

**South African National Department of Health
Rapid Review Report
Component: COVID-19**

TITLE: NSAIDs as treatment for COVID-19

Date: 19 November 2021

Key findings

- ➔ A rapid review of the evidence was conducted to evaluate the effectiveness of NSAIDs to treat adult patients for COVID-19.
- ➔ We performed a comprehensive search of four electronic databases up to 4 November 2021 and identified one eligible trial by Horby *et al.*, 2021. The randomised, controlled, open-label platform trial compared the use of aspirin compared with usual care in 14,892 participants hospitalised with COVID-19 between November 2020 and March 2021.
- ➔ Overall, aspirin did not reduce mortality time to discharge, progression to mechanical ventilation or resolution of symptoms/ discharge from hospital compared to usual care. This adequately powered trial also reported no reduction in thrombotic events but there was an increase in bleeding including major bleeding.
- ➔ Adding aspirin to the standard of care for hospitalized patients with COVID-19 did not to improve clinically important outcomes, and the balance of benefit and harms of its use does not support inclusion in current guidelines.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
	X				

Recommendation: The Committee does not recommend aspirin for the treatment of COVID-19, except in the context of a clinical trial.

Rationale: The available evidence indicates that aspirin is no more effective than standard care in treating patients with COVID-19. No other RCTs investigating other NSAIDs (other than aspirin) were identified.

Level of Evidence: Moderate to high certainty evidence

(Refer to appendix 2 for the evidence to decision framework)

NEMLC MAC on COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

PROSPERO registration: CRD42021286710

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) include the nonselective cyclooxygenase (COX) inhibitors (ibuprofen, aspirin (acetylsalicylate), diclofenac, naproxen, indomethacin) and selective COX2 inhibitors (celecoxib, rofecoxib, etoricoxib, lumiracoxib, valedocoxib).

Aspirin has antiplatelet and anti-inflammatory effects as an inhibitor of COX-1 and decreases thromboxane A₂ synthesis, platelet aggregation, and thrombus formation. Aspirin decreases platelet-neutrophil aggregates in the lungs, potentially reducing inflammation, and increases lipoxin formation, which restores pulmonary endothelial cell function. Aspirin may have anti-coagulant properties and impact on endothelial dysfunction noted in COVID-19.

Aspirin decreases interleukin-6 (IL-6), C-reactive protein (CRP), and macrophage colony-stimulating factor in patients with cardiovascular disease and it is postulated that it may impact similarly to the pro-inflammatory phase of COVID-19. Concerns emerged regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) increasing the risk of adverse effects in individuals with COVID-19 emerged early in the pandemic. However, this has not been confirmed and in general NSAIDs are regarded as an alternative agent to manage the symptoms of COVID-19.

COVID-19 treatment guidelines (last updated 4 August 2021) from the National Institutes of Health (NIH) reported a strong expert opinion recommendation that patients with COVID-19 who are receiving NSAIDs for an underlying medical condition *should not discontinue* therapy unless discontinuation is otherwise warranted by their clinical condition. Additionally, the guideline reported strong expert opinion recommendation for strategies for using antipyretic therapy (e.g., acetaminophen, NSAIDs) in patients with COVID-19 *should remain similar* to the approaches used in other patients (NIH guideline)

This review aimed to assess the use of NSAIDs in patients with COVID-19 infections on mortality, the acute respiratory distress syndrome (ARDS), acute organ failure, health care utilization (including hospitalization, intensive care unit (ICU) admission, supplemental oxygen use, and mechanical ventilation).

RESEARCH QUESTION: What is the effectiveness of NSAIDs for managing COVID-19?

METHODS

A comprehensive search in four of electronic databases was conducted – Cochrane Library COVID-19 study register, PubMed, LOVE platform on 1 October 2021, and the COVID-nma.com Living review database on 8 October 2021. These databases systematically search PubMed, Embase, MedRxiv, WHO's ICTRP and clinicaltrials.gov. The full search strategy can be found in Appendix 1.

Retrieved sources were imported into the Covidence software for title and abstract, and then full text screening. Screening of records, selection of articles and data extraction was done independently and in duplicate by two reviