 100 mg once daily. The participants in the P2Y12 inhibitor arm received clopidogrel 75 mg once daily without a loading dose, prasugrel (60 mg loading dose followed by 10 mg daily (if aged < 75 years and weight ≥ 60 kg) or 5 mg daily (if aged ≥ 75 years or weight < 60 kg)), ticagrelor 60 mg twice daily without a loading dose ([REMAP-CAP 2022](#)).

In [Bohula 2022 \(COVID-PACT\)](#), the control group received standard care plus prophylactic or therapeutic anticoagulation (enoxaparin 40 mg subcutaneously once daily, unfractionated heparin intravenously continuous targeting the activated partial thromboplastin time (aPTT) at a level that is 1.5 to 2.5 times longer than the control value, or enoxaparin 1 mg/kg subcutaneously every 12 hours). The intervention group received antiplatelet therapy with clopidogrel plus standard care and prophylactic anticoagulation or therapeutic anticoagulation: the intervention group with prophylactic anticoagulation received clopidogrel 300 mg orally once, followed by clopidogrel 75 mg orally once daily plus enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 IU subcutaneously three times daily. Participants with antiplatelet therapy plus full-dose anticoagulation received clopidogrel 300 mg orally once, followed by clopidogrel 75 mg orally once daily plus unfractionated heparin intravenously continuous targeting the activated partial thromboplastin time (aPTT) at a level that is 1.5 to 2.5 times longer than the control value, or enoxaparin 1 mg/kg subcutaneously every 12 hours.

In [Eikelboom 2022 \(ACTCOVID\)](#), the control group received standard care or standard care plus additionally (in a first randomisation) colchicine 0.6 mg twice daily for three days and then 0.6 mg once daily for 25 days. The intervention group received oral acetylsalicylic acid 100 mg once daily as a tablet for 28 days, or oral acetylsalicylic acid 100 mg once daily as a tablet for 28 days plus (in a first randomisation) colchicine 0.6 mg twice daily for 3 days and then 0.6 mg once daily for 25 days.

Outcomes

Three trials reported 28-day mortality ([Berger 2022](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)); [REMAP-CAP 2022](#) also reported 90-day mortality and 180-day mortality. [Bohula 2022 \(COVID-PACT\)](#) reported all-cause mortality without concrete description of the time frame of follow-up, but probably up to day 21.

Two studies reported all-cause mortality up to longest follow-up (45 days) for non-hospitalised participants with mild COVID-19 ([Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#)).

The worsening of clinical status up to day 28, defined as new need for invasive mechanical ventilation or death, was reported for the hospitalised participants in [Horby 2021 \(RECOVERY\)](#) and [REMAP-CAP 2022](#).

The improvement of clinical status up to day 28, defined as participants discharged alive from hospital, was reported in [Horby 2021 \(RECOVERY\)](#) and at day 21 in the [Berger 2022](#) trial.

Thrombotic events up to the longest follow-up were reported in four trials for participants with moderate to severe COVID-19 ([Berger 2022](#); [Bohula 2022 \(COVID-PACT\)](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)) and by two studies for participants with mild COVID-19 who were not hospitalised ([Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#)). The time frames for the longest follow-up in participants with moderate to severe COVID-19 were 28 days ([Berger 2022](#); [Bohula 2022 \(COVID-PACT\)](#); [Horby 2021 \(RECOVERY\)](#)) or unclear ([REMAP-CAP 2022](#)). In participants with mild COVID-19, [Connors 2021 \(ACTIV-4B\)](#) reported this outcome at 45 days (and added 30-day safety follow-up to the 45 days) and [Eikelboom 2022 \(ACTCOVID\)](#) reported thrombotic events that had occurred up to day 45.

The safety outcomes major bleeding and serious adverse events during study treatment were reported for up to 28 days for the hospitalised participants in three studies ([Berger 2022](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)), although the longest follow-up of [REMAP-CAP 2022](#) for major bleeding was 14 days. These outcomes were reported in the outpatient setting by [Connors 2021 \(ACTIV-4B\)](#) and [Eikelboom 2022 \(ACTCOVID\)](#) for up to 45 days (again, [Connors 2021 \(ACTIV-4B\)](#) reported data after the additional 30-day safety follow-up). Admission to hospital or death was reported for the outpatient setting in [Connors 2021 \(ACTIV-4B\)](#) and [Eikelboom 2022 \(ACTCOVID\)](#) up to day 45.

The need for new dialysis was reported in [Horby 2021 \(RECOVERY\)](#) at day 28 for non-hospitalised participants.

[REMAP-CAP 2022](#) reported quality of life of participants at day 180, including use of the EQ-5D-5L (EuroQol-5 dimensions -5 levels questionnaire), which is a preference-based health-related quality of life (HRQoL) instrument comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L utility score is calculated from the individual response to each item and ranges from -0.593 (score of 0 is equivalent to death) to 1.00 (full health), with higher values indicating better health states. In addition, respondents were asked to indicate their present health state on a visual analogue scale (EQ VAS) ranging from the worst imaginable health state (0) to the best imaginable health state (100).

Ongoing studies

We identified 14 ongoing RCTs ([ChiCTR2000030055](#); [CTRI/2020/08/027503](#); [CTRI/2021/03/032059](#); [CTRI/2021/06/034254](#); [IRCT20180205038626N7](#); [NCT04363840](#); [NCT04365309](#); [NCT04445623](#); [NCT04703608](#); [NCT04768179](#); [NCT04808895](#); [NCT04937088](#); [NCT05073718](#); [Sharma 2021](#)).

The majority of studies are investigating acetylsalicylic acid. One study is investigating other antiplatelets, namely prasugrel hydrochloride ([NCT04445623](#)).

The 14 ongoing RCTs plan to recruit between 36 and 1200 participants. According to the trial registries, two studies were due to complete in 2020, three studies aimed to complete in 2021, two studies were to have finished in 2022, and one is due to complete during 2023. Six other studies did not give information on a planned completion date.

Four of the ongoing trials are still recruiting ([Bohula 2022 \(COVID-PACT\)](#); [IRCT20180205038626N7](#); [NCT04703608](#); [NCT04483960](#)). Six have not recruited yet ([CTRI/2020/08/027503](#); [CTRI/2021/03/032059](#); [NCT04445623](#); [NCT04768179](#); [NCT04808895](#); [NCT05073718](#)), and one study is enrolling by invitation ([NCT04365309](#)).

Please refer to [Table 1](#) for further details on the planned completion dates and planned number of participants per study.

Studies awaiting assessment

We classified three studies as awaiting assessment. One was published, but later withdrawn from the preprint server it was originally published on ([RESIST 2021](#)). Two studies are listed as having completed according to the trial registries, but no results have been published yet ([NCT04391179](#); [NCT04659109](#)). If eligible, they will be considered in the next review update.

Excluded studies

We excluded two studies at full-text screening as these studies did not evaluate antiplatelets ([NCT04483960](#); [Eikelboom 2022 \(ACTCOVID19 hospitalised\)](#)).

Risk of bias in included studies

Using the risk of bias 2 (RoB 2) tool recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2021a](#)), we assessed the methodological quality and risk of bias for the outcomes of the results of six RCTs ([Berger 2022](#); [Bohula 2022 \(COVID-PACT\)](#); [Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)). The RoB 2 table is accessible at zenodo.org/record/7637454.

Overall judgement in studies including individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

For [Horby 2021 \(RECOVERY\)](#), we rated the risk of bias for the outcome '28-day mortality' for hospitalised participants to be high due to deviations from the intended intervention. In the intervention group of this study, 10% of participants never obtained the treatment and 31% did not receive it consistently. In the corresponding control group, 210 (3%) participants received treatment with acetylsalicylic acid. Reasons for deviation from the intended intervention were not given. This was also the reason to rate high risk for 'improvement up to day 28: discharged alive', and 'need for new dialysis up to day 28'. Concerning the outcomes 'major bleeding up to longest follow-up' and 'thrombotic events up to longest follow-up', we additionally had some concerns regarding bias in the measurement of those events, since the study was unblinded and the overall bias for those endpoints was rated high risk due to deviations from intended interventions.

Assessing [Bohula 2022 \(COVID-PACT\)](#), we rated the risk of bias to be high due to imbalanced high rates of cross-overs (deviations from intended interventions) for the outcomes 'major bleeding up to longest follow-up', 'thrombotic events up to longest follow-up' and 'all-cause mortality up to the longest follow-up'. Additionally, the planned duration of treatment was not specified nor given in the study/registry/publication, so we were not able to judge whether there were deviations from intended interventions. We also identified unbalanced co-interventions and unclear time frames of the treatments and follow-up.

In [Berger 2022](#), we rated the risk of bias to be low for the outcomes 'major bleeding up to longest follow-up', 'any thrombotic event up to longest follow-up', '28-day mortality' and 'improvement up to day 28: discharged alive' for hospitalised participants, since those outcomes were assessed according to the protocol and the allocation was randomised. The trial was an open-label design.

For [REMAP-CAP 2022](#), we rated the risk of bias for the outcome 28-day mortality for hospitalised participants to be 'some concerns' due to deviations from the intended intervention and a bias in the measurement of the outcome. The deviations from intended interventions were also the reason why we rated the risk of bias to be 'some concerns' for the outcomes 'any thrombotic event', 'major bleeding up to longest follow-up' and 'serious adverse events up to longest follow-up' in this study. Regarding the outcome 'worsening up to day 28: participants with new need for invasive mechanical ventilation or death', we rated the risk of bias to be high in this study. The reasons for this assessment were two-fold: firstly due to missing outcome data, as we found that outcome reported for only 60.5% (1104 out of 1824) of the randomised participants. Secondly, some concerns arose due to deviations from intended interventions (missing information whether there were cross-overs or whether the assigned medication was really taken). The study undertook a follow-up after 180 days for the outcome '180-day mortality', and we assessed there to be some concerns about bias because there was no information about whether there were cross-overs or whether the assigned medication was really taken. Additionally, the design was unblinded and there were missing outcome data (only some of the study centres reported this outcome).

Overall judgements in studies including individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

Concerning [Connors 2021 \(ACTIV-4B\)](#), we rated the risk of bias to be low for the outcome 'all-cause mortality up to day 45' since this outcome was assessed according to the protocol, the allocation was randomised and the trial was double-blind. These reasons were also applied for the endpoints 'admission to hospital or death up to day 45', 'major bleeding up to longest follow-up' and 'thrombotic events up to longest follow-up', where we detected no risk of bias using the RoB 2 tool.

In [Eikelboom 2022 \(ACTCOVID\)](#), we rated the risk of bias for the outcomes 'thrombotic events up to longest follow-up', 'admission to hospital or death up to day 45', 'all cause mortality up to day 45' and 'serious adverse events up to longest follow-up' as some concerns because 7.9% of the participants discontinued the intervention. It is not clear whether this happened due to the trial context or how this could affect the outcome.

Effects of interventions

See: [Summary of findings 1 Antiplatelets in hospitalised adults with moderate to severe COVID-19](#); [Summary of findings 2 Antiplatelets in non-hospitalised adults with COVID-19](#)

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

We present our certainty in the evidence for prioritised outcomes for antiplatelets (plus standard care) compared to standard care

(with/without placebo) in hospitalised individuals with COVID-19 (moderate to severe disease) in [Summary of findings 1](#).

Prioritised outcomes

All-cause mortality up to day 28, day 60, time-to-event and up to longest follow-up

We identified three studies reporting this outcome for 17,249 hospitalised participants ([Berger 2022](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)): 168 of 1000 participants treated with antiplatelets died within 28 days. Antiplatelets probably result in little to no difference in 28-day mortality (RR 0.95, 95% CI 0.85 to 1.05; risk difference (RD) 9 fewer per 1000, 95% CI from 26 fewer to 9 more; $I^2 = 26\%$; moderate-certainty evidence; [Analysis 1.1](#)). Our main reason to downgrade was serious risk of bias due to deviations from intended interventions.

[REMAP-CAP 2022](#) reported 180-day mortality at longest follow-up in an extra publication ([REMAP-CAP 2023](#)). Therapy with antiplatelets led to an adjusted hazard ratio of 0.85 (credibility interval 0.71 to 1.03) compared with standard care, reported from the fully adjusted Bayesian model (adjusted for other treatments from other domains, site, time, sex and age). Antiplatelets may result in little to no difference in 180-day mortality (RR 0.97, 95% CI 0.82 to 1.15; 1,312 participants; RD 10 fewer per 1000, 95% CI from 58 fewer to 49 more; $I^2 =$ not applicable; low-certainty evidence; [Analysis 1.8](#)). Upon personal request to the authors of the study, it was impossible to obtain the frequentist confidence intervals of the adjusted hazard ratio. As there was only one study reporting this outcome and due to risk of bias, we rated the evidence as low certainty for this outcome.

Clinical status at day 28 and up to longest follow-up

Worsening of clinical status up to day 28: participants with clinical deterioration (new need for invasive mechanical ventilation) or death

We identified two studies with 15,266 participants reporting this outcome ([Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)). Considering the reported event rates across participants, we estimated that 218 of 1000 participants experience this outcome up to 28 days when treated with antiplatelets or standard care alone. Antiplatelets probably result in little to no difference in worsening up to day 28 (RR 0.95, 95% CI 0.90 to 1.01; RD 12 fewer per 1000, 95% CI 29 fewer to 30 more; $I^2 = 0\%$; moderate-certainty evidence; [Analysis 1.2](#)). Our main reason to downgrade was serious risk of bias due to deviations from intended interventions. This outcome was not reported for other time points.

Improvement of clinical status up to day 28: participants discharged alive

We identified two studies with 15,454 participants reporting this outcome ([Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)). Considering the reported event rates across participants, we estimated that 743 of 1000 participants experience this outcome at up to 28 days when treated with antiplatelets. Antiplatelets probably result in little to no difference in improvement (discharged alive) up to day 28 (RR 1.00, 95% CI 0.96 to 1.04; RD 0 participants per 1000, 95% CI 29 fewer to 30 more; $I^2 = 71\%$; moderate-certainty evidence; [Analysis 1.3](#)). Our main reason to downgrade was serious risk of bias due

to deviations from intended interventions. This outcome was not reported for other time points.

Thrombotic events up to longest follow-up

All included studies reported thrombotic events up to longest follow-up for 17,518 participants ([Berger 2022](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)). Fifty-two per 1000 participants assigned to be treated with antiplatelets experienced a thrombotic event (such as pulmonary embolism, myocardial infarction, ischaemic cerebrovascular event, systemic arterial thromboembolism and deep venous thrombosis). Antiplatelets probably result in a slight reduction of thrombotic events (RR 0.90, 95% CI 0.80 to 1.02; RD 5 fewer per 1000, 95% CI 11 fewer to 1 more; $I^2 = 0\%$; moderate-certainty evidence; [Analysis 1.4](#)). Our main reason to downgrade was serious risk of bias due to deviations from intended interventions.

Safety of antiplatelets up to longest follow-up

Serious adverse events up to longest follow-up

One study reported this outcome for 1815 participants ([REMAP-CAP 2022](#)). Considering the reported event rates across participants, we estimated that 7 of 1000 participants experience a serious adverse event when treated with antiplatelets. Antiplatelets may result in a slight increase in serious adverse events (Peto OR 1.57, 95% CI 0.48 to 5.14; RD 2 more per 1000, 95% CI 3 fewer to 19 more; I^2 not applicable; low-certainty evidence; [Analysis 1.5](#)). Our main reason to downgrade was very serious imprecision: only one out of three studies contributed data, with very low event rates and a very wide confidence interval.

Adverse events during study treatment

None of the included studies reported non-serious adverse events according to our definition (i.e. adverse events that occurred during the study period, defined as number of participants with any event). [Horby 2021 \(RECOVERY\)](#) only reported suspected unexpected serious adverse reactions (SUSAR), but other serious or non-serious adverse events were not recorded (only information about use of renal dialysis, documented new major cardiac arrhythmia, major bleeding, thrombotic events or non-coronavirus infections).

Major bleeding up to longest follow-up

All included studies reported major bleeding, for a total of 17,527 participants ([Berger 2022](#); [Bohula 2022 \(COVID-PACT\)](#); [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#)). In the safety population, 16 of 1000 participants treated with antiplatelets had a major bleeding event. Antiplatelets probably increase the occurrence of major bleeding events (Peto OR 1.68, 95% CI 1.29 to 2.19; RD 6 more per 1000, 95% CI 2 more to 11 more; $I^2 = 11\%$; moderate-certainty evidence; [Analysis 1.6](#)). Our main reason to downgrade was serious risk of bias due to deviations from intended interventions.

Additional outcomes

Quality of life

This outcome was reported for day 180 for a very small subgroup of participants (N = 84 acetylsalicylic acid, N = 83 clopidogrel, N = 96 placebo) in one study ([REMAP-CAP 2022](#)). Results are therefore very uncertain.

Using the EQ-5D-5L utility score, antiplatelet treatment lead to a mean (SD) of 0.69 (0.27) (N = 163) versus 0.63 (0.30) (N = 95) in the control group (scale from 0 to 1, higher values represent better outcomes). Single domains of the questionnaire were presented separately for acetylsalicylic acid, P2Y12 inhibitors (clopidogrel) and control.

The study also reported the EQ VAS for day 180. Treatment with acetylsalicylic acid resulted in a mean (SD) score of 65.7 (22.3). The score for treatment with P2Y12 inhibitors was 71.3 (20.1), and the score for standard care was 66.1 (21.0) (scale from 0 to 100, higher values represent better outcomes).

Duration of hospitalisation, or time to discharge from hospital

[Horby 2021 \(RECOVERY\)](#) reported the median time to hospital discharge up to day 28, with the median being eight days in the acetylsalicylic acid group and nine days in the standard care group (each IQR 5 to > 28 days).

Need for new dialysis (up to 28 days)

We identified one study with participants randomised to either acetylsalicylic acid or standard care reporting the new need for dialysis up to day 28 in 14,771 participants ([Horby 2021 \(RECOVERY\)](#)). Considering the reported event rates across participants, we estimated that 37 of 1000 participants experience this outcome at up to 28 days when treated with platelet inhibitors. Treatment with antiplatelets resulted in no difference in the need for dialysis at up to day 28 (Peto OR 0.99, 95% CI 0.84 to 1.18; RD 1 fewer per 1000, 95% CI 6 fewer to 6 more; [Analysis 1.7](#)).

Other planned outcomes were not reported: admission to the ICU, ventilator-free days (ventilator-free defined as WHO Clinical Progression Scale ≤ 6 for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e. WHO Clinical Progression Scale ≥ 7).

Subgroup analyses

We performed a subgroup analysis for the prioritised outcome 28-day mortality ([Analysis 2.1](#)), stratified by the type of antiplatelet agent that was used (cyclooxygenase inhibitor, i.e. acetylsalicylic acid; or P2Y12 inhibitors, i.e. either clopidogrel, ticagrelor or prasugrel). Of our included studies conducted amongst participants with moderate to severe COVID-19, [Horby 2021 \(RECOVERY\)](#) and [REMAP-CAP 2022](#) used a cyclooxygenase inhibitor. [Berger 2022](#) and the multi-armed trial [REMAP-CAP 2022](#) compared P2Y12 inhibitors to standard care. Overall, there was no evidence for subgroup differences for the outcome all-cause mortality up to day 28 (P = 0.82).

We performed a subgroup analysis related to standard care or standard care with therapeutic anticoagulation. [Berger 2022](#) treated participants with therapeutic dose heparin. [Horby 2021 \(RECOVERY\)](#) medicated participants in the reported subgroup with lower/higher dose low molecular weight heparins as thromboprophylaxis. We found data for the critically ill participants in [REMAP-CAP 2022](#) who were either treated with low/intermediate doses of heparin or who got subtherapeutic/therapeutic doses of heparin. The study did not report those subgroups for the moderately ill participants. We did not identify subgroup differences for the outcome all-cause mortality at up to day 28 (P = 0.12) ([Analysis 2.2](#)).

Sensitivity analyses

Please find our sensitivity analyses in [Table 2](#). We performed the following analyses.

- Comparison of the fixed-effect versus random-effects statistical model. Performing a sensitivity analysis of the fixed-effect model did not make any relevant change to the effect.
- Comparison of studies with a low risk of bias or some concerns versus studies with a high risk of bias. When excluding [Horby 2021 \(RECOVERY\)](#) due to a high risk of bias, the direction of the effect changed, but without relevant impact on the overall little to no difference on all-cause mortality up to day 28 (RR 1.02, 95% CI 0.63 to 1.62, 2357 participants).
- Comparison of preprints versus peer-reviewed articles. For the outcome 28-day mortality, we found only a preprint that was withdrawn later ([RESIST 2021](#)); therefore, we did not conduct this sensitivity analysis.
- Comparison of premature termination of studies with completed studies. As we did not identify any prematurely ended studies, we did not perform this sensitivity analysis.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

We present our certainty in the evidence for prioritised outcomes for antiplatelets in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) in [Summary of findings 2](#).

We found no study including participants with asymptomatic SARS-CoV-2 infection. Two included studies considered people with mild disease ([Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#)).

Prioritised outcomes

All-cause mortality at day 28, day 60, time-to-event and up to longest follow-up

We identified two studies with 4209 participants randomised to either acetylsalicylic acid or placebo reporting this outcome ([Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#)). Considering the reported event rates across participants, we estimated that 6 of 1000 participants die at up to 45 days when treated with placebo or standard care alone. Antiplatelets may result in little to no difference in all-cause mortality up to day 45 (Peto OR 1.00, 95% CI 0.45 to 2.22; RD 0 fewer per 1000, 95% CI 3 fewer to 7 more; 2 studies; 4209 participants; low-certainty evidence; [Analysis 3.1](#)). The main reason to downgrade was very serious imprecision (low number of events and wide confidence interval).

Admission to hospital or death at longest follow-up

We identified two studies with 4209 participants randomised to either acetylsalicylic acid or placebo reporting this outcome ([Connors 2021 \(ACTIV-4B\)](#); [Eikelboom 2022 \(ACTCOVID\)](#)). Considering the reported event rates across participants, we estimated that 31 of 1000 participants had to be hospitalised or died at up to 45 days when treated with placebo or standard care alone. The evidence is very uncertain about the effects of antiplatelets on admission to hospital (for cardiovascular reasons) or death up to day 45 (Peto OR 0.79, 95% CI 0.57 to 1.10; RD 8 fewer per 1000, 95% CI 16 fewer to 4 more; 2 studies, 4209 participants; very low-certainty evidence; [Analysis 3.2](#)). The main reasons to downgrade were very serious imprecision (low number of events

and wide confidence interval) and serious indirectness (one study only reported death due to a cardiovascular event, the other study included major thrombosis in this outcome's definition).

Symptom resolution

We found no studies that reported symptom resolution outcomes (all initial symptoms resolved (asymptomatic) at day 14, day 28 and up to longest follow-up or duration to symptom resolution).

Quality of life

This outcome was not reported.

Any thrombotic event up to longest follow-up

We identified two studies with 4209 participants randomised to either acetylsalicylic acid or placebo reporting this outcome (Connors 2021 (ACTIV-4B); Eikelboom 2022 (ACTCOVID)). Considering the reported event rates across participants, we estimated that 1 of 1000 participants experience a thrombotic event at up to 45 days when treated with placebo or standard care alone. Antiplatelets may slightly decrease the incidence of new thrombotic events (Peto OR 0.37, 95% CI 0.09 to 1.46; RD 2 fewer per 1000, 95% CI 3 fewer to 1 more; 2 studies, 4209 participants; low-certainty evidence; Analysis 3.3). The main reason to downgrade was very serious imprecision (low number of events and wide confidence interval).

Safety of antiplatelets up to longest follow-up

Serious adverse events up to longest follow-up

We identified one study with 3881 participants randomised to either acetylsalicylic acid or placebo reporting this outcome (Eikelboom 2022 (ACTCOVID)). Considering the reported event rates across participants, we estimated that 16 of 1000 participants experience serious adverse events when treated with antiplatelets. Antiplatelets may make little to no difference on the incidence of serious adverse events (Peto OR 1.00, 95% CI 0.60 to 1.64; RD 0 fewer per 1000, 95% CI 6 fewer to 10 more; 1 study; 3881 participants; low-certainty evidence; see Analysis 3.4). The main reason to downgrade was very serious imprecision (low number of events and wide confidence interval).

Adverse events during study treatment

None of the included studies reported non-serious adverse events according to our definition in participants with mild COVID-19 (i.e. adverse events that occurred during the study period, defined as number of participants with any event).

Major bleeding up to longest follow-up

We identified one study with 328 participants reporting this outcome (Connors 2021 (ACTIV-4B)). The evidence is very uncertain about the effects of antiplatelets on the incidence of new major bleeding events, as there were no events in 164 participants treated with acetylsalicylic acid or 164 participants treated with placebo. The evidence is very uncertain about the effects of antiplatelets on major bleeding up to day 45 (RR not applicable; 1 study, 328 participants; very low-certainty evidence). We downgraded three levels due to extremely serious imprecision: low sample size, low number of events, only one small RCT reporting this outcome.

Additional outcomes

The included studies did not report on additional outcomes, such as time to symptom onset, length of hospital stay, time to discharge (for any subgroup of participants hospitalised during course of disease) and admission to the ICU.

DISCUSSION

Summary of main results

We included six studies in this review, of which four reported the effects of antiplatelets plus standard care compared to standard care alone (with/without placebo) in 17,541 hospitalised participants with moderate to severe COVID-19 (see Summary of findings 1), and two studies reported effects in 4209 non-hospitalised participants with mild COVID-19 (see Summary of findings 2).

Moderate-certainty evidence suggests that antiplatelets probably make little to no difference to all-cause mortality up to 28 days, or to either worsening or improvement of clinical status (up to day 28), but probably result in a slight reduction of thrombotic events up to the longest follow-up in participants with moderate or severe COVID-19. The time frames for 'the longest follow-up' were 28 days (Berger 2022; Bohula 2022 (COVID-PACT); Horby 2021 (RECOVERY)) or unclear (REMAP-CAP 2022) in participants with moderate to severe COVID-19. In participants with mild COVID-19, Connors 2021 (ACTIV-4B) reported this outcome at 45 days (and added 30-day safety follow-up to the 45 days), and Eikelboom 2022 (ACTCOVID) reported thrombotic events that had occurred up to day 45. There is low-certainty evidence that antiplatelets may result in little to no difference in 180-day mortality. They may result in a slight increase in serious adverse events up to the longest follow-up and probably slightly increase the occurrence of major bleeding events up to the longest follow-up. Adverse events were not reported.

In participants with mild COVID-19, we found low-certainty evidence that antiplatelets may result in little to no difference in 45-day mortality and serious adverse events, but may slightly decrease the incidence of new thrombotic events. The effects on the combined outcome 'admission to hospital or death up to day 45' and on major bleeding events are very uncertain. Quality of life and non-serious adverse events were not reported.

Overall completeness and applicability of evidence

Overall completeness

Overall, this review identified a lack of evidence about the effect of antiplatelets for the following outcomes and groups.

- Adverse events and serious adverse events related to antiplatelets (only two of six studies reported serious adverse events and none reported adverse events according to standard definition).
- People with asymptomatic SARS-CoV-2 infection or mild COVID-19 (only two studies contributed data for people with mild COVID-19, with very low event rates for all reported outcomes).
- Quality of life among people with any severity of the disease.

We identified 14 ongoing RCTs and three studies awaiting classification that compare antiplatelets to placebo, standard care

alone or other treatments. We aim to include these in updates of this review.

Applicability of evidence

We identified the following issues that may reduce the applicability of the evidence.

- A small portion of included participants had negative/unknown test results (in [Horby 2021 \(RECOVERY\)](#); [REMAP-CAP 2022](#) only 97% of participants had a positive test result).
- The impact of vaccination status on the different outcomes was not accessible, because the outcomes were not separately reported for the subgroup of vaccinated participants; the same was the case for subgroups stratified by sex and age (there were only some age subgroups reported by [Horby 2021 \(RECOVERY\)](#)).
- The studies took place in high- to moderate-income countries; no low-income countries contributed to the evidence we found. The six included studies were conducted in 12 different countries, mainly from high-income countries (Canada, France, Germany, Italy, the Netherlands, Spain, the UK, the USA) and upper-middle-income countries (Brazil), but also from lower-middle-income countries (India, Indonesia, Nepal), see [World Bank 2022](#).
- The applicability of the [Connors 2021 \(ACTIV-4B\)](#) study is limited: "median time from diagnosis to randomization was 7 days (IQR, 3-10 days), and the median time from randomization to initiation of study treatment was 3 days (IQR, 2-5 days)" ([Connors 2021 \(ACTIV-4B\)](#)), so probably those participants with a more severe course of the disease would have already been admitted to hospital before randomisation took place (i.e. the sickest people were already in hospital so were not included in the randomisation). Moreover, the study reported only the admission to hospital "due to cardiovascular events" and not due to all causes.
- Critical appraisal of selected outcomes (thrombotic event, major bleeding, serious adverse events) considering death as a competing event: as most of the studies reported the outcome itself and a combination of the outcome with death (such as 'thrombotic event or death'), we discussed the option to report those combined endpoints to adjust better for the competing risk of death (i.e. in people who died the event could still have occurred, so the deaths could disguise the true value). However, because the event rates were rather low compared to mortality event rates (which were often a multiple of the outcome's event rates), we judged that the combined outcomes would not be representative of the effect of interest. Finally, it seemed more appropriate to us to report those outcomes as separate events, but caution must be taken when interpreting those effect estimates.
- Potentially decreased applicability to Omicron, the variant most prevalent later in the pandemic (studies were conducted between September 2020 and June 2021; the Omicron variant was first described in November 2021 ([WHO 2021c](#))).

Quality of the evidence

Antiplatelets plus standard care versus standard care for the treatment of people with moderate to severe COVID-19

We have moderate certainty in the evidence for: 28-day all-cause mortality, worsening or improvement of clinical status, thrombotic events and major bleeding events; and we have low certainty in the

identified evidence for safety outcomes (serious adverse events) and 180-day mortality. Our main reason for downgrading certainty for effectiveness outcomes was serious study limitations due to deviations from intended interventions, especially in unblinded studies. An additional concern related to safety outcomes was very serious imprecision, as the largest study did not report safety data and the only study contributing data had very low event rates and a very wide confidence interval.

Antiplatelets plus standard care versus standard care (plus placebo) for the treatment of people with asymptomatic SARS-CoV-2 infection or mild COVID-19

We have low certainty in the identified evidence for the outcomes all-cause mortality (at day 45), thrombotic events (up to day 45) and serious adverse events (up to day 45), due to the low number of events and wide confidence intervals. Therefore, we downgraded two levels due to serious imprecision.

We have very low certainty in the identified evidence for the composite outcome admission to hospital or death (up to day 45) due to serious imprecision and serious indirectness, as very few events (deaths/hospital admissions) occurred and confidence intervals were wide. Concerning the outcome major bleeding events (up to the longest follow-up), we have very low certainty due to extremely serious imprecision. There was only one study reporting this outcome, with a low number of event rates and small sample size. Therefore, we downgraded three levels for extremely serious imprecision.

Potential biases in the review process

We were committed at all times to following the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2021a](#)), to avoid potential biases in the review process.

An experienced medical information specialist developed an all-encompassing search strategy, which was peer-reviewed by another information specialist. We included all identified published studies, but also kept track of studies that were either still ongoing or labelled as completed in the study registry, to avoid overlooking any upcoming publication. The search included relevant electronic databases as well as clinical trial registries. We contacted principal investigators and requested additional information of our interest. In addition to peer-reviewed full-text articles, we also included preprints (one of which was withdrawn and one of which was shortly later published as a peer-reviewed version). We are confident that we identified all relevant studies to date and will monitor ongoing studies closely, as well as full publication of preprints, after the publication of this review.

We performed sensitivity analyses with a fixed-effect model and excluding studies at high risk of bias for the main outcome, but did not find any relevant differences in all-cause mortality up to day 28. One study reported longer follow-up ([REMAP-CAP 2022](#), 90-day and 180-day mortality) and found a potential small effect (adjusted hazard ratio with credibility intervals) favouring treatment with antiplatelets. For 180-day mortality, the corresponding risk ratio suggests an insignificant very small effect with a wide confidence interval crossing the zero effect line. Due to imprecision and risk of bias, we downgraded by two levels. We would need more studies reporting comparably long-term results to ascertain any effect on 90-day mortality.

We performed all steps of this review in duplicate, and consulted with at least one other review author (mostly in the team) in case of any disagreement. Since the publication of the review protocol, we have considered competing events carefully. We discussed whether we should revise our outcomes to take this issue into account, but decided to report outcomes as 'worsening up to day 28', 'thrombotic events', 'serious adverse events' and 'major bleeding' without the combination with death to avoid impact on the incidences of those events. We described each included study in full detail and made explicit judgements on individual risk of bias.

Agreements and disagreements with other studies or reviews

Despite there being reviews of other COVID-19 treatments, we did not identify many systematic reviews evaluating antiplatelets. Most reviews did not perform the essential steps for a systematic research synthesis, such as a comprehensive literature search, risk of bias assessment and evidence certainty grading. More importantly, they used only retrospective cohort studies, or pooled randomised controlled trials with retrospective cohort studies. Two systematic reviews reported a large effect favouring antiplatelets in terms of mortality (Wang 2021; Wijaya 2021). However, they included observational studies, which could be confounded. As we performed a rigorous evaluation of all available randomised controlled trials, our results differ substantially from these two systematic reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current evidence, in adults with moderate to severe coronavirus disease 2019 (COVID-19) the use of antiplatelets plus standard care in comparison to standard care probably results in little to no difference to mortality (up to day 28) or clinical progression (worsening or improvement). They probably slightly decrease thrombotic events but slightly increase the occurrence of major bleeding events. Low-certainty evidence suggests that antiplatelets may make little or no difference to 180-day mortality and may result in a slight increase in serious adverse events. We do not know whether antiplatelets have any impact on adverse events, as these results were reported too heterogeneously. For all outcomes, the 95% confidence interval includes both benefit and harm and our certainty in the evidence is moderate to low. We acknowledge that the true effect may slightly differ from the reported effect.

For people with a confirmed diagnosis of mild COVID-19, antiplatelets may have little to no effect on mortality up to day 45 or on the incidence of serious adverse events when compared to standard care with/without placebo, but they may slightly decrease the incidence of new thrombotic events. The evidence is very uncertain about the effect of antiplatelets compared to standard care with/without placebo regarding the outcomes 'admission to hospital or death up to day 45' and major bleeding. The included trials did not report on quality of life or non-serious adverse events during study treatment.

Implications for research

There is a need for more long-term data (e.g. 180-day mortality) and data on patient-relevant outcomes such as adverse events and

quality of life; most studies did not report these outcomes, or they were reported in an inconclusive way.

Moderate-certainty evidence suggests that there is probably little to no difference in 28-day all-cause mortality for hospitalised participants, so further research on this population might be low priority in future.

Because the virus has evolved and adapted rapidly in recent years, it is important to keep the science up to date. Therefore, new studies should report subgroup results for vaccinated persons and individuals with different COVID-19 variants, such as Omicron. Above all, good-quality research can help to fight the pandemic. Health-based policy interventions generally require scientifically justifiable studies that research prognostic effectiveness before policy implementation, and for evaluations afterwards. This highlights the urgent need for adequately powered randomised controlled trials (RCTs) with comparable study arms.

As we only identified two RCTs that included non-hospitalised people with mild disease treated with antiplatelets, efforts should be made to collect good-quality data regarding these people, and for those who are asymptomatic.

We identified 14 ongoing RCTs. Publications of these ongoing studies may resolve some uncertainties and allow better judgement regarding the effectiveness of antiplatelets for the treatment of COVID-19. In addition, three studies are already completed but have not yet been published, therefore their results are not included. In accordance with the approach of this review, we will update our search and include eligible trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Berger 2022

Study characteristics

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| Methods | <ul style="list-style-type: none"> Trial design: open-label, Bayesian, adaptive randomised clinical trial Type of publication: journal publication Setting: hospitalised participants Recruitment dates: September 2020 to June 2021 Country: USA, Brazil, Italy, Spain Language: English Number of centres: n.i. Inclusion criteria <ul style="list-style-type: none"> Laboratory confirmed COVID-19 + hospitalised without the need for intensive care (non-critically ill cohort) D-dimer level 2-fold or greater than the upper limit of normal (determined at each hospital site) or 60 to 84 years of age If younger than 60 years, enrolment if at least 1 of the following criteria met: oxygen requirement > 2 L per minute or hypertension, diabetes, chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m²), cardiovascular disease, or a body mass index of 35 or greater Exclusion criteria <ul style="list-style-type: none"> If 72 hours or more had elapsed from the hospital admission for COVID-19 or SARS-CoV-2 infection confirmation Hospital discharge expected within 72 hours Contraindication to P2Y12 inhibitors or a clinical requirement for dual antiplatelet therapy |
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Berger 2022 (Continued)

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| | <ul style="list-style-type: none"> • Trial registration number: NCT04505774 • Date of trial registration: 10 August 2020 |
| Participants | <ul style="list-style-type: none"> • Age: mean age, 52.7 (SD, 13.5) years • Gender: 41.5% women • Ethnicity: 58.5% White, 28.7% Hispanic, 26.2% Black, 2.9% Asian, 3.3% American Indian or Alaska Native • Number of participants (recruited/allocated/evaluated): 562/293 were randomised to receive a therapeutic dose of heparin plus a P2Y12 inhibitor, 269 to receive therapeutic heparin as standard care/ 562 evaluated • Severity of disease: symptomatic SARS-CoV-2 infection (COVID-19), laboratory confirmed, hospitalised without need for intensive care unit treatment (non-critically ill cohort) • Additional diagnoses: cardiovascular disease 43.7% intervention vs 55.8% standard care (hypertension, heart failure, coronary artery disease, peripheral artery disease, cerebrovascular disease), other diseases and chronic conditions: diabetes, chronic kidney disease, liver disease, respiratory disease (COPD, asthma) • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): 65.5% vs 62.5% glucocorticoids, 56.0% vs 47.6% remdesivir, 15.0% vs 13.4% acetylsalicylic acid, anticoagulant therapy 10.6% vs 14.5%, 2.7% vs 3.9% IL-6 inhibitors, 77.8% vs 78.4% low-flow oxygen, 0.8% vs 0.4% high-flow nasal cannula |
| Interventions | <ul style="list-style-type: none"> • Intervention: therapeutic dose anticoagulation + P2Y12 inhibitor (heparin standard care with an added P2Y12), of whom 63.2% received ticagrelor and 36.8% clopidogrel (89.5% with recommended loading dose) for 14 days or until hospital discharge; whichever occurred first • Control: therapeutic dose anticoagulation for 14 days or until hospital discharge; whichever occurred first |
| Outcomes | <p>Composite primary outcome</p> <ul style="list-style-type: none"> • Organ support-free days evaluated on an ordinal scale that combined in-hospital death (assigned a value of -1) and, for those who survived to hospital discharge, the number of days free of respiratory or cardiovascular organ support up to day 21 of the index hospitalisation (range, -1 to 21 days; higher scores indicate less organ support and better outcomes) <p>Components of the primary outcome</p> <ul style="list-style-type: none"> • Alive and free of organ support • Alive with organ support • Death (in-hospital) up to day 28 • Survival to hospital discharge • Death (overall) up to day 21 <p>Secondary outcomes (at day 28) and individual components</p> <ul style="list-style-type: none"> • Major thrombotic event (myocardial infarction, pulmonary embolism, ischaemic stroke, systemic arterial embolism) or in-hospital death • Any thrombotic event (major thrombotic events plus deep venous thrombosis) or in-hospital death • Major bleeding event or in-hospital death <p>Components of the secondary outcomes</p> <ul style="list-style-type: none"> • In-hospital death • Major thrombotic event • Any thrombotic event • Major bleeding event |
| Notes | <ul style="list-style-type: none"> • Funded by the National Institutes of Health |

Berger 2022 (Continued)

- Sponsor: National Heart, Lung, and Blood Institute
- Grants received by study authors: diverse national institutes (i.e. AHA, Agency for Healthcare Resources, etc.), Astra Zeneca, Janssen, Amgen, and Amarin, Cerus Corp, Abbott Vascular, Siemens, and BioTelemetry, Bayer Pharmaceuticals, Boehringer Ingelheim, Medtronic, Merck, Pfizer, Portola, and Sanofi, Bristol Myers Squibb, Amgen, Novartis, and Novo Nordisk, Cerenovus, Basking Biosciences, Lumosa, Diamedica, Sharp & Dohme, Omron Healthcare Inc, Amgen, Espero BioPharma, Sunovion Pharmaceuticals, Haemonetics, Instrumentation Laboratories, Accriva, Haemonetics, and Haima Therapeutics

Bohula 2022 (COVID-PACT)

Study characteristics

Methods

- Trial design: multicentre, 2 × 2 factorial, open-label RCT
- Type of publication: journal article
- Setting: hospital (participants on ICU or being cared for in a non-ICU room by an ICU team)
- Recruitment dates: 5 August 2020 to 2 March 2022
- Country: USA
- Language: English
- Number of centres: 34 centres
- Inclusion criteria: age ≥ 18 years (male or female), acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), currently admitted to an ICU, were at that level of care for ≤ 96 hours before randomisation, and did not have an indication for full-dose anticoagulation. ICU level of care was defined as (1) being admitted to an ICU or (2) being cared for in a non-ICU room by an ICU team or requiring advanced respiratory support (i.e. invasive mechanical ventilation, noninvasive positive pressure ventilation, or high-flow nasal canula for respiratory insufficiency), continuous vasopressor use, or mechanical circulatory support
- Exclusion criteria: ongoing (> 48 hours) or planned full-dose (therapeutic) anticoagulation for any indication, patients who meet the following criterion are excluded from the second randomisation (antiplatelet therapy vs no antiplatelet therapy); ongoing or planned antiplatelet therapy, including aspirin monotherapy, ongoing or planned treatment with dual antiplatelet therapy, contraindication to antithrombotic therapy or high risk of bleeding due to conditions including, but not limited to, any of the following: history of intracranial haemorrhage, known CNS tumour or CNS vascular abnormality, active or recent major bleeding within the past 30 days with untreated source, platelet count < 70,000 or known functional platelet disorder, fibrinogen < 200 mg/dL, international normalised ratio (INR) > 1.9, history of heparin-induced thrombocytopenia, ischaemic stroke within the past 2 weeks, pregnancy, study staff or their healthy family, any condition which in the investigator's assessment might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study; patients for whom further care is being forgone at the decision of the patient, family, and/or treating team ("comfort measures only"); participants who meet the following criterion are excluded from the second randomisation (antiplatelet therapy vs no antiplatelet therapy): 1. Ongoing or planned antiplatelet therapy, including aspirin monotherapy
- Trial registration number: NCT04409834
- Date of trial registration: 1 June 2020

Participants

- Age: ≥ 18
- Gender (intervention vs control, counts (%)): female 58 (39) vs 60 (43)
- Ethnicity (intervention vs control, counts (%)): white 115 (83) vs 91 (71) (statistically significant difference), Hispanic 28 (21) vs 25 (20)
- Number of participants (recruited/allocated/evaluated): 750/682/672398 screened, 390 randomised, 292 of them in the antiplatelet domain/292 evaluated (152 in antiplatelet stratum, 140 in control group). Recruitment stopped early due to decrease in ICU patients with COVID-19
- Severity of disease: acute SARS-CoV-2 infection (COVID-19) requiring ICU level of care, were at that level of care for ≤ 96 hours before randomisation, oxygen by mask or nasal canula 1 (0.7) vs 3 (2.1),

Bohula 2022 (COVID-PACT) (Continued)

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| | <p>noninvasive ventilation or high-flow nasal canula 128 (85) vs 115 (82), invasive ventilation 21 (14) vs 22 (16)</p> <ul style="list-style-type: none"> Additional diagnoses (intervention vs control, counts (%)): hypertension 76 (51) vs 76 (54), diabetes 40 (27) vs 41 (29), atherosclerotic cardiovascular disease 10 (6.7) vs 9 (6.4), active cancer 8 (5.3) vs 5 (3.6), current or past smoking 56 (37) vs 49 (35), chronic kidney disease 10 (6.7) vs 11 (7.9), pulmonary disease 31 (21) vs 29 (21) Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen by mask or nasal canula, noninvasive ventilation or high-flow nasal canula, invasive mechanical ventilation |
| Interventions | <p>Intervention: antiplatelet therapy with clopidogrel PLUS standard care, or clopidogrel PLUS therapeutic anticoagulation PLUS standard care</p> <ul style="list-style-type: none"> Control: standard care, or standard care PLUS therapeutic anticoagulation Doses <ul style="list-style-type: none"> Full-dose anticoagulation + antiplatelet therapy: unfractionated heparin IV continuous targeting the activated partial thromboplastin time (aPTT) of 1.5 to 2.5X control, or enoxaparin 1 mg/kg subcutaneously every 12 hours + clopidogrel 300 mg orally x1, followed by clopidogrel 75 mg orally once daily. Full-dose anticoagulation + no antiplatelet therapy: unfractionated heparin IV continuous targeting the activated partial thromboplastin time (aPTT) of 1.5 to 2.5X control, or enoxaparin 1 mg/kg every 12 hours Prophylactic anticoagulation + antiplatelet therapy: enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 IU subcutaneously 3 times a day + clopidogrel 300 mg orally once, followed by clopidogrel 75 mg orally daily Prophylactic anticoagulation + no antiplatelet therapy: enoxaparin 40 mg subcutaneously daily or unfractionated heparin 5000 IU subcutaneously 3 times a day Route of administration: NR For studies including a control group: comparator (type): prophylactic anticoagulation + no antiplatelet therapy Treatment details of control group (standard care, e.g dose, route of administration): <ul style="list-style-type: none"> Prophylactic anticoagulation + no antiplatelet therapy: enoxaparin 40 mg subcutaneously daily or unfractionated heparin 5000 IU subcutaneously 3 times a day Concomitant therapy: NR Treatment cross-overs: 31% of participants randomised to clopidogrel discontinued therapy, higher rate of cross-over from standard-dose prophylactic anticoagulation to full-dose anticoagulation Duration of follow-up: until hospital discharge or up to day 28 Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcome: venous or arterial thrombotic event</p> <p>Hierarchical composite: death due to venous or arterial thrombosis, pulmonary embolism, clinically evident deep vein thrombosis, type 1 MI, ischaemic stroke, systemic embolism or acute limb ischaemia, or clinically silent DVT</p> <p>Secondary outcomes: clinically evident venous or arterial thrombotic events</p> <p>Hierarchical composite: death due to venous or arterial thrombosis, pulmonary embolism, clinically evident deep vein thrombosis, type 1 MI, ischaemic stroke, systemic embolism or acute limb ischaemia</p> <p>Additional outcomes</p> <p>Bleeding, cardiovascular death/non-cardiovascular and unknown deaths</p> |
| Notes | <ul style="list-style-type: none"> Sponsor/funding: The TIMI Study Group, Brigham and Women's Hospital COIs: NR |

Bohula 2022 (COVID-PACT) (Continued)

- Other: NR

Connors 2021 (ACTIV-4B)

Study characteristics

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| Methods | <ul style="list-style-type: none"> • Trial design: multicentre, adaptive, randomised, double-blind, placebo-controlled platform trial • Type of publication: journal publication • Setting: non-hospitalised participants • Recruitment dates: September 2020 to June 2021 • Country: United States • Language: English • Number of centres: 52 • Inclusion criteria <ul style="list-style-type: none"> ◦ COVID-19 + in past 14 days ◦ Platelets > 100,000 ◦ eGFR > 30 mL/min • Exclusion criteria <ul style="list-style-type: none"> ◦ Hospitalised for COVID-19 ◦ Active cancer ◦ Recent major bleeding ◦ Contradiction/other indication for anticoagulation ◦ Pregnancy (or lactating) • Trial registration number: NCT04498273 • Date of trial registration: 4 August 2020 |
| Participants | <ul style="list-style-type: none"> • Age: median (IQR); 54 years (IQR, 46 to 59) • Gender: 59.1% women • Ethnicity: 12.7% Black, 28.1% Hispanic • Number of participants (recruited/allocated/evaluated): 657 randomised, of whom 164 were randomised to receive acetylsalicylic acid, 164 to receive placebo, 165 to receive apixaban in prophylactic dose and 164 to receive apixaban in therapeutic dose • Severity of disease: symptomatic SARS-CoV-2 infection (COVID-19) verified by positive polymerase chain reaction or antigen test • Additional diagnoses (intervention vs control): hypertension 34% vs 33%, diabetes (self-reported) 18% vs 14%, history of smoking 24% vs 19% • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <p>Study arms</p> <ul style="list-style-type: none"> • Placebo • Drug: prophylactic dose apixaban 2.5 mg • Drug: therapeutic dose apixaban 5.0 mg • Drug: acetylsalicylic acid 81 mg <p>Details of intervention</p> <ul style="list-style-type: none"> • Antiplatelet agent: low-dose acetylsalicylic acid 81 mg orally once a day for 45 days • Control group: matching placebo once a day |
| Outcomes | <p>Primary outcome: composite of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischaemic stroke, hospitalisation for cardiovascular or pulmonary events and all-cause mortality for up to 45 days after treatment initiation</p> |

Connors 2021 (ACTIV-4B) (Continued)

Secondary outcomes: individual components of the primary study end point as well as mortality without antecedent hospitalisation

Notes

Sponsor: This study was, in part, funded by National Institutes of Health (NIH) Agreement 1OT2H-L156812-01. Specifically, the ACTIV-4B trial was supported by Other Transition Authorities from the National Heart, Lung, and Blood Institute (NHLBI). Grantee institutions included the University of Pittsburgh; the University of Illinois Chicago; and the Brigham and Women's Hospital. The trial drugs and matching placebo were donated by the Bristol Myers Squibb–Pfizer Alliance.

COI

- Dr Connors reported receiving personal fees from Bristol Myers Squibb, Pfizer, Abbott, Alnylam, Takeda, Roche, and Sanofi and that his institution has received research funding from CSL Behring.
- Dr Brooks reported receiving personal fees for data and safety monitoring board membership from Cerus Corporation.
- Dr Krishnan reported receiving grants from Sergey Brin Family Foundation Research in COVID. Dr Bledsoe reported receiving grants payable his institution from the National Institutes of Health (NIH) for clinical trial work and receiving consulting fees from JAJ LLC.
- Dr Kirwan reported receiving grants from SOCAR Research SA.
- Dr Everett reported receiving consulting fees from Johnson & Johnson, Gilead, and Merck.
- Dr Hou reported receiving grants from Brigham and Women's Hospital, NIH, Novartis, and CalciMedica.
- Dr Haight reported receiving grants and nonfinancial support from OneFlorida.
- Dr Wilson reported receiving personal fees from Pfizer, Bristol Myers Squibb, Alexion, Janssen, and Paratek and receiving grants from Gilead.
- Dr Ridker reported receiving grants from Bristol Myers Squibb and Pfizer and serving as a consultant for work unrelated to this study for Corvidia, Novartis, Flame, Agepha, Inflazome, AstraZeneca, Janssen, Civi Biopharm, SOCAR, Novo Nordisk, Upton, Omeicos, and Boehringer Ingelheim.
- No other authors reported disclosures.

Eikelboom 2022 (ACTCOVID)

Study characteristics

Methods

- Trial design: open-label, parallel-group, factorial RCT
- Type of publication: journal article
- Setting: community patients
- Recruitment dates: 27 August 2020 to 10 February 2022
- Country: Brazil, Canada, Colombia, Ecuador, Egypt, India, Nepal, Pakistan, Philippines, Russian Federation, South Africa, United Arab Emirates
- Language: English
- Number of centres: 48 clinical sites
- Inclusion criteria: symptomatic and laboratory-confirmed diagnosis of COVID-19; age ≥ 30 years; high risk: either age ≥ 70 or one of the following: male; obesity (BMI ≥ 30); chronic cardiovascular, respiratory or renal disease; active cancer; diabetes; within 7 days (ideally 72 hours) of diagnosis, or worsening clinically
- Exclusion criteria: General: advanced kidney disease; advanced liver disease; pregnancy (known or potential) or lactation, Colchicine: allergy or planned use; current or planned use of cyclosporine, verapamil, HIV protease inhibitor, azole antifungal, or macrolide antibiotic (except azithromycin); ASA: allergy; high risk of bleeding, current or planned use of other anti-thrombotic drugs (e.g. P2Y12 inhibitors, direct oral anticoagulants, vitamin K antagonists, heparins)
- Trial registration number: NCT04324463

Eikelboom 2022 (ACTCOVID) (Continued)

- Date of trial registration: 27 March 2020

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| Participants | <ul style="list-style-type: none"> • Age: initially ≥ 18 years, after interim analysis adjusted to ≥ 30 years • Gender: intervention 1195 (61.4%) vs control 1155 (59.7%) • Ethnicity (intervention vs control) <ul style="list-style-type: none"> ◦ Arab 1021 (52.5%) vs 1017 (52.5%) ◦ White European 424 (21.8%) vs 431 (22.3%) ◦ Latin American 164 (8.4%) vs 156 (8.1%) ◦ South Asian 241 (12.4%) vs 228 (11.8%) ◦ Other Asian (2.6%) vs 58 (3.0%) ◦ Other 44 (2.3%) vs 45 (2.3%) • Number of participants (recruited/allocated/evaluated): 3917/3917/3881 |
| Interventions | <ul style="list-style-type: none"> • Intervention: standard care plus oral acetylsalicylic acid 100 mg once daily as a tablet for 28 days with/without (in a first randomisation) colchicine 0.6 mg twice daily for 3 days and then 0.6 mg once daily for 25 days • Control: standard care with/without (in a first randomisation) colchicine 0.6 mg twice daily for 3 days and then 0.6 mg once daily for 25 days |
| Outcomes | <ul style="list-style-type: none"> • Primary outcome: composite of major thrombosis (includes pulmonary embolism, acute limb ischaemia, stroke and myocardial infarction), hospitalisation or death • Secondary outcome: any thrombosis (major thrombosis plus venous thromboembolism) • Additional exploratory outcomes: composite of hospitalisation or respiratory death and individual components of composites |
| Notes | Sponsor/funding: Canadian Institutes for Health Research, Bayer, Population Health Research Institute, Hamilton Health Sciences Research Institute, and ThistleDown Foundation |

Horby 2021 (RECOVERY)

Study characteristics

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| Methods | <ul style="list-style-type: none"> • Trial design: open-label, phase 2 + 3 RCT • Type of publication: journal article • Setting: hospitalised participants • Recruitment dates: 1 November 2020 to 21 March 2021 • Country: UK, Indonesia, Nepal • Language: English • Number of centres: 177 in the UK, 2 in Indonesia, 2 in Nepal • Inclusion criteria: hospitalised, SARS-CoV-2 infection (clinically suspected or laboratory confirmed) • Exclusion criteria: if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient, for patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial; no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial • Trial registration number: NCT04381936 • Date of trial registration: 11 May 2020 |
| Participants | <ul style="list-style-type: none"> • Age: mean (SD); 59.2 years (SD 14.1) in the intervention group and 59.3 years (SD 14.3) in the control group |

Horby 2021 (RECOVERY) (Continued)

- Gender: 4570 (62%) male in the intervention group and 4631 (61%) in the control group
- Ethnicity: 5474 (74%, intervention) vs 5655 (75% control) White, 1176 (16%, intervention) vs 1202 (16%, control) Black, Asian and minority, 701 (10%, intervention) vs 684 (9%, control) unknown
- Number of participants (recruited/allocated/evaluated): 22,560/7351 (aspirin) and 7541 (standard care)/7351 (aspirin) and 7541 (standard care)
- Severity of disease: moderate to severe
- Additional diagnoses: diabetes (22% each group), heart disease (11% intervention group vs 10% standard care group), chronic lung disease (19% each group), tuberculosis and HIV (< 0.5% per group), severe liver disease (1% each group), severe kidney impairment (3% each group), any of the above (43% each group)
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Concomitant therapy: use of corticosteroids (94% each group)

Interventions

- Drugs: aspirin 150 mg orally once daily until discharge
- Comparator: standard care, no details reported
- Concomitant therapy: NR
- Treatment cross-overs: only 6587 (90%) participants in the intervention group received at least one dose of aspirin and 210 (3%) participants in the control group received at least one dose of aspirin.
- Duration of follow-up: 28 days
- Compliance with assigned treatment: only 5040 (77%) participants in the intervention group took their allocated medication most days following randomisation
- SARS-CoV-2 test result: positive 97% (each group), negative 1% (each group), unknown 2% (each group), number of PCR-positive unknown

Outcomes

Primary outcome

1. All-cause mortality

Secondary outcomes

1. Duration of hospital stay; median time to being discharged alive, discharged from hospital within 28 days
2. Receipt of invasive mechanical ventilation or death
3. Invasive mechanical ventilation

Additional outcomes

1. Need for (and duration of) ventilation
2. Need for non-invasive ventilation
3. Need for renal replacement
4. Successful cessation of invasive mechanical ventilation
5. Number of patients who had thrombotic events
6. Major bleeding events
7. Major cardiac arrhythmias

Notes

- Sponsor/funding: UK Research and Innovation (Medical Research Council), National Institute of Health Research, and the Wellcome Trust through the COVID-19 Therapeutics Accelerator
- COIs: the authors report no COI
- Other: NR

REMAP-CAP 2022

Study characteristics

Antiplatelet agents for the treatment of adults with COVID-19 (Review)

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REMAP-CAP 2022 (Continued)

Methods

- Trial design: Bayesian, adaptive, open-label randomised platform trial
- Type of publication: journal publication
- Setting: hospitalised patients
- Recruitment dates: 30 October 2020 to 23 June 2021 for the first publication, follow-up until 2 March 2022
- Country: Canada, France, Germany, India, Italy, Nepal, the Netherlands, the UK
- Language: English
- Number of centres: 105
- Platform inclusion criteria
 - Adult (18 years old) patients admitted to hospital with acute illness due to suspected or proven COVID-19 infection
- Antiplatelet therapy domain-specific inclusion criteria
 - COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
 - Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract sections or both has occurred or is intended to occur
- Platform exclusion criteria
 - Death is imminent and inevitable within the next 24 hours AND one or more of the patient, the surrogate decision maker, or the attending physician are not committed to full active treatment
 - Patient is expected to be discharged from hospital today or tomorrow
 - More than two weeks have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven COVID-19 infection
 - Previous participation in REMAP within the last 90 days
- Antiplatelet therapy domain-specific exclusion criteria
 - More than 48 hours has elapsed since ICU admission
 - Clinical or laboratory bleeding risk or both that is sufficient to contraindicate antiplatelet therapy
 - Patient is already receiving antiplatelet therapy OR NSAID (non-steroidal anti-inflammatory drug) or a clinical decision has been made to commence antiplatelet or NSAID therapy
 - Enrolment in a trial evaluating anticoagulation or antiplatelet therapy for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
 - Patients older than 75 years AND otherwise eligible for the therapeutic anticoagulation domain
 - Creatinine clearance < 30 mL/min, or receiving renal replacement therapy or extracorporeal membrane oxygenation (ECMO)
 - The treating clinicians believe that participation in the domain would not be in the best interests of the patient
 - Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
 - Known or suspected pregnancy will result in exclusion from the P2Y12 inhibitor intervention
 - Administration or intention to administer lopinavir/ritonavir will result in exclusion from the P2Y12 inhibitor intervention at sites that are using clopidogrel and ticagrelor as the P2Y12 inhibitor
- Trial registration number: NCT02735707
- Date of trial registration: 13 April 2016 (study was already designed before COVID-19 became relevant)

Participants

- Age: median age (IQR) 57.0 years
- Gender: 33.4 % female
- Ethnicity: Asian 11.2 %, Black 3.2 %, Mixed 2.7%, White 77.3%, Other 5.5%
- Number of participants (recruited/allocated/evaluated): 6775/1824/1795
- 97% (1370 of 1411) in the critically ill and 98% (237 of 241) in non-critically ill participants with confirmed COVID-19 were evaluated, for the 180-day publication only the initially critically ill were evaluated

REMAP-CAP 2022 (Continued)

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|---------------|---|
| | <ul style="list-style-type: none"> Severity of disease: acute illness due to suspected or proven COVID-19; divided into critically ill or non-critically ill group <ul style="list-style-type: none"> Critically ill: patients admitted to an ICU and receiving respiratory organ support (invasive or noninvasive mechanical ventilation including via high-flow nasal cannula if the flow rate was at least 30 L/min and the fraction of inspired oxygen was at least 0.4) or cardiovascular organ support (receipt of vasopressors or inotropes), n = 1532 Non-critically ill: all others, n = 263 Additional diagnoses: diabetes 21.9%, respiratory disease 18.8%, kidney disease 3.5%, severe cardiovascular disease 4.0%, any immunosuppressive condition 4.0% Previous treatments within 48 h of recruitment: steroids 97.0%, remdesivir 21.9%, tocilizumab 38.7%, sarilumab 9.3%, low molecular weight heparin/unfractionated heparin/direct oral anticoagulants in different dosing |
| Interventions | <ul style="list-style-type: none"> Control arm: standard care, possibly with other intervention arms of REMAP-CAP Intervention arms: <ul style="list-style-type: none"> Acetylsalicylic acid arm: 75 mg to 100 mg once daily P2Y12 arm: clopidogrel 75 mg once daily without a loading dose, prasugrel (60 mg loading dose followed by 10 mg daily (if aged < 75 years and weight ≥ 60 kg) or 5 mg daily (if aged ≥ 75 years or weight < 60 kg)), ticagrelor 60 mg twice daily without a loading dose |
| Outcomes | <p>Primary outcomes: organ support-free days to day 21, survival to hospital discharge</p> <p>Secondary outcomes: 90-day mortality, progression to intubation, ECMO or death, days free from organ support (respiratory, cardiovascular), length of stay in the hospital, hospital mortality, death or major thrombotic events, major bleeding, serious adverse events, etc.</p> |
| Notes | <p>Sponsor: the Platform for European Preparedness Against (Re-)Emerging Epidemics (PREPARE) consortium of the European Union, FP7-HEALTH-2013-INNOVATION-1 (grant 602525), the Rapid European COVID-19 Emergency Research Response (RECOVER) consortium of the European Union's Horizon 2020 Research and Innovation Programme (grant 101003589), the Australian National Health and Medical Research Council (grant APP1101719), the Health Research Council of New Zealand (grant 16/631), the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program (grant 158584), the NIHR and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (grant CTN 2014-012), the University of Pittsburgh Medical Center (UPMC) Learning While Doing Program, the Translational Breast Cancer Research Consortium, the French Ministry of Health (grant PHRC-20-0147), the Minderoo Foundation, and the Wellcome Trust Innovations Project (grant 215522). Dr Shankar-Hari is funded by an NIHR clinician scientist fellowship (grant CS-2016-16-011) and Dr Gordon is funded by an NIHR research professorship (grant RP-2015-06-18).</p> <p>19 authors had pharmaceutical grants</p> |

ASA: acetylsalicylic acid; COI: conflicts of interest; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; eGFR: estimated glomerular filtration rate; ICU: intensive care unit; IQR: interquartile range; IV: intravenous; n.i.: no information; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

| Study | Reason for exclusion |
|--|-------------------------|
| Eikelboom 2022 (ACTCOVID19 hospitalised) | Ineligible intervention |
| NCT04483960 | No platelet inhibitor |

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT04391179

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|---------------|--|
| Methods | <ul style="list-style-type: none"> • Trial design: proof-of-concept, single-centre, single-blinded, placebo-controlled, randomised trial • Type of publication: trial registry • Setting: hospital • Recruitment dates: between May 2020 and January 2021 • Country: USA • Language: English • Number of centres: single-centre • Inclusion criteria: age ≥ 18 years, willing and able to provide informed consent prior to performing study procedures unless they have a legally authorised representative (LAR), confirmed coronavirus (SARS-CoV-2) infection, currently hospitalised or anticipated hospitalisation requiring supplemental oxygen • Exclusion criteria: in the opinion of at least two physicians, unlikely to survive for > 48 hours from screening, concurrent enrolment in a clinical trial of a cytokine inhibitor (targeting IL-6, IL-6R, IL-1, or Janus kinase) - use of remdesivir is permitted, currently on invasive mechanical ventilation, hypotension defined as systolic blood pressure < 90 mmHg on two readings at least 4 hours apart, pregnant or breastfeeding, concurrent dual antithrombotic therapy (aspirin or P2Y12 inhibitor (e.g. clopidogrel, ticagrelor) plus anticoagulation to treat deep venous thrombosis or pulmonary embolism, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5 times upper limit of normal, haemoglobin < 8 g/dl, or platelets $< 50,000$ per mm^3, history of recent major bleeding, defined in accordance with the criteria of the International Society on Thrombosis and Hemostasis (ISTH), any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study • Trial registration number: NCT04391179 • Date of trial registration: 18 May 2020 • Prospective completion date: February 2022 |
| Participants | <ul style="list-style-type: none"> • Age: 18 to 65 • Gender: female (33.3%)/male (66.7%) • Ethnicity: Hispanic or Latino (1 %)/not Hispanic or Latino (94.9%)/unknown or not reported (4%) • Number of participants (recruited/allocated/evaluated): 160/99/96 • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnoses: NR • Previous treatments: currently hospitalised or anticipated hospitalisation requiring supplemental oxygen |
| Interventions | <p>Intervention: dipyridamole 100 mg by mouth 4 times a day for 14 days</p> <p>Control: placebo given by mouth 4 times a day for 14 days</p> <p>Concomitant therapy: NR</p> <p>Treatment cross-overs: NR</p> <p>Duration of follow-up: NR</p> <p>Compliance with assigned treatment: NR</p> |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Per cent change in D-dimer (baseline, up to approximately 14 days after last study drug administration) 2. Number of participants with wins at each level of a hierarchical composite rank score (up to approximately 30 days after hospital discharge). Compare each dipyridamole patient head to head |

NCT04391179 (Continued)

against each placebo patient using a hierarchical composite rank score; a) death, b) days on mechanical ventilation, c) dichotomised (yes/no) decrease in daily average SpO₂/FiO₂ of at least 50 units relative to day 1 at anytime during the observation period, d) cumulative sum of COVID ordinal score during study hospitalisation.

Secondary outcomes

1. Days alive and free of organ support (up to approximately 28 days after last study drug administration score). Organ support is defined as receipt of invasive mechanical ventilation, vasopressor therapy, ECMO support, or dialysis
2. Individual component of composite endpoint - death (up to approximately 30 days after hospital discharge), death of any cause during duration of study participation
3. Individual component of composite endpoint - days on mechanical ventilation (up to 14 days after study drug administration)
4. Individual component of composite endpoint - SpO₂/FiO₂ (as shown by participant count) (up to 14 days after study drug administration). Binary outcome indicating patients whose SpO₂/FiO₂ dropped 50 points relative to baseline at any time during hospitalisation.
5. Individual component of composite endpoint - cumulative sum of WHO Ordinal Scale for Clinical Improvement scores during hospitalisation or through 14 days after study drug administration, whichever occurs first

Notes

- Sponsor/funding: University Michigan
- COIs: NR

NCT04659109

Methods

- Trial design: randomised, double-blind, multicentre, placebo-controlled, parallel-group, fixed-dose, phase II study
- Type of publication: trial registration
- Setting: hospital
- Recruitment dates: completed
- Country: France
- Language: English
- Number of centres: NR
- Inclusion criteria: male or female hospitalised patients ≥ 18 years; having given their written consent; having a positive RT-PCR test for COVID-19; presenting with symptoms of COVID-19, (including: cough OR shortness of breath or difficulty breathing OR at least 2 of the following: fever, defined as any body temperature 38 °C, chills, repeated shaking with chills, muscle pain, headache, sore throat, new loss of taste or smell, presenting with signs of moderate but progressive pulmonary disease (with: respiratory symptoms (cough, dyspnoea, etc.), uni- or bilateral ground-glass opacities, or pulmonary infiltrates on chest radiograph and/or CT scan, clinical and biological evidence of progression over the past 48 hours); effective birth control that should have been in place for at least 2 months in non-menopausal women and 4 months for men after IMP administration; women of child-bearing potential must have negative results of a urinary or plasma pregnancy test (serum HCG).
- Exclusion criteria: patients requiring immediate admission to the ICU; patients requiring invasive mechanical ventilation, acute respiratory distress syndrome (ARDS) of another origin; concomitant pulmonary infection (pneumoniae) with another agent, notably bacterial or fungal; patients under immunosuppressive agents; childbirth within < 10 days; pregnancy or breastfeeding; prior cardiopulmonary resuscitation < 10 days; allergy or hypersensitivity to drugs of the same class; participation in another interventional clinical trial within 30 days prior to the inclusion.
- Trial registration number: NCT04659109
- Date of trial registration: 9 December 2020

Participants

- Age: ≥ 18 years

NCT04659109 (Continued)

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| | <ul style="list-style-type: none"> Gender: male and female Ethnicity: NR Number of participants (recruited/allocated/evaluated): NR, but 60 planned Severity of disease: hospitalised participants WHO Clinical Progression Scale 4-5 Additional diagnoses: NR Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR Percentage of positive PCR: 100% (due to inclusion criteria) |
| Interventions | <ul style="list-style-type: none"> Intervention (e.g dose, route of administration): 1000 mg glenzocimab per day for 3 days, IV Control: placebo, IV Concomitant therapy: NR Treatment cross-overs: NR Duration of follow-up: 40 days planned Treatment cross-overs: NR Compliance with assigned treatment: NR |
| Outcomes | <ul style="list-style-type: none"> Primary outcome: progression from moderate to severe assessed at day 4 is a composite failure endpoint, defined as the occurrence of at least one of the following failure events: respiratory rate (RR) ≥ 30/min, or oxygen saturation (SpO₂) $\leq 93\%$ in resting state, or oxygen pressure/ inspired fraction (PaO₂/FiO₂) ≤ 200 mmHg, death occurring prior to or on day 4 Secondary outcomes, assessed up to day 40 unless otherwise specified <ul style="list-style-type: none"> All-cause mortality WHO-COVID-19 scale NEWS-2 scale Respiratory rate status (RR) Hypoxaemia status SpO₂ status CHEST CT-Scan (or in exceptional cases, chest radiogram) Oxygen-free days Admission to the ICU ICU-free days Hospital-free days Clinical recovery and time to clinical recovery Cure and time to cure Incidence, nature and severity of adverse events, serious adverse events (SAEs), suspected unexpected serious adverse reaction (SUSARs) and Treatment-Emergent Adverse Events (TEAEs) Incidence of bleeding-related events Incidence of hypersensitivity reactions Changes from baseline on blood pressure Changes from baseline on heart rate Changes from baseline on neuroforaminal stenosis Changes from baseline on INR (international normalised ratio)/PTT (prothrombin time test) Other biochemical markers not of interest to our review |
| Notes | <ul style="list-style-type: none"> Sponsor/funding: Acticor Biotech First posted: 9 December 2020 Last update posted: 13 September 2021 |

RESIST 2021

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| Methods | <ul style="list-style-type: none"> Trial design: RCT, open-label, phase 2 + 3 |
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RESIST 2021 (Continued)

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| | <ul style="list-style-type: none"> Type of publication: preprint Setting: hospital, National Cancer Institute (NCI), Jhajjar, Haryana Recruitment dates: completed Country: India Language: English Number of centres: 1 (single-centre) Inclusion criteria: age from 40 to 75 years, both genders, RT-PCR positive for SARS-CoV-19 infection, symptoms; WHO clinical improvement ordinal score 3 to 5 requiring hospital admission, consenting to participate in the trial Exclusion criteria: critical illness with WHO clinical improvement ordinal score > 5, documented significant liver disease/dysfunction (AST/ALT > 240), myopathy and rhabdomyolysis (CPK > 5x normal), allergy or intolerance to statins, allergy or intolerance to aspirin, patients taking the following medications: cyclosporine, HIV protease inhibitors, hepatitis C protease inhibitor, telaprevir, fibric acid derivatives (gemfibrozil), niacin, azole antifungals (itraconazole, ketoconazole) clarithromycin and colchicine, prior statin use (within 30 days), prior aspirin use (within 30 days), history of active GI bleeding in past 3 months, coagulopathy, thrombocytopenia (platelet count < 100,000/dL), pregnancy, active breastfeeding, patient unable to take oral or nasogastric medications Trial registration number: CTRI/2020/07/026791 Date of trial registration: 25 July 2020 |
| Participants | <ul style="list-style-type: none"> Age: 40 to 75 years Gender: 650 male/250 female Ethnicity: NR Number of participants (recruited/allocated/evaluated): 900/900/800 Severity of disease: SARS-CoV-2 infection (COVID-19)- WHO Ordinal Scale for Clinical Improvement 3, 4, 5 Additional diagnoses: NR Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR Percentage of positive PCR: 100% (due to inclusion criteria) |
| Interventions | <ol style="list-style-type: none"> Intervention: aspirin oral tablet aspirin 75 mg once daily for 10 days or till discharge, whichever is later Intervention: atorvastatin: oral tablet atorvastatin 40 mg once daily for 10 days or till discharge, whichever is later Intervention: aspirin + atorvastatin: oral tablet aspirin 75 mg once daily for 10 days or till discharge, whichever is later, + oral tablet atorvastatin 40 mg once daily for 10 days or till discharge, whichever is later Comparator: conventional therapy for COVID-19 infected patients <p>Concomitant therapy: NR</p> <p>Treatment cross-overs: NR</p> <p>Duration of follow-up: all study participants were followed up for 10 days or until hospital discharge, whichever was later</p> <p>Treatment cross-overs: NR</p> <p>Compliance with assigned treatment: NR</p> |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> Clinical deterioration characterised by progression to WHO clinical improvement ordinal score ≥ 6 (i.e. endotracheal intubation, non-invasive mechanical ventilation, pressor agents, RRT, ECMO, and mortality) <p>Secondary outcomes</p> |

RESIST 2021 (Continued)

1. Change in serum inflammatory markers (ESR, CRP, and IL-6), Trop I, CPK from time zero to fifth day of study enrolment or seventh day after symptom onset, whichever is later
2. ICU admission
3. In-hospital mortality
4. Length of hospital stay
5. Length of ICU stay
6. Progression to acute respiratory distress syndrome
7. Progression to shock
8. Safety concerns - e.g. myalgia, myopathy, rhabdomyolysis, hepatotoxicity, bleeding (minor and major) and others (if any)

Additional outcomes: NR

Notes

- Sponsor/funding: The TIMI Study Group/no funding source
- COIs: the authors declare that there is no conflict of interest
- Other: approved by Institute Ethics Committee

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IV: intravenous; NR: not reported; RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

ChiCTR2000030055

| | |
|--------------|--|
| Study name | Multicentre study for the treatment of Dipyridamole with novel coronavirus pneumonia (COVID-19) |
| Methods | <ul style="list-style-type: none"> • Trial design: prognosis, parallel multicentre trial • Type of publication: trial registration • Recruitment dates: February 2020 to March 2020 • Country: China • Language: English • Number of centres: multicentre (6 centres) • Inclusion criteria: suspected cases of neo-coronary pneumonia (outside Hubei province), clinically diagnosed cases (in Hubei province), and light/general confirmed cases, severe/critical confirmed cases, aged 18 to 70 years • Exclusion criteria: patients with presence, coagulopathy or hypotension; pregnant and lactating women; people with allergies or allergies to Xuebijing Injection and its components; severe basic diseases that affect survival, including: uncontrolled malignant tumours that have metastasised and cannot be removed, blood diseases, cachexia, active bleeding, severe malnutrition, HIV, etc.; pulmonary tumours caused by obstructive pneumonia, severe interstitial fibrosis, alveolar proteinosis, allergic alveolitis; continued use of immunosuppressive agents or organ transplants in the last 6 months; extracorporeal life support (ECMO, ECCO2R, RRT); expected deaths within 48 hours; clinicians judge inappropriate. • Trial registration number: ChiTR2000030055 • Date of trial registration: February 2020 • Prospective completion date: NR |
| Participants | <ul style="list-style-type: none"> • Age: 18 to 70 years • Gender: female/male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 460 planned • Severity of disease: severe disease (diagnosis of severe case was made if patients met any of the following criteria: (1) respiratory failure which requiring mechanical ventilation; (2) shock; (3) combined with other organ failure, need to be admitted to ICU) • Additional diagnosis: NR |

ChiCTR2000030055 (Continued)

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| Interventions | <ul style="list-style-type: none"> • Drug: dipyridamole 150 mg via orally 3 times a day for 7 days • Concomitant therapy: all patients received antiviral (ribavirin, 0.5 g, every 12 hours), corticoid (methylprednisolone sodium succinate, 40 mg, qd), oxygen therapy, and nutritional support as necessary • Treatment cross-overs: NR • Duration of follow-up: NR • Compliance with assigned treatment: NR |
| Outcomes | <ul style="list-style-type: none"> • Primary outcomes: complete blood count, CRP, blood coagulation, D-dimer, virological examination of pharyngeal swab, pulmonary imaging • Secondary outcomes: NR • Additional outcomes: NR |
| Starting date | March 2020 |
| Contact information | Qingling Zhang <ul style="list-style-type: none"> • Tel.: +86 13609068871 • E-mail: zqling68@hotmail.com • Address: 151 Yanjiang Road West, Yuexiu District, Guangzhou, Guangdong, China |
| Notes | Funding: National Key R&D Program of China, National Natural Science Foundation of China, Taikang Insurance Group Co., Ltd and Beijing Taikang Yicai Foundation and philanthropy donation from individuals. |

CTRI/2020/08/027503

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|--------------|--|
| Study name | Low Dose aspirin in Moderate to Severe SARS- CoV-2 Infected Patients: A Pilot Randomized Controlled Trial |
| Methods | <ul style="list-style-type: none"> • Trial design: RCT, open-label • Type of publication: trial registry • Setting: hospital • Recruitment dates: not yet recruiting • Country: India • Language: English • Number of centres: NR • Inclusion criteria: adult (aged between 18 and 65 years) patients with laboratory-confirmed SARS-CoV-2 infection with hypoxaemia (defined by room air SpO2 94%) at the time of randomisation will be included • Exclusion criteria: refusal to participate, mechanically ventilated patients, patients with P/F ratio, patients with any known coagulation disorder, patients with known platelet function disorder, patients who are already on antiplatelet therapy, patients with thrombocytopenia (platelet count 8), patients with any previous intracranial pathology, patients with known gastric/ duodenal ulcer, patients with history of gastro-intestinal bleeding within 3 months, pregnant women or women who are breastfeeding their children, or known allergy to aspirin • Trial registration number: CTRI/2020/08/027503 • Date of trial registration: 31 August 2020 • Prospective completion date: not reported |
| Participants | <ul style="list-style-type: none"> • Age: 18 to 65 years • Gender: NR • Ethnicity: NR |

CTRI/2020/08/027503 (Continued)

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| | <ul style="list-style-type: none"> Number of participants (recruited/allocated/evaluated): 60/NR/NR Severity of disease: SARS-CoV-2 infection (COVID-19) Additional diagnoses: hypoxaemia Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ul style="list-style-type: none"> Drug: low-dose aspirin (75 mg OD) for 10 days along with standard care Control: standard care will include standard practice of the institute at that time Concomitant therapy: NR Treatment cross-overs: NR Duration of follow-up: NR Treatment cross-overs: NR Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcome: SpO₂/ FiO₂ ratio in day 1 to 7 post randomisation in both the groups</p> <p>Secondary outcomes</p> <ol style="list-style-type: none"> Ventilation-free days (VFD) High-flow nasal oxygen and/or NIV-free days (NVFD) in both the groups Supplemental oxygen-free days (OFD) Mortality Duration of hospital stay Incidence of new onset non-respiratory organ dysfunction (AKI) Adverse effects Incidence of lower limb deep vein thrombosis <p>Additional outcomes: NR</p> |
| Starting date | NR |
| Contact information | Contact: Dr Souvik Maitra, 08146727891, souvikmaitra@live.com |
| Notes | <ul style="list-style-type: none"> Sponsor/funding: The TIMI Study Group COIs: NR Other: approved by Institute Ethics Committee |

CTRI/2021/03/032059

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|------------|---|
| Study name | Investigator initiated study to evaluate the effect of Marketed Colchicine 0.5mg given along marketed Aspirin 75mg with SOC and Marketed aspirin 75mg with SOC on COVID 19 patients |
| Methods | <ul style="list-style-type: none"> Trial design: open-label, randomised, 2-arm clinical trial Type of publication: trial registry Setting: outpatient Recruitment dates: not yet recruiting Country: India Language: English Number of centres: 1 Inclusion criteria: 40 years, positive oropharyngeal/nasal swab RT-PCR for SARS-CoV-2, diagnosed not more than 2 days ago diagnosis, patients with moderate symptoms (moderate symptoms cough, weakness fatigue, sore throat, fever > 38.5 °C, clinical signs of pneumonia as per PI and features of dyspnoea/hypoxia including respiratory rate 24/min, resting SpO₂65), type 2 diabetes |

CTRI/2021/03/032059 (Continued)

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| | <p>mellitus, obesity, moderate to severe asthma, smoking current or former, cancer active history, COPD, chronic heart disease, cardiomyopathy, pulmonary hypertension</p> <ul style="list-style-type: none"> Exclusion criteria: less than 40 years and older than 80 years, with severe COVID-19 symptoms requiring immediate hospitalisation, severe COVID-19: pneumonia with respiratory rate > 30 breaths/min, severe respiratory distress, SpO2 for 2 days ago using oropharyngeal/nasal swab, history of cardiopulmonary resuscitation, patient with a known history of DVT, PE, stroke, atrial fibrillation, mechanical heart valve, recent stent placement or any other cardiovascular event or any other condition for which the patient is taking systemic anticoagulation/antiplatelet therapy (LMWH, coumadin, clopidogrel and/or other similar classes of therapy) prior to study enrolment. Trial registration number: CTRI/2021/03/032059 Date of trial registration: 17 March 2021 Prospective completion date: NR |
| Participants | <ul style="list-style-type: none"> Age: 40 to 80 years Gender: female/male Ethnicity: NR Number of participants (recruited/allocated/evaluated): 62 planned Severity of disease: patients with moderate symptoms Additional diagnosis: NR Previous treatments: NR |
| Interventions | <ol style="list-style-type: none"> Marketed colchicine 0.5 mg given along marketed aspirin 75 mg with standard care twice daily Marketed aspirin 75 mg with standard care twice daily |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> Management of inflammation and thrombotic condition through specific biomarkers Symptomatic improvement through the NEWS score and 8-point ordinal score <p>Secondary outcomes: safety</p> <p>Additional outcomes: NR</p> |
| Starting date | Enrolment planned for 2- March 2021 |
| Contact information | Dr Vispute Abhay Shantaram, 9819428656, surgician@gmail.com |
| Notes | Sponsors/funding: SRV Hospital, Dr Mandakini Parihar Marg Opposite LokmanyaTilak Terminus, Tilak Nagar, Chembur, Mumbai, Maharashtra |

CTRI/2021/06/034254

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|------------|---|
| Study name | Clinical trial of APMV2020 in Covid 19 subjects |
| Methods | <ul style="list-style-type: none"> Trial design: randomised, parallel-group, active controlled trial Type of publication: trial registry Setting: outpatient Recruitment dates: open to recruitment Country: India Language: English Number of centres: 2 Inclusion criteria: age: 18 to 60 years, confirmed COVID-19 patient with positive RT-PCR test, mild symptomatic patients having no signs of severe disease, home/institutional quarantined patients |

CTRI/2021/06/034254 (Continued)

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| | <p>with no necessity of dedicated hospital admission at the time of screening, participant willing to provide consent and follow up for study duration</p> <ul style="list-style-type: none"> Exclusion criteria: patients with autoimmune disease or self-reports HIV or syphilis infection, patients suffering from disorders where aspirin is contraindicated and/or as per the discretion of investigator, proves to be unfit for the study as per the investigator's discretion, pregnant or lactating women, requiring hospital admission at screening, any other comorbidity which is critical stage at screening which in investigator discretion finds subject not suitable for the trial participation Trial registration number: CTRI/2021/06/034254 Date of trial registration: 15 June 2021 Prospective completion date: NR |
| Participants | <ul style="list-style-type: none"> Age: 18 to 60 years Gender: female/male Ethnicity: NR Number of participants (recruited/allocated/evaluated): 60 planned Severity of disease: mild SARS-CoV-2 Infection (COVID-19) (see inclusion criteria) Additional diagnosis: NR Previous treatments (e.g. experimental drugs, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> Tablet containing aspirin and promethazine hydrochloride orally twice a day for 10 days, dose NR Multivitamin and multimineral tablet orally twice a day for 10 days, dose NR <p>Along with standard care as per MoHFW guidelines for 10 days</p> <ul style="list-style-type: none"> Concomitant therapy: NR Treatment cross-overs: NR Duration of follow-up: NR Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> Improvement of clinical symptoms including fever, headache, diarrhoea, breathlessness, cough, anosmia, fatigue and myalgia on 10 point VAS scale 0- no symptom and 10-severe symptom Reduction in elevated levels of inflammatory markers such as CRP, LDH ferritin and D-dimer Changes in blood oxygen level SPO₂, time point: screening day 3, day 5 and day 10 <p>Secondary outcomes</p> <ol style="list-style-type: none"> Requirement of hospitalisation Requirement of admission to intensive care unit Tolerability Safety evident by adverse events: time point: screening days 3, 5 and 10 <p>Additional outcomes: NR</p> |
| Starting date | NR |
| Contact information | <p>Mr Taasin Ahmed Shah, 912225817126, tdcruz@meyer.co.in</p> <p>Ms Tania Dcruz, 912225817126, tdcruz@meyer.co.in</p> |
| Notes | Sponsors/funding: Meyer Organics Pvt. Ltd A-303, Road No. 32, Wagle Estate, Thane - 400 604. (India) |

IRCT20180205038626N7

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|---------------------|--|
| Study name | The investigation of the effectiveness of ASA usage on the incidence of cardiovascular events in patients with coronavirus (COVID-19) A clinical trial study |
| Methods | <ul style="list-style-type: none"> • Trial design: randomised single-blinded trial, phase 2 • Type of publication: trial registry • Setting: Razi Hospital, Rasht • Recruitment dates: 5 December 2020 • Country: Iran • Language: English • Number of centres: NR • Inclusion criteria: all patients admitted with a diagnosis of COVID-19 based on CT scan or PCR; over 18 years • Exclusion criteria: patients admitted to the ICU. Patients with a history of ulcers and gastrointestinal problems. Patients receiving aspirin. Patients with a history of thrombotic events such as heart attack or stroke or a history of atrial fibrillation, congestive heart failure, active bleeding or coagulation disorders such as thrombocytopenia. • Trial registration number: IRCT20180205038626N7 • Date of trial registration: 27 December 2020 • Prospective completion date: not reported |
| Participants | <ul style="list-style-type: none"> • Age: > 18 years • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 36/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnoses: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> 1. Daily aspirin 80 mg for 3 months 2. Standard treatment for 3 months <ul style="list-style-type: none"> • Concomitant therapy: NR • Treatment cross-overs: NR • Duration of follow-up: NR • Treatment cross-overs: NR • Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Thromboembolic events 2. Cardiovascular accidents 3. Brain accidents <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Death <p>Additional outcomes: NR</p> |
| Starting date | NR |
| Contact information | Contact: Zahra Ahmadnia, +98 13 3361 8177, zahmadnia@gums.ac.ir |
| Notes | <ul style="list-style-type: none"> • Sponsor/funding: Rasht University of Medical Sciences • COIs: NR |

IRCT20180205038626N7 (Continued)

- Other: NR

NCT04363840

| | |
|---------------------|---|
| Study name | The LEAD COVID-19 Trial: Low-risk, Early aspirin and Vitamin D to Reduce COVID-19 Hospitalizations (LEAD COVID-19) |
| Methods | <ul style="list-style-type: none"> • Trial design: randomised clinical trial, open-label, phase 2 • Type of publication: trial registry • Setting: hospital • Recruitment dates: terminated • Country: USA • Language: English • Number of centres: NR • Inclusion criteria: patients > 18 years, written informed consent • Exclusion criteria: pregnant patients or prisoners, history of GI bleeding or peptic ulcer disease, or spontaneous bleeding from other sites; history of thrombocytopenia; history of chronic kidney disease; concurrent use of nonsteroidal anti-inflammatory drugs, or steroids, hypervitaminosis D and associated risk factors: renal failure, liver failure, hyperparathyroidism, sarcoidosis, histoplasmosis, new (within 24 hours) COVID-19 diagnosis • Trial registration number: NCT04363840 • Date of trial registration: 27 April 2020 • Prospective completion date: December 2020 |
| Participants | <ul style="list-style-type: none"> • Age: > 18 years • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1080/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnoses: vitamin D deficiency, coagulopathy, disseminated intravascular coagulation • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> 1. Aspirin 81 mg to be taken orally once daily for 14 days 2. Aspirin 81 mg to be taken orally once daily for 14 days + dietary supplement: vitamin D 50,000 IU to be taken orally once weekly for 2 weeks 3. Control: observation <ul style="list-style-type: none"> • Concomitant therapy: NR • Treatment cross-overs: NR • Duration of follow-up: NR • Treatment cross-overs: NR • Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes: hospitalisation</p> <p>Secondary outcomes: NR</p> <p>Additional outcomes: NR</p> |
| Starting date | 1 May 2020 |
| Contact information | Contact: Frank H Lau, MD 504 412 1240, flau@lsuhsc.edu |

NCT04363840 (Continued)

Notes

Due to missing funding the trial was not started

- Sponsor/funding: Louisiana State University Health Sciences Center in New Orleans
- COIs: NR
- Other: NR

NCT04365309

| Study name | Protective Effect of Aspirin on COVID-19 Patients (PEAC) |
|---------------|---|
| Methods | <ul style="list-style-type: none"> • Trial design: RCT, open-label, phase 2 + 3 • Type of publication: trial registry • Setting: Xijing Hospital • Recruitment dates: enrolling by invitation • Country: China • Language: English • Number of centres: NR • Inclusion criteria: meets one of the following criteria for confirmation of a novel coronavirus infection with pneumonia: 1. Detection of novel coronavirus nucleic acid is positive in respiratory or blood specimens by real-time -PCR, 2. Virus gene sequencing of respiratory or blood specimen is highly homologous with known novel coronavirus; not taken aspirin for nearly one month prior to the screening period. • Exclusion criteria: women who have recently been pregnant or breast-feeding, having a history of active gastrointestinal bleeding in the past 3 months, blood routine examination showed that the platelet count was $< 30 \times 10^9/L$, patients with coagulation disorders, unable to understand the potential risks and benefits of the study, and unable to follow up the evaluation as required, having no capacity for civil conduct, a history of drug or alcohol abuse, allergic to aspirin, influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human partial lung virus, mycoplasma pneumoniae, chlamydia pneumonia, bacterial pneumonia, organic pneumonia, etc., patients with cardiac stent placement (< 1 year), any more complex medical problems that may interfere with research behaviour or lead to increased risk, such as malignant tumours, blood diseases, liver diseases, AIDS, viral hepatitis, etc, chest image confirmed pulmonary involvement, fever: $\geq 36.7^\circ C$ under the armpit, $\geq 38.0^\circ C$ in the oral cavity or $\geq 38.6^\circ C$ in the rectum and eardrum; respiratory frequency ≥ 24 times/min or at least one cough, onset time ≤ 14 days • Trial registration number: NCT04365309 • Date of trial registration: 28 April 2020 • Prospective completion date: June 2020 |
| Participants | <ul style="list-style-type: none"> • Age: 18 to 85 years • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 128/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) (including mild, common, severe and critically ill) • Additional diagnoses: pneumonia • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> 1. Patients in the NCP aspirin group were given aspirin 100 mg/d orally after admission and aspirin for 14 days after discharge 2. Standard therapy <ul style="list-style-type: none"> • Concomitant therapy: NR • Treatment cross-overs: NR • Duration of follow-up: NR |

NCT04365309 (Continued)

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|---------------------|--|
| | <ul style="list-style-type: none"> • Treatment cross-overs: NR • Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Clinical recovery time (TTCR) 2. The time of SARS-CoV-2 overcasting <p>Secondary outcomes: NR</p> <p>Additional outcomes: NR</p> |
| Starting date | 10 February 2020 |
| Contact information | NR |
| Notes | <ul style="list-style-type: none"> • Sponsor/funding: Xijing Hospital • COIs: NR • Other: NR |

NCT04445623

| | |
|---------------|---|
| Study name | Prasugrel in Severe COVID-19 Pneumonia (PARTISAN) |
| Methods | <ul style="list-style-type: none"> • Trial design: RCT, open-label, phase 3 • Type of publication: trial registry • Setting: hospital • Recruitment dates: not yet recruiting • Country: Italy • Language: English • Number of centres: NR • Inclusion criteria: COVID-19 pneumonia, age over 18 years, willingness to express consent • Exclusion criteria: active neoplasia or in maintenance therapy, pregnancy and breastfeeding, any absolute contraindication to the use of antiplatelet drugs, pathological bleeding in progress, recent major bleeding at any location, need to use therapeutic doses of oral anticoagulants or heparins, need to use antiplatelet in combination for clinical indication, hypersensitivity to the active substance prasugrel or any of the excipients, clinical history of stroke or transient ischaemic attack (TIA), severe liver failure (Child-Pugh class C) • Trial registration number: NCT04445623 • Date of trial registration: 24 June 2020 • Prospective completion date: January 2021 |
| Participants | <ul style="list-style-type: none"> • Age: 18 to 99 years • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 128/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnoses: thrombosis • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> 1. Active comparator: film-coated tablets of prasugrel hydrochloride (10 mg daily dose after loading dose of 60 mg) orally once daily for 15 days 2. Placebo comparator: film-coated tablets of placebo orally once daily for 15 days <ul style="list-style-type: none"> • Concomitant therapy: NR |

NCT04445623 (Continued)

- Treatment cross-overs: NR
- Duration of follow-up: NR
- Treatment cross-overs: NR
- Compliance with assigned treatment: NR

| | |
|---------------------|---|
| Outcomes | <p>Primary outcomes</p> <p>1. P/F ratio at day 7</p> <p>Secondary outcomes</p> <p>1. Daily P/F ratio</p> <p>2. Daily need for oxygen supply</p> <p>3. Need for ICU</p> <p>4. Death</p> <p>5. MOF</p> <p>6. Discharge</p> <p>7. Clinical progression of the disease SOFA score</p> <p>8. Clinical progression of the disease APACHE II</p> <p>9. Venous thrombosis/ pulmonary embolism/thrombosis</p> <p>10. Need for CT imaging</p> <p>11. Daily Temperature</p> <p>12. Daily blood pressure</p> <p>13. Daily total blood count Hemoglobin</p> <p>14. Daily total blood count Red Blood Cells</p> <p>15. Daily total blood count Leukocytes</p> <p>16. Daily total blood count Platelets</p> <p>17. Daily indices of organ damage Liver</p> <p>18. Indices of inflammation C-reactive protein</p> <p>19. Indices of haemostasis PT</p> <p>20. Daily progression at imaging (chest-X-ray)</p> <p>21. Major bleeding</p> <p>22. Total bleeding</p> <p>23. Unexpected clinical or laboratory findings</p> <p>24. Indices of inflammation D-dimer</p> <p>25. Indices of inflammation Fibrinogen</p> <p>26. Indices of inflammation IL-6</p> <p>27. Indices of inflammation IL-1</p> <p>28. Daily indices of organ damage kidney</p> <p>29. Daily indices of organ damage heart</p> <p>30. Haemostasis aPTT</p> <p>31. Haemostasis VASP PRI</p> <p>32. Haemostasis platelet-leukocytes aggregates</p> <p>Additional Outcomes: NR</p> |
| Starting date | 1 July 2020 |
| Contact information | <ul style="list-style-type: none"> • Contact: Pietro Minuz, Professor 045-8124414 ext +39 pietro.minuz@univr.it • Contact: Marco Cattaneo, Professor 02-50323095 ext +39 marco.cattaneo@unimi.it |
| Notes | <ul style="list-style-type: none"> • Sponsor/funding: Azienda Ospedaliera Universitaria Integrata Verona • COIs: NR • Other: NR |

NCT04703608

| | |
|---------------|--|
| Study name | Prevention and Treatment for COVID -19 (Severe Acute Respiratory Syndrome Coronavirus 2 SARS-CoV-2) Associated Severe Pneumonia in the Gambia (PaTS-COVID) |
| Methods | <ul style="list-style-type: none"> • Trial design: RCT, single-blinded, phase 3 • Type of publication: trial registry • Setting: hospitals and private households • Recruitment dates: still recruiting • Country: Gambia and other part of Western Africa • Language: English • Number of centres: multicentre • Inclusion criteria <ul style="list-style-type: none"> ◦ Cohort1: individuals ≥ 5 years of age with confirmed COVID-19 mild disease or moderate pneumonia defined as: mild disease - influenza-like illness, with any of the following symptoms cough, fever, headache, sore throat, nasal congestion/runny nose, body pains (myalgia), fatigue (malaise), diarrhoea, abdominal pain, anorexia, nausea or vomiting without evidence of pneumonia or hypoxia, moderate pneumonia, clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) with no need for supplemental oxygen (oxygen saturation $\geq 90\%$ on room air or RR between 20 and 30 bpm), household contacts, individuals ≥ 5 years of age living in the same household with the index cases from cohort 1 will be offered to participate into the study, living in the same household is defined as those individuals who are planning to sleep in and eat from same 'cooking pot' during the following 2 weeks ◦ Cohort 2: individuals ≥ 12 years of age with suspected or confirmed COVID-19 associated severe pneumonia defined as signs of pneumonia (fever, cough, dyspnoea or fast breathing) plus one of: oxygen saturation (SpO₂) $< 90\%$ on room air OR respiratory rate > 30 breaths/minute, suspected COVID-19 disease is defined as clinically or radiologically suspected as determined by the most senior clinician available: clinically suspected signs and symptoms of pneumonia (as defined above) AND patient living in or recent travel to region with community transmission OR close contact with known COVID-19 patient AND no alternative diagnosis to explain the clinical picture OR, radiologically suspected typical radiological signs of COVID-19 on chest X-ray or lung ultrasound • Exclusion criteria: pregnant women will be excluded from both Cohort 1 and Cohort 2. Patients with allergies to the investigational products will be excluded Cohort 1 (Ivermectin). Lactating mothers will be excluded. Cohort 2 (aspirin): taking aspirin or other non-steroidal anti-inflammatory drugs for any reason, any bleeding disorder (e.g. frequent nose bleeds, haemophilia), active or recurrent peptic ulcer disease (defined as currently on triple therapy or had more than 1 course of triple therapy in the past 12 months, does not count symptoms of gastritis or on omeprazole as peptic ulcer disease), current active gastrointestinal haemorrhage, severe liver disease or severe kidney disease (severe liver disease defined as cirrhosis with portal hypertension and history of variceal bleeding; severe kidney disease defined as stage 4/5 KD, eGFR < 30 mL/min), gout, suspected intra-cerebral haemorrhage, diagnosed with a stroke on this admission • Trial registration number: NCT04703608 • Date of trial registration: 11 January 2021 • Prospective completion date: March 2022 |
| Participants | <ul style="list-style-type: none"> • Age: > 5 years • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1200/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnoses: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> 1. Aspirin 150 mg daily for 28 days or until hospital discharge or death 2. Placebo comparator |

NCT04703608 (Continued)

- Concomitant therapy: NR
- Treatment cross-overs: NR
- Duration of follow-up: NR
- Treatment cross-overs: NR
- Compliance with assigned treatment: NR

| | |
|---------------------|--|
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Cohort 1 Index case: percentage of patients with COVID-19 associated mild disease/moderate pneumonia progressing to severe pneumonia + Percentage of patients with COVID-19 associated mild disease/moderate pneumonia progressing within 14 days after recruitment into severe pneumonia 2. Cohort 1 Household contacts: percentage of HH members that get infected with SARS-CoV-2 + percentage of HH members that get infected with SARS-CoV-2 during the 14 days following recruitment 3. Cohort 2: percentage of COVID-19 associated severe pneumonia patients worsening their condition + percentage of COVID-19 associated severe pneumonia patients meeting the criteria of failure defined as worsening their condition from baseline (on admission) for a period of at least 24 hours, scale as follows: <ol style="list-style-type: none"> a. On or requiring supplemental oxygen given by nasal cannula or face mask to maintain SpO₂ within target range b. On or requiring non-invasive (e.g. CPAP or BiPAP) or invasive ventilatory support to maintain SpO₂ within target range (or not maintaining SpO₂ within target range with supplemental oxygen given by nasal cannula or face mask) 4. Death during hospitalisation <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Cohort 1 index cases: days from recruitment to virological clearance ± days from recruitment to virological clearance defined as one negative SARS-CoV2 virus RT-PCRs 2. Days from recruitment until clinical recovery ± days from recruitment until clinical recovery defined as 2 consecutive days of no fever ($T \leq 37.5^{\circ}\text{C}$) and normal respiratory rate (as per normal range for age and WHO definitions) (only once if day 28 as end of follow-up) 3. IgG geometric mean titre 4. Household contacts IgG geometric mean titre 5. Percentage of HH members infected that develop COVID-19 symptoms 6. Cohort 2 - hours from recruitment to hospital discharge 7. Hours of duration on oxygen supplementation 8. Death ratio during hospitalisation 9. Death ratio at 28 days after enrolment 10. Death ratio at 90 days after enrolment 11. Occurrence of clinical thrombotic and embolic events 12. Occurrence of clinical episodes of gastrointestinal bleeding 13. Change in CRP and D-dimer levels between baseline (enrolment) and day 3 to 5 14. Persisting breathlessness at 28 days and 90 days after enrolment 15. Self-reported health at 28 days and 90 days <p>Additional outcomes</p> <ol style="list-style-type: none"> 1. Poor self-reported health assessed by a linear self-reported health scale from the EQ-5D questionnaire in person or by telephone |
| Starting date | 22 January 2021 |
| Contact information | Contact: Anna Roca, PhD, +220 4495442 ext 2305, aroca@mrc.gm |
| Notes | <ul style="list-style-type: none"> • Sponsor/funding: London School of Hygiene and Tropical Medicine |

NCT04703608 (Continued)

- COIs: NR
- Other: NR

NCT04768179

| | |
|---------------|--|
| Study name | Safety & Efficacy of Low Dose aspirin / Ivermectin Combination Therapy for Treatment of Covid-19 Patients (IVCOM) |
| Methods | <ul style="list-style-type: none"> • Trial design: RCT open-label, phase 2 + 3 • Type of publication: trial registry • Setting: hospital • Recruitment dates: not yet recruiting • Country: Uganda • Language: English • Number of centres: NR • Inclusion criteria: provision of signed and dated informed consent form, willingness to comply with all study procedures and availability over the study duration, patients aged above 18 years to 64 years • Exclusion criteria: participants with known hypersensitivity to ivermectin, clinical diagnosis of severe renal and hepatic impairment, pregnancy or breastfeeding, co-treatment with either strong cytochrome p-450 inducers including: rifampicin, carbamazepine and barbiturates or inhibitors: isoniazid, clofazimine that might potentially affect ivermectin disposition and clinical outcomes, comorbidities including asthma, loa loa as assessed by travel history to Angola, Cameroon, Chad, Central African Republic, Congo, DR Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria and Sudan in the last 4 years, persons clinically diagnosed with and receiving treatment for any diathesis and PUD, active participation in another clinical trial, PCR positive for SARS-CoV-2 (COVID-19) from any of the MOH COVID-19 accredited testing laboratories, moderately ill COVID-19 patients score 3 (hospitalised with no oxygen therapy) to 4 (hospitalised with oxygen by mask or nasal prongs) according to the WHO ordinal scale for clinical improvement which translates to moderate to severe COVID-19 patients according to the Ministry of Health Uganda COVID-19 disease category • Trial registration number: NCT04768179 • Date of trial registration: 24 February 2021 • Prospective completion date: 30 September 2021 |
| Participants | <ul style="list-style-type: none"> • Age: 18 to 64 years • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 490/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnoses: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> 1. Intervention: 3-day ivermectin 200 µg/kg/day + 14-day 75 mg aspirin/day + standard care 2. Intervention: 3-day ivermectin 600 µg/kg/day + 14-day 75 mg aspirin/day + standard care 3. Control: standard care <ul style="list-style-type: none"> • Concomitant therapy: NR • Treatment cross-overs: NR • Duration of follow-up: NR • Treatment cross-overs: NR • Compliance with assigned treatment: NR |
| Outcomes | Primary outcomes |

NCT04768179 (Continued)

1. SARS COV 2 Viral clearance
2. World Health Organization COVID-19 ordinal improvement score

Secondary outcomes

1. Clinical recovery
2. Spectrum and severity of adverse events
3. Maximum Plasma concentration
4. Minimum Plasma concentration
5. Area Under the Curve

| | |
|---------------------|---|
| Starting date | 19 February 2020 |
| Contact information | <ul style="list-style-type: none"> • Contact: Jackson Mukonzo, PhD 256758113468 mukojack@yahoo.co.uk • Contact: Rita Nakato, MSc nakato.ritah@gmail.com |
| Notes | <ul style="list-style-type: none"> • Sponsor/funding: Makerere University • COIs: NR • Other: NR |

NCT04808895

| | |
|--------------|---|
| Study name | Acetylsalicylic Acid in the Prevention of Severe SARS-CoV2 Pneumonia in Hospitalised Patients With COVID-19 (Asperum) |
| Methods | <ul style="list-style-type: none"> • Trial design: RCT, double-blind, phase 3 • Type of publication: trial registry • Setting: medical area ward dedicated to COVID-19 patients • Recruitment dates: not yet recruiting • Country: Italy • Language: English • Number of centres: multicentre • Inclusion criteria: in a medical area ward dedicated to COVID-19 patients, positivity by RT-PCR of the search for genetic material of SARS-CoV-2, COVID-19 pneumonia with moderate clinical picture based on clinical parameters, O₂ saturation > 94% with maximum FiO₂ 32%, respiratory acts < 30/minute, age > 18 years, consent to participate in the study • Exclusion criteria: any antithrombotic treatment including acetylsalicylic acid, active bacterial infection, active or in maintenance therapy neoplasm, inability to provide consent, any contraindication to the acetylsalicylic acid use, active peptic disease, active major pathological bleeding, recent (<30 days) major bleeding, recent intracranial bleeding, need to use therapeutic doses of oral anticoagulants or heparins, need to use combination antiplatelet drugs for clinical indication, hypersensitivity to acetylsalicylic acid or to any of the excipients, hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), severe hepatic insufficiency (Child-Pugh class C), severe heart failure (NYHA class 3-4), platelet count less than 150,000/mm³, haemostasis alteration (INR > 1.5, APTT > 1.5), plasma fibrinogen < 100 mg/dL, blood pressure > 160/100 mmHg, concomitant treatment with serotonin reuptake inhibitors, participation in another pharmacological clinical trial • Trial registration number: NCT04808895 • Date of trial registration: 22 March 2021 • Prospective completion date: 31 August 2021 |
| Participants | <ul style="list-style-type: none"> • Age: > 18 • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 204/NR/NR |

Antiplatelet agents for the treatment of adults with COVID-19 (Review)

NCT04808895 (Continued)

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|---------------|--|
| | <ul style="list-style-type: none"> Severity of disease: SARS-CoV-2 infection (COVID-19) Additional diagnoses: thrombosis pulmonary Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR |
| Interventions | <ol style="list-style-type: none"> Acetylsalicylic acid: tablets of 100 mg daily dose, for 15 days, on the first day 3 tablets Placebo: 1 tablet daily dose, for 15 days, on the first day 3 tablets <ul style="list-style-type: none"> Concomitant therapy: NR Treatment cross-overs: NR Duration of follow-up: NR Treatment cross-overs: NR Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> Prevention of clinical worsening Prevention of lung function worsening Prevention of death <p>Secondary outcomes</p> <ol style="list-style-type: none"> Change in body temperature Change in oxygen saturation Change in blood gases Change in blood cell count Change in blood oxygen Change in clinical markers of lung function Change in clinical markers of liver damage Change in clinical markers of hearth damage Change in clinical markers of renal damage Effects on blood cell count Effects on CRP Effects on D-dimer Effects on interleukin-1 Effects on interleukin-6 Effects on fibrinogen Effects on plasma albumin Effects on prothrombin time Effects on activated partial thromboplastin time Effects on serum thromboxane Effects on thromboxane metabolite Effects on platelet count Effects on reticulated platelets Effects on platelet/leukocyte conjugates Effects on plasma P-selectin Effects on P-selectin expression Clinical mixed outcome of lung function, ROX score Clinical mixed outcome of lung function, SOfa score Clinical mixed outcome of lung function, Apache index Clinical mixed outcome of lung function, need to perform CT scan due to worsening of blood gases Clinical mixed outcome of lung function, need to transfer the patient to ICU Clinical mixed outcome of lung function, need for mechanical ventilation Clinical mixed outcome of lung function, days without need of mechanical ventilation Clinical mixed outcome of lung function, venous thromboembolism |

NCT04808895 (Continued)

34. Clinical mixed outcome of lung function, pulmonary thrombosis
35. Clinical mixed outcome of lung function, cardiovascular event
36. Clinical mixed outcome of lung function, death
37. Clinical mixed outcome of lung function, multiorgan failure
38. Clinical mixed outcome of lung function, discharge due to resolution of signs and symptoms
39. Safety outcomes, Major or clinically relevant bleeding
40. Safety outcomes, total bleeding based on ISTH bleeding score
41. Safety outcomes, minor bleeding according to ISTH BS
42. Safety outcomes, decrease in platelet count below 100 x 10⁹/L
43. Safety outcomes, decrease of at least 2 g/dL Hb levels
44. Safety outcomes, need for blood transfusion
45. Safety outcomes, alterations of clinical or laboratory parameters

Additional outcomes: NR

| | |
|---------------------|--|
| Starting date | 1 April 2021 |
| Contact information | Contact: Pietro Minuz, Professor, +39 045-8124414, pietro.minuz@univr.it Contact: Marco Cattaneo, Professor, +390250323095, marco.cattaneo@unimi.it |
| Notes | <ul style="list-style-type: none">• Sponsor/funding: Azienda Ospedaliera Universitaria Integrata Verona• COIs: NR• Other: NR |

NCT04937088

| | |
|------------|---|
| Study name | Outpatient Liquid Aspirin (OLA) |
| Methods | <ul style="list-style-type: none">• Trial design: randomised single-group assignment• Type of publication: trial registry• Setting: outpatient• Recruitment dates: recruiting• Country: USA• Language: English• Number of centres: single-centre• Inclusion criteria: > 40 years, written informed consent, within 24 hours of COVID-19 diagnosis, serum 250HD levels drawn at time of COVID-19 laboratory workup• Exclusion criteria: asymptomatic patients, patients already taking ASA and other anticoagulant/antiplatelet therapies including but not limited to clopidogrel, heparin, low molecular weight heparin, coumadin, apixaban, pregnant patients, prisoners, history of GI bleeding or peptic ulcer disease or spontaneous bleeding from other sites, thrombocytopenia (platelets < 130,000/ul) at time of COVID diagnosis, anaemia at time of COVID diagnosis (defined as haemoglobin level < 12 g/dL in women), history of chronic kidney disease, concurrent use of nonsteroid anti-inflammatory drugs or steroids, hypervitaminosis F and associated risk factors: renal failure, liver failure, hyperparathyroidism, sarcoidosis, histoplasmosis; known allergy to aspirin, inability to tolerate oral medications, known history of aspirin-included asthma, history of bleeding problems, patients who cannot avoid drinking 3 or more alcoholic drinks every day during 30-day course of ASA treatment, patients who cannot stop taking other nonprescription NSAIDs during 30-day course of ASA treatment, patients requiring hospitalisation (for any reason) at time of screening, patients taking or who plan to take on an outpatient basis remdesivir, dexamethasone, or other therapies for treatment of COVID• Trial registration number: NCT04937088• Date of trial registration: 16 June 2021 |

NCT04937088 (Continued)

- Prospective completion date: 30 June 2022

| | |
|---------------------|---|
| Participants | <ul style="list-style-type: none"> • Age: > 40 years • Gender: female/male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 200/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) • Additional diagnosis: NR • Previous treatment: NR |
| Interventions | <ol style="list-style-type: none"> 1. Aspirin 150 mg liquid formulation (2.5% w/w) taken once daily by mouth for 30 days 2. Placebo: soy bean oil, identical packaging as the active arm, taken once daily by mouth for 30 days <ul style="list-style-type: none"> • Concomitant therapy: NR • Treatment cross-overs: NR • Duration of follow-up: NR • Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Reduced COVID-19 related hospitalisations at 6 months <p>Secondary outcomes: NR</p> <p>Additional outcomes: NR</p> |
| Starting date | 6 December 2021 |
| Contact information | Frank Lau, MD 504-412-1240, flau@lsuhsc.edu |
| Notes | Louisiana State University Health Sciences Center in New Orleans, Innovate UK |

NCT05073718

| | |
|--------------|--|
| Study name | ASA-SARS / NCT05073718 |
| Methods | <ul style="list-style-type: none"> • Trial design: multicentre, double-blind, placebo-controlled RCT • Type of publication: trial registry • Recruitment dates: not yet recruiting • Country: Spain • Language: English • Number of centres: multicentre • Inclusion criteria: pregnant women with a positive SARS-CoV-2 antigen test and a confirmatory positive SARS-CoV-2 PCR test • Exclusion criteria: on regular ASA administration, on long-term non-steroidal anti-inflammatory medication, bleeding disorders, history of peptic ulceration, history of hypersensitivity to ASA, participation in another clinical trial, inability to co-operate with the requirements of the study, severe COVID-19 disease (with any of the following: respiratory rate > 30 breaths/min; severe respiratory distress; SPO2 < 93% on room air; acute respiratory distress syndrome; sepsis with acute organ dysfunction, treatment resistant hyperemesis gravidarum) • Trial registration number: NCT05073718 • Date of trial registration: 11 October 2021 • Prospective completion date: October 2023 |
| Participants | <ul style="list-style-type: none"> • Age: aged 18 years or older |

NCT05073718 (Continued)

| | |
|---------------------|---|
| | <ul style="list-style-type: none"> • Gender: female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 398 planned • Severity of disease: positive SARS-CoV-2 antigen test and a confirmatory positive SARS-CoV-2 PCR test, severe cases excluded • Additional diagnoses: NR |
| Interventions | <ol style="list-style-type: none"> 1. Low-dose acetylsalicylic acid (LDASA, 150 mg daily) from the first or second trimester up to 36 weeks gestation and prophylactic doses of low molecular weight heparin 2. Placebo from the first or second trimester up to 36 weeks gestation and prophylactic doses of low molecular weight heparin <ul style="list-style-type: none"> • Concomitant therapy: NR • Treatment cross-overs: NR • Duration of follow-up: NR • Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes (time frame: up to 37 weeks)</p> <ol style="list-style-type: none"> 1. Rate of composite adverse maternal and perinatal adverse outcome including foetal death, preterm pre-eclampsia, maternal thromboembolic complications, placental abruption, preterm birth and small for gestational age <p>Secondary outcomes (time frame: up to 37 weeks)</p> <ol style="list-style-type: none"> 1. Prevalence of SARS-CoV-2 infection and COVID-19 disease during pregnancy 2. Incidence of COVID-19-related admissions 3. Incidence of all-cause admissions 4. Incidence of all-cause outpatients attendances 5. Mean duration of symptom-sings of COVID-19 6. Frequency and severity of adverse events 7. Incidence of preeclampsia 8. Incidence of maternal thromboembolic complications and placental abruption 9. Maternal mortality rate 10. Incidence of histological placental abnormalities in SARS-CoV-2 infected pregnant women 11. Prevalence of preterm birth (< 37 weeks of gestation age) 12. Prevalence of small for gestational age 13. Prevalence of embryo and foetal losses (miscarriages and stillbirths) 14. Proportion of adverse perinatal outcome 15. Neonatal morbidity 16. Neonatal mortality rate <p>Additional outcomes: NR</p> |
| Starting date | Estimated start date: 15 January 2022 |
| Contact information | Laura Garcia, Dr. +34932275400, laura.garcia@isglobal.org |
| Notes | Sponsor/collaborators: Barcelona Institute for Global Health, Hospital Universitario de Torrejon Madrid, Hospital Universitario Infanta Leonor, Fundacio Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Hospital del Mar, Hospital Central de Maputo Mozambique |

Sharma 2021

| | |
|---------------|--|
| Study name | A Randomized Open-Label Trial To Evaluate The Efficacy And Safety Of Triple Therapy With aspirin, Atorvastatin, And Nicorandil In Hospitalised Patients With SARS Cov-2 Infection: A Structured Summary Of A Study Protocol For A Randomized Controlled Trial |
| Methods | <ul style="list-style-type: none"> • Trial design: single-centre, prospective, two-arm parallel design, open-label randomised control superiority trial • Type of publication: trial registry • Setting: hospital • Recruitment dates: 21 May 2021 • Country: India • Language: English • Number of centres: single-centre • Inclusion criteria: SARS-CoV-2 RT-PCR/RAT positive with pneumonia, without ARDS at presentation (presence of clinical features of dyspnoea, hypoxia, fever, cough, SpO₂ < 94% room air and respiratory rate > 24/minute), hospital admission • Exclusion criteria: liver disease/dysfunction (AST/ALT > 240), myopathy and rhabdomyolysis (CPK > 5x normal), allergy or intolerance to statins, allergy or intolerance to aspirin, patient taking the following medications: cyclosporine, HIV protease inhibitors, hepatitis C protease inhibitor, telaprevir, fibric acid derivatives (gemfibrozil), niacin, azole, antifungals (itraconazole, ketoconazole) clarithromycin, colchicine, prior statin use (within 30 days), prior aspirin use (within 30 days), history of active GI bleeding in past 3 months, coagulopathy, thrombocytopenia (platelet count < 100,000/dL), pregnancy, active breastfeeding, patient unable to take oral or nasogastric medications, altered mental status, shock at presentation, acute renal failure, acute coronary syndrome, sepsis, ARDS • Date of trial registration: 8 April 2021 • Prospective completion date: NR |
| Participants | <ul style="list-style-type: none"> • Age: > 18 • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 396/NR/NR • Severity of disease: SARS-CoV-2 infection (COVID-19) and requiring hospitalisation • Additional diagnoses: pneumonia • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): symptomatic treatment with antipyretics, adequate hydration, anticoagulation with low molecular weight heparin, intravenous remdesivir, corticosteroids, oxygen support; treatment for comorbid conditions as per guidelines |
| Interventions | <ol style="list-style-type: none"> 1. Intervention (triple therapy): aspirin 325 mg starting dose, followed by 75 mg once daily for 10 days or till hospital discharge; atorvastatin 40 mg once daily for 10 days or till hospital discharge; nicorandil 10 mg starting dose; followed by 5 mg twice daily for 10 days or till hospital discharge, standard care for COVID management as per national guidelines, symptomatic treatment (with antipyretics, adequate hydration, anticoagulation with low molecular weight heparin, intravenous remdesivir, corticosteroids, oxygen support) 2. Control: standard care, symptomatic treatment <ul style="list-style-type: none"> • Concomitant therapy: symptomatic treatment • Treatment cross-overs: NR • Duration of follow-up: during the hospital stay or for 10 days, whichever is longer • Compliance with assigned treatment: NR |
| Outcomes | <p>Primary outcomes</p> <ol style="list-style-type: none"> 1. In-hospital mortality <p>Secondary outcomes</p> |

Sharma 2021 (Continued)

1. Any progression to ARDS
2. Shock
3. Acute kidney injury
4. Impaired consciousness
5. Length of hospital stay
6. Length of mechanical ventilation (invasive plus non-invasive)

Additional outcomes: NR



















| | |
|---------------------|---|
| Starting date | 8 April 2021 |
| Contact information | Ambudhar Sharma, 9418048268, moc.liamg@414rahdubma Charu Sharma, moc.liamg@4891rahdubma Sujeet Raina, moc.liamg@aniarteejus |
| Notes | |

COI: conflict of interest; ECMO: extracorporeal membrane oxygenation; NR: not reported; RCT: randomised controlled trial







RISK OF BIAS

Legend:  Low risk of bias  High risk of bias  Some concerns

Risk of bias for analysis 1.1 All-cause mortality up to day 28

| Study | Bias | | | | | Overall |
|-----------------------|---|---|---|--|---|---|
| | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | |
| Berger 2022 |  |  |  |  |  |  |
| Horby 2021 (RECOVERY) |  |  |  |  |  |  |
| REMAP-CAP 2022 |  |  |  |  |  |  |

Risk of bias for analysis 1.2 Worsening up to day 28: participants with new need for invasive mechanical ventilation or death

| Study | Bias | | | | | Overall |
|-----------------------|---|---|---|--|---|---|
| | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | |
| Horby 2021 (RECOVERY) |  |  |  |  |  |  |

| Bias | | | | | | |
|----------------|-----------------------|--|----------------------|----------------------------|-----------------------------------|---------|
| Study | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | Overall |
| REMAP-CAP 2022 | | | | | | |

Risk of bias for analysis 1.6 Major bleeding events

| Bias | | | | | | |
|--------------------------|-----------------------|--|----------------------|----------------------------|-----------------------------------|---------|
| Study | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | Overall |
| Berger 2022 | | | | | | |
| Bohula 2022 (COVID-PACT) | | | | | | |
| Horby 2021 (RECOVERY) | | | | | | |
| REMAP-CAP 2022 | | | | | | |







Risk of bias for analysis 1.7 Need for new dialysis up to day 28

| Bias | | | | | | |
|-----------------------|-----------------------|--|----------------------|----------------------------|-----------------------------------|---------|
| Study | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | Overall |
| Horby 2021 (RECOVERY) | | | | | | |

Risk of bias for analysis 1.9 All-cause mortality up to longest follow-up

| Bias | | | | | | |
|--------------------------|-----------------------|--|----------------------|----------------------------|-----------------------------------|---------|
| Study | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | Overall |
| Bohula 2022 (COVID-PACT) | | | | | | |

Risk of bias for analysis 3.4 Serious adverse events

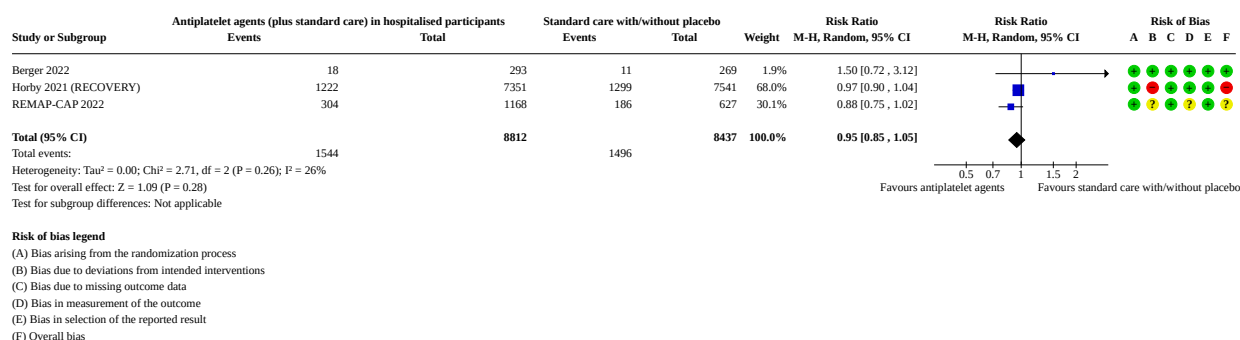
| Study | Bias | | | | | Overall |
|---------------------------|---|---|---|--|---|---|
| | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | |
| Eikelboom 2022 (ACTCOVID) |  |  |  |  |  |  |

DATA AND ANALYSES

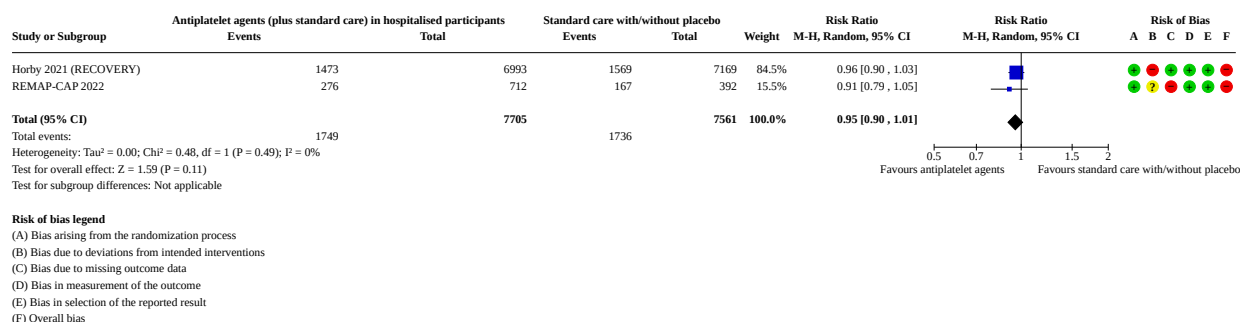
Comparison 1. Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------------|---------------------|
| 1.1 All-cause mortality up to day 28 | 3 | 17249 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.85, 1.05] |
| 1.2 Worsening up to day 28: participants with new need for invasive mechanical ventilation or death | 2 | 15266 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.90, 1.01] |
| 1.3 Improvement up to day 28: discharged alive | 2 | 15454 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.96, 1.04] |
| 1.4 Thrombotic events | 4 | 17518 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.80, 1.02] |
| 1.5 Serious adverse events | 1 | 1815 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.57 [0.48, 5.14] |
| 1.6 Major bleeding events | 4 | 17527 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.68 [1.29, 2.19] |
| 1.7 Need for new dialysis up to day 28 | 1 | 14771 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.99 [0.84, 1.18] |
| 1.8 180-day mortality | 1 | 1312 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.82, 1.15] |
| 1.9 All-cause mortality up to longest follow-up | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

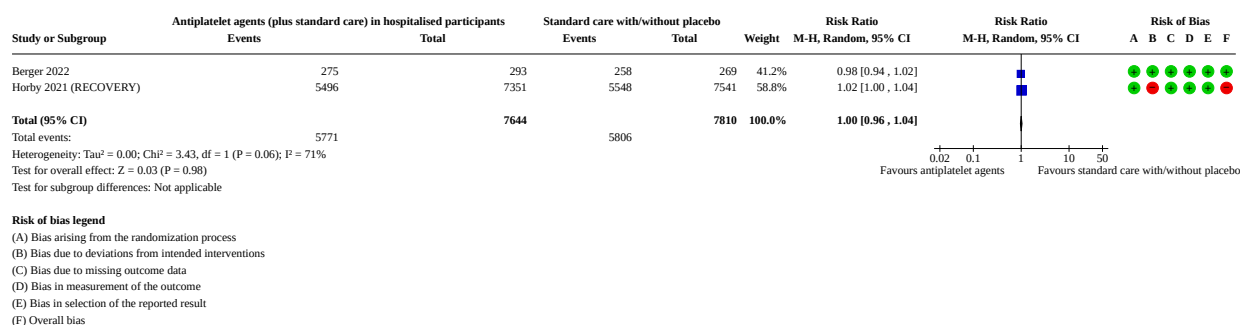
Analysis 1.1. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 1: All-cause mortality up to day 28



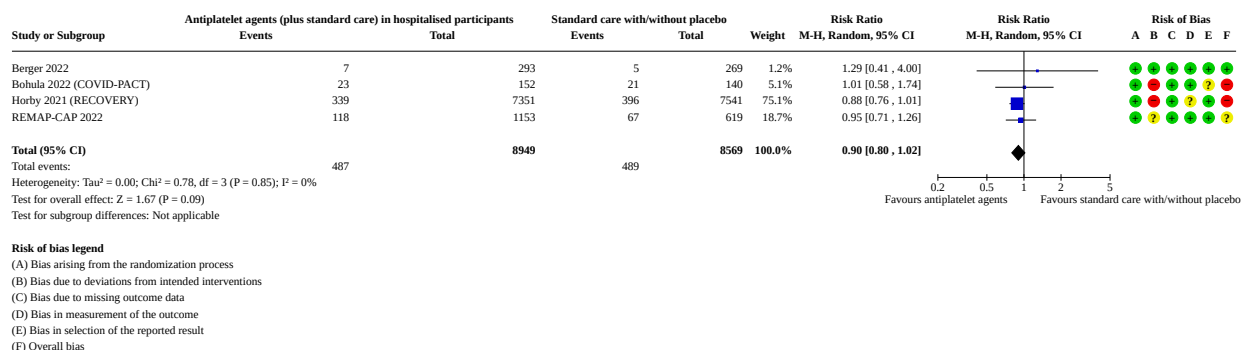
Analysis 1.2. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 2: Worsening up to day 28: participants with new need for invasive mechanical ventilation or death



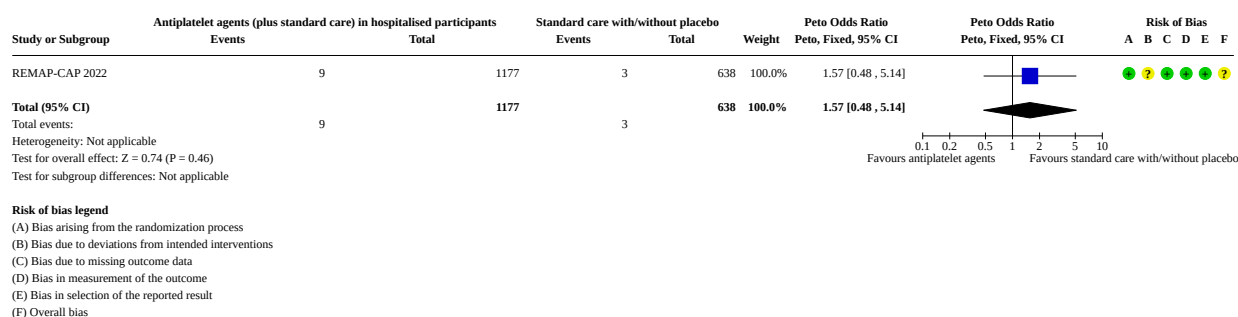
Analysis 1.3. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 3: Improvement up to day 28: discharged alive



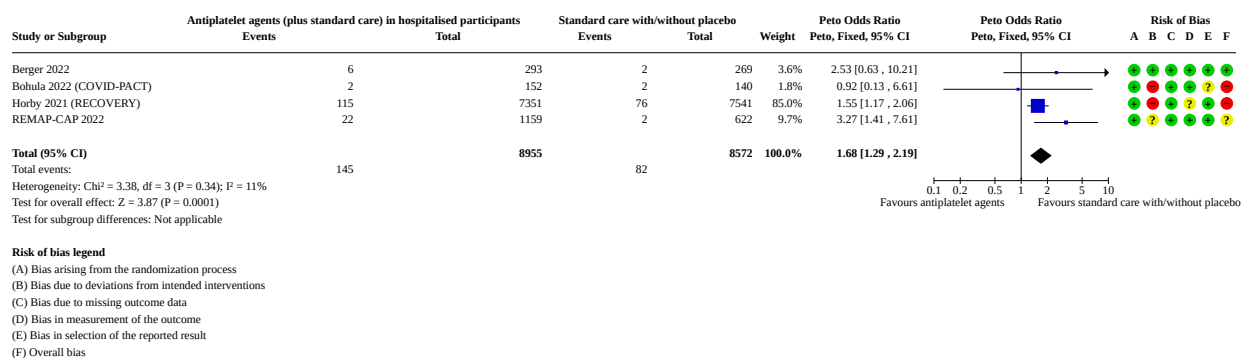
Analysis 1.4. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 4: Thrombotic events

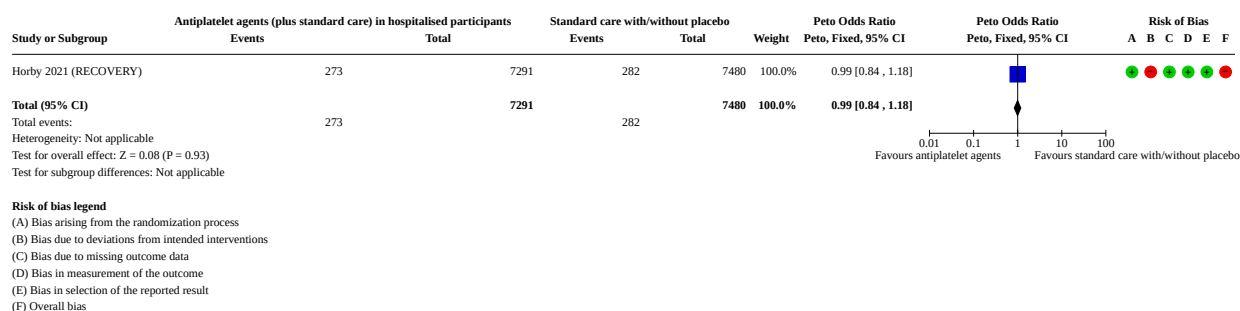
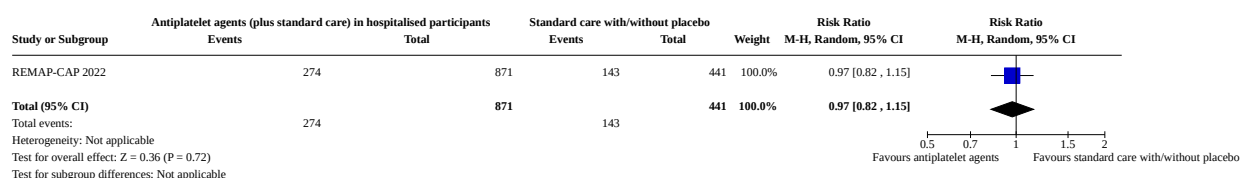
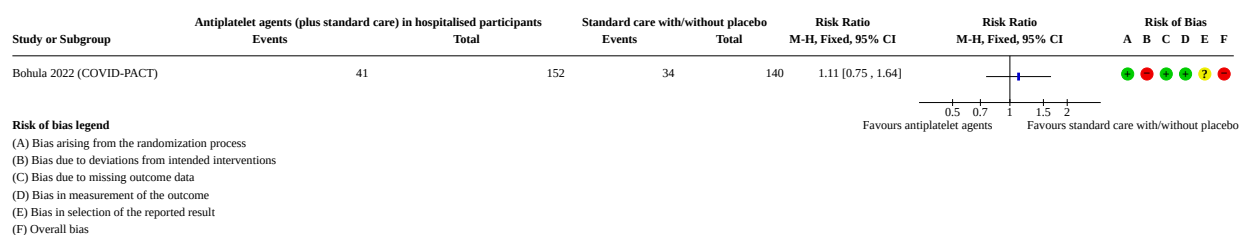


Analysis 1.5. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 5: Serious adverse events



Analysis 1.6. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 6: Major bleeding events

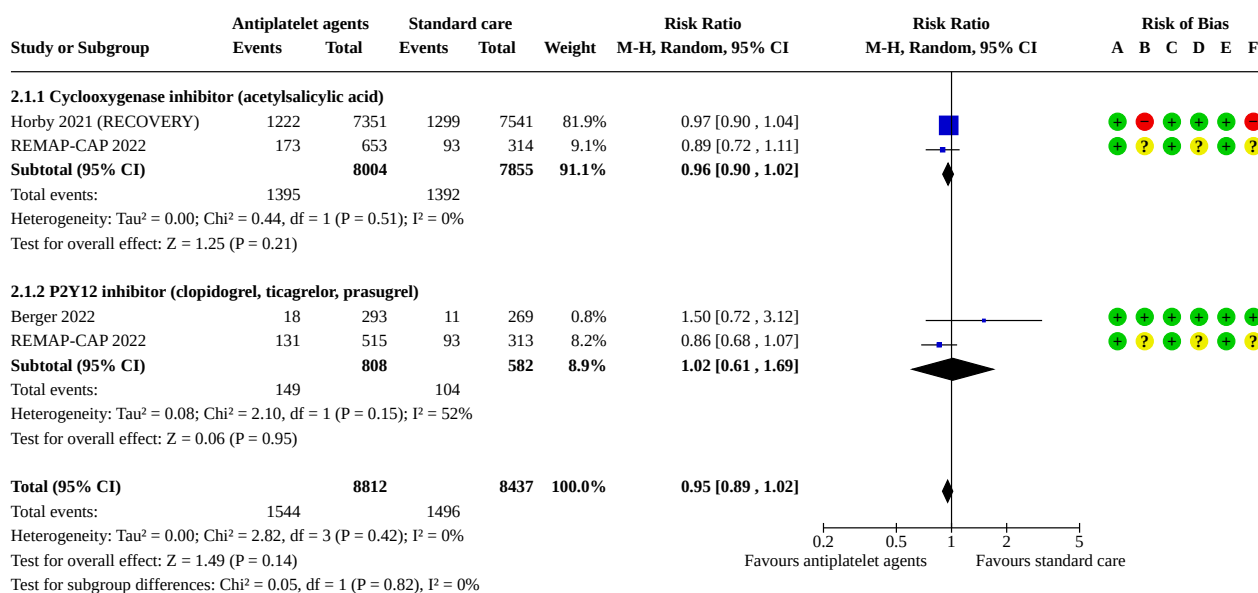


Analysis 1.7. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 7: Need for new dialysis up to day 28**Analysis 1.8. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 8: 180-day mortality****Analysis 1.9. Comparison 1: Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, Outcome 9: All-cause mortality up to longest follow-up****Comparison 2. Subgroup analysis: Effects on mortality up to day 28**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|----------------------------------|-------------------|
| 2.1 Subgroup analysis (type of antiplatelet agent): cyclooxygenase inhibitors or ADP receptor/P2Y12 inhibitors in participants with moderate to severe COVID-19 | 3 | 17249 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.89, 1.02] |
| 2.1.1 Cyclooxygenase inhibitor (acetylsalicylic acid) | 2 | 15859 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.90, 1.02] |
| 2.1.2 P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel) | 2 | 1390 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.61, 1.69] |
| 2.2 Subgroup analysis: concomitant therapeutic dose anticoagulation or prophylactic anticoagulation | 3 | 15828 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.83, 1.13] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|----------------------------------|-------------------|
| 2.2.1 Antiplatelet agents plus standard care (including prophylactic anticoagulation) | 2 | 15024 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.77, 1.10] |
| 2.2.2 Antiplatelet agents plus therapeutic anticoagulation | 2 | 804 | Risk Ratio (M-H, Random, 95% CI) | 1.27 [0.88, 1.84] |

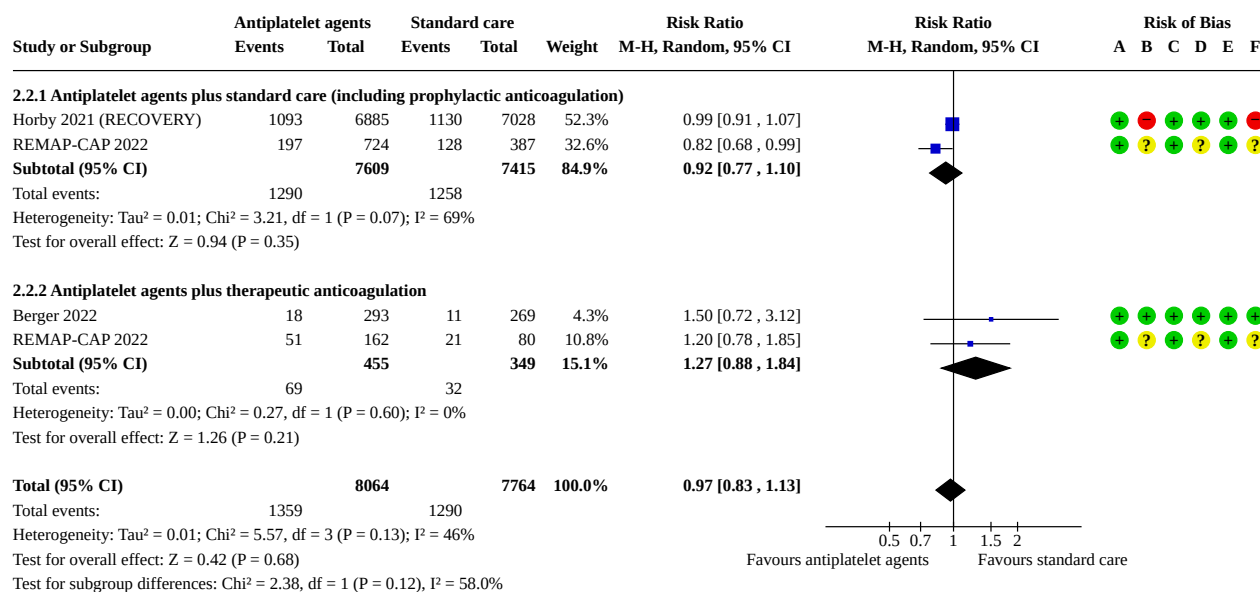
Analysis 2.1. Comparison 2: Subgroup analysis: Effects on mortality up to day 28, Outcome 1: Subgroup analysis (type of antiplatelet agent): cyclooxygenase inhibitors or ADP receptor/P2Y12 inhibitors in participants with moderate to severe COVID-19



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result
- (F) Overall bias

Analysis 2.2. Comparison 2: Subgroup analysis: Effects on mortality up to day 28, Outcome 2: Subgroup analysis: concomitant therapeutic dose anticoagulation or prophylactic anticoagulation



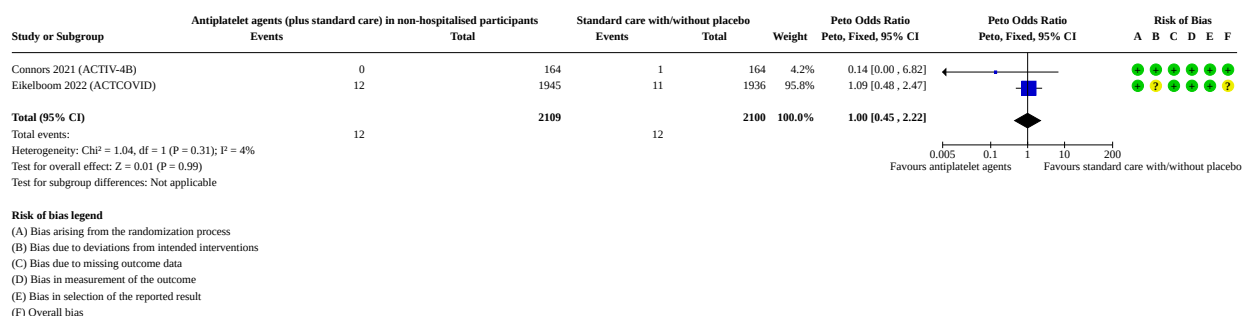
Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result
- (F) Overall bias

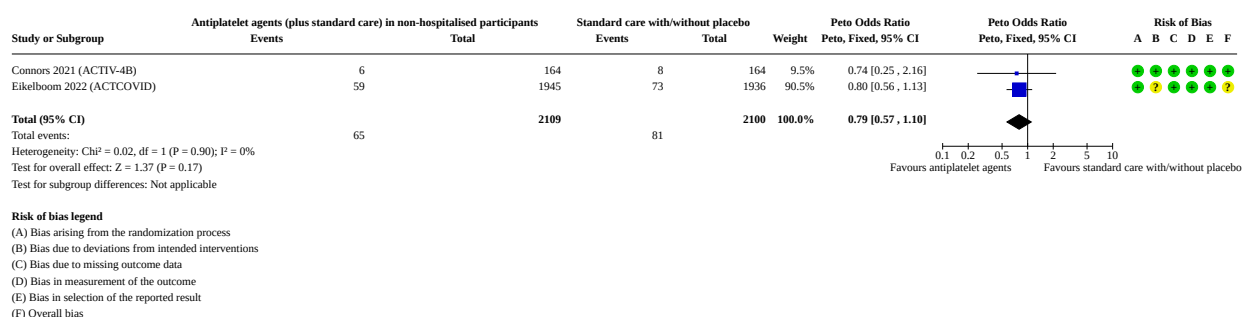
Comparison 3. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic to mild disease

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|---------------------------------------|-------------------|
| 3.1 All-cause mortality up to longest follow-up (45 days) | 2 | 4209 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.00 [0.45, 2.22] |
| 3.2 Admission to hospital or death up to day 45 | 2 | 4209 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.79 [0.57, 1.10] |
| 3.3 Thrombotic events | 2 | 4209 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.37 [0.09, 1.46] |
| 3.4 Serious adverse events | 1 | 3881 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.00 [0.60, 1.64] |

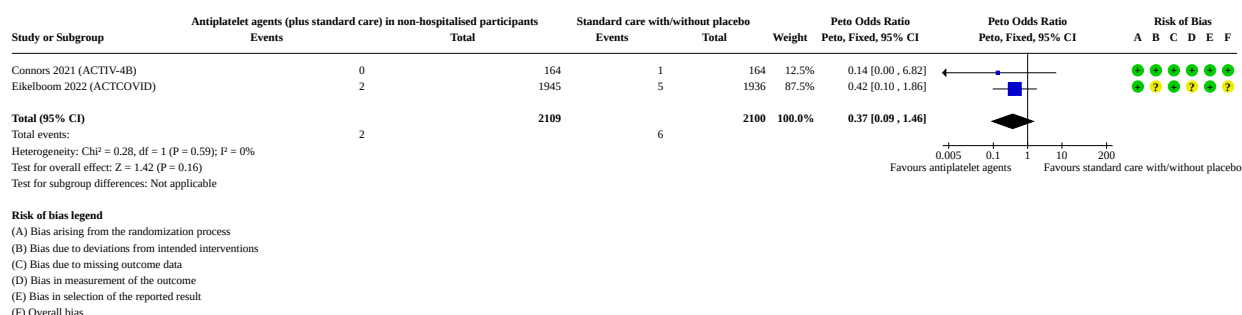
Analysis 3.1. Comparison 3: Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic to mild disease, Outcome 1: All-cause mortality up to longest follow-up (45 days)



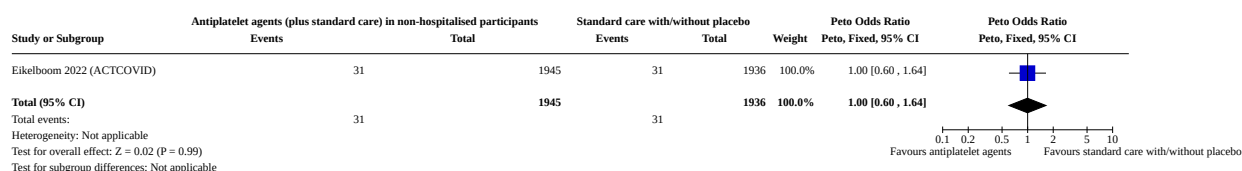
Analysis 3.2. Comparison 3: Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic to mild disease, Outcome 2: Admission to hospital or death up to day 45



Analysis 3.3. Comparison 3: Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic to mild disease, Outcome 3: Thrombotic events



Analysis 3.4. Comparison 3: Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic to mild disease, Outcome 4: Serious adverse events



ADDITIONAL TABLES

Table 1. Characteristics of ongoing studies

| Study ID | Title | Intervention | Comparator | Other study interventions | Planned number of participants | Setting | Planned completion date | Link |
|-------------------------------------|---|----------------------|---------------|---------------------------|--------------------------------|--------------------------------|-------------------------|--|
| ChiCTR2000030055 | Multicentre study for the treatment of Dipyridamole with novel coronavirus pneumonia | Dipyridamole | Standard care | None | 460 | Hospital | NR | covid-19.cochrane.org/studies/crs-13247467 |
| IRCT20180205038625 | The Investigation of the Effectiveness of ASA Usage on the Incidence of Cardiovascular Events in Patients with Corona Virus (COVID-19) A Clinical Trial Study | Acetylsalicylic acid | Placebo | None | 36 | Hospital | NR | en.irct.ir/trial/52374 |
| NCT04703608 | Prevention and Treatment for COVID -19 (Severe Acute Respiratory Syndrome Coronavirus 2 SARS-CoV-2) Associated Severe Pneumonia in the Gambia | Acetylsalicylic acid | Placebo | Ivermectin | 1200 | Hospital and private household | March 2022 | clinicaltrials.gov/ct2/show/record/NCT04703608?cond=NCT%3A+04703608&draw=2&rank=1 |
| NCT04808895 | Acetylsalicylic Acid in the Prevention of Severe SARS-CoV2 Pneumonia in Hospitalised Patients With COVID-19 | Acetylsalicylic acid | Placebo | None | 204 | NR | July 2021 | clinicaltrials.gov/ct2/show/record/NCT04808895?cond=NCT%3A+04808895&draw=2&rank=1 |
| CTRI/2020/08/012550 | Low Dose Aspirin in Moderate to Severe SARS- CoV-2 Infected Patients: A Pilot Randomized Controlled Trial | Acetylsalicylic acid | Standard care | None | 60 | Hospital | NR | www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=44980&EncHid=&modid=&compid=%27,%2744980det%27 |
| NCT04768179 | Safety and Efficacy of Low Dose Aspirin / Ivermectin Combination Therapy for Treatment of Covid-19 Patients | Acetylsalicylic acid | Standard care | Ivermectin | 490 | Hospital | June 2021 | clinicaltrials.gov/ct2/show/NCT04768179?cond=NC-T04768179&draw=1&rank=1 |
| NCT04363840 | The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations | Acetylsalicylic acid | Observation | Vitamin D | 1080 | Hospital | December 2020 | clinicaltrials.gov/ct2/show/NCT04363840?cond=04363840&draw=2&rank=1 |



Table 1. Characteristics of ongoing studies (Continued)

| | | | | | | | | |
|-------------------------------------|---|-------------------------|--------------------------------------|----------------------------|-----|------------|--------------|--|
| NCT04445623 | Prasugrel in Severe COVID-19 Pneumonia | Prasugrel hydrochloride | Placebo | None | 128 | Hospital | January 2021 | clinicaltrials.gov/ct2/show/NCT04445623?cond=NCT%3A+04445623&draw=1&rank=1 |
| NCT04365309 | Protective Effect of Aspirin on COVID-19 Patients | Acetylsalicylic acid | Standard care | None | 128 | Hospital | June 2020 | clinicaltrials.gov/ct2/show/NCT04365309?cond=NCT%3A+04365309&draw=2&rank=1 |
| NCT05073718 | Acetylsalicylic Acid in COVID-19 (ASA-SARS) | Acetylsalicylic acid | Placebo | Prophylactic doses of LMWH | 398 | NR | October 2023 | https://clinicaltrials.gov/ct2/show/NCT05073718 |
| CTRI/2021/03/011055 | Investigator Initiated Study to Evaluate the Effect of Marketed Colchicine 0.5mg Given Along Marketed Aspirin 75mg with SOC and Marketed Aspirin 75mg with SOC on COVID 19 patients | Acetylsalicylic acid | Colchicine | None | 63 | Outpatient | NR | www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=53115&EncHid=&modid=&compid=%27,%2753115det%27 |
| NCT04937088 | Outpatient Liquid Aspirin (OLA) (OLA COVID) | Acetylsalicylic acid | Placebo | None | 200 | Outpatient | June 2022 | clinicaltrials.gov/ct2/show/NCT04937088 |
| CTRI/2021/06/001164 | Clinical trial of APMV2020 in Covid 19 Subjects | Acetylsalicylic acid | Multivitamin and multimineral tablet | Promethazine hydrochloride | 60 | Outpatient | NR | www.cochranelibrary.com/central/doi/10.1002/central/CN-02327762/full |
| Sharma 2021 | A Randomized Open-Label Trial to Evaluate the Efficacy and Safety of Triple Therapy with Aspirin, Atorvastatin, and Nicorandil in Hospitalised Patients with SARS Cov-2 Infection | Acetylsalicylic acid | Standard care | Atorvastatin, nicorandil | 396 | Hospital | NR | trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05361-y |

NR: not reported

Table 2. Sensitivity analysis for the primary outcome all-cause mortality up to day 28 for people with moderate to severe COVID-19

| Outcome | Main analysis using random-effects model | Main analysis using fixed-effect model | Risk of bias (excluding studies ^a at high risk of bias) |
|----------------------------------|---|---|--|
| All-cause mortality up to day 28 | RR 0.95 , 95% CI 0.85 to 1.05; 3 RCTs, 17,249 participants | RR 0.96 , 95% CI 0.90 to 1.02; 3 RCTs, 17,249 participants | RR 1.02 , 95% CI 0.63 to 1.62; 2 RCTs, 2357 participants |

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio

^aExcluded study with high risk of bias: [Horby 2021 \(RECOVERY\)](#)

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

"platelet antiaggregant" OR "platelet antiaggregants" OR "platelet anti-aggregant" OR "platelet anti-aggregants" OR "agglutination inhibitor" OR "agglutination inhibitors" OR "aggregation inhibitor" OR "aggregation inhibitors" OR "platelet inhibitor" OR "platelet inhibitors" OR "antiplatelet" OR "anti-platelet" OR "anti-platelets" OR "antiaggreg*" OR "platelet anti-aggregation" OR aspirin* OR "acetylsalicylic acid" OR "acetyl salicylic acid" OR acetysal* OR acylpyrin* OR aloxiprimum* OR colfarit* OR dispril* OR easprin* OR ecotrin* OR endosprin* OR magnecyl* OR micristin* OR polopirin* OR polopiryna* OR solprin* OR solupsan* OR zorprin* OR aggrenox*

Study characteristics:

- 1) "Intervention assignment": randomised, unclear
- 2) "Study design": parallel/crossover, unclear

Web of Science

#1 TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2" OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#2 TI=(antiplatelet* OR anti-platelet* OR antiaggreg* OR anti-aggreg* OR (platelet* NEAR/5 inhibit* OR antagonis*) OR (thrombocyt* NEAR/5 inhibit* OR antagonis*)) OR AB=(antiplatelet* OR antiplatelet* OR antiaggreg* OR antiaggreg* OR (platelet* NEAR/5 inhibit* OR antagonis*)) OR (thrombocyt* NEAR/5 inhibit* OR antagonis*))

#3 TI=(aspirin* OR "acetylsalicylic acid" OR "acetyl salicylic acid" OR acetysal* OR acylpyrin* OR aloxiprimum* OR colfarit* OR dispril* OR easprin* OR ecotrin* OR endosprin* OR magnecyl* OR micristin* OR polopirin* OR polopiryna* OR solprin* OR solupsan* OR zorprin* OR aggrenox*) OR AB=(aspirin* OR "acetylsalicylic acid" OR "acetyl salicylic acid" OR acetysal* OR acylpyrin* OR aloxiprimum* OR colfarit* OR dispril* OR easprin* OR ecotrin* OR endosprin* OR magnecyl* OR micristin* OR polopirin* OR polopiryna* OR solprin* OR solupsan* OR zorprin* OR aggrenox*)

#4 #2 OR #3

#5 TI=(random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

#6 #1 AND #4 AND #5

Searched in Science Citation Index Expanded and Emerging Sources Citation Index

World Health Organization COVID-19 Global literature on coronavirus disease

Antiplatelet agents for the treatment of adults with COVID-19 (Review)

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Advanced search in the search fields: title, abstract, subject

platelet inhibitor* or antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* or aspirin* or acetylsalicylic acid or "acetyl salicylic acid" or acetysal* or acylpyrin* or aloxiprimum* or colfarit* or dispril* or easprin* or ecotrin* or endosprin* or magnecyl* or micristin* or polopirin* or polopiryna* or solprin* or solupsan* or zorprin* or aggrenox*

AND

random* or placebo or trial or groups or "phase 3" or "phase3" or p3 or "pIII"

Epistemonikos, L*OVE List Coronavirus disease (COVID-19)

LOVE list / COVID-19

searched by PICO:

prevention or treatment:

- pharmacological interventions
 - antithrombotics
 - Antiplatelets (only primary studies; filter results by RCT)

CONTRIBUTIONS OF AUTHORS

AF: clinical expertise, conception and writing of the review, study selection, data extraction, risk of bias, GRADE assessments, proofreading of the manuscript.

SM: conception and writing of the review, data extraction, screening, risk of bias, proofreading of the manuscript

LE: conception, clinical and methodological expertise and advice, proofreading of the manuscript.

AM: methodological expertise and advice, risk of bias assessment, writing and proofreading of the manuscript.

MA: conception, methodological expertise and advice, study selection, data extraction, proofreading of the manuscript.

MS: clinical input, proofreading of the manuscript

IM: development of the search strategy

SW: methodological expertise and advice, data extraction, risk of bias assessment, proofreading of the manuscript.

RP: conception, methodological expertise and advice, data assessment, writing and proofreading of the manuscript.

RR: methodological expertise and advice, risk of bias assessment, writing and proofreading of the manuscript.

NS: conception, methodological expertise and advice, study selection, data assessment, conception, writing and proofreading of the manuscript.

DECLARATIONS OF INTEREST

AF: works as an Intensive Care Medicine Physician and is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

SM: none known; she is a staff member of Cochrane Haematology, but was not involved in the editorial process for this review.

RR: none known.

AM: none known.

MS: none known.

LE: she is Co-ordinating Editor of Cochrane Haematology, but was not involved in the editorial process for this review. She is an investigator on the REMAP-CAP trial but was not involved in the data extraction or risk of bias assessment of this trial.

SW: none known; she is Content Editor of Cochrane Anaesthesia, but was not involved in the editorial process for this review.

IM: none known; she is an Information Specialist of Cochrane Haematology, but was not involved in the editorial process for this review.

Antiplatelet agents for the treatment of adults with COVID-19 (Review)

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MA: none known.

RP: none known.

NS: none known; she is Co-ordinating Editor of Cochrane Haematology, but was not involved in the editorial process for this review.

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Internal sources

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- Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Department of Infectious Diseases and Respiratory Medicine

- University Hospital Leipzig, Germany

Department of Anesthesiology and Intensive Care Medicine

External sources

- Federal Ministry of Education and Research of Germany, Germany

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised improvement and worsening outcomes together with the German COVID-19 guideline panel to consider the competing event of death. Our definition of clinical status was less dependent on the need of respiratory support - that is the reason why some outcomes became secondary outcomes and the following outcomes were deleted.

- Liberation from supplemental oxygen in patients, i.e. WHO ≤ 4 on the Clinical Progression Scale (for the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≥ 5), including duration to liberation.
- Weaning or liberation from invasive mechanical ventilation in patients, i.e. WHO ≤ 6 (for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e. WHO ≥ 7), including duration from liberation.
- Need for non-invasive mechanical ventilation or high-flow oxygen, i.e. WHO = 6 (for the subgroup of participants not requiring non-invasive or non-invasive mechanical ventilation, or high-flow oxygen at baseline, i.e. WHO ≤ 5);
- Need for oxygen by mask or nasal prongs, i.e. WHO = 5 (for the subgroup of participants not requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≤ 4).

Quality of life outcomes were moved to secondary outcomes, since we did not want to overload the summary of findings tables and the safety outcomes seemed more important to us.

The subgroup analysis of severity was not possible due to a lack of information in the studies.

Originally, we had planned to perform a subgroup analyses of the following characteristics.

- Age of participants (divided into applicable age groups, e.g. children, 18 to 65 years, 65 years and older), suggesting that older participants may benefit more from treatment with antiplatelet agents, as they are at higher risk for thrombotic events.
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression), suggesting that participants with some diseases that increase thrombotic risk may benefit more.
- Timing of first dose administration with illness onset, suggesting that an earlier treatment may prevent deterioration.

Due to insufficient data, we were not able to perform these subgroup analyses.

We had a longer reflectional process involving clinical experts about whether we should meta-analyse different antiplatelet types together, as we did in our review. We decided to perform a subgroup analysis stratified by the antiplatelet agent that was used, to rule out a relevant differences between drugs.

NOTES

Reviews of this series partly share information in the background section and methodology based on the first published reviews about monoclonal antibodies ([Kreuzberger 2021](#)) and convalescent plasma ([Iannizzi 2023](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin; Asymptomatic Infections; *COVID-19; *Platelet Aggregation Inhibitors; SARS-CoV-2

MeSH check words

Adult; Humans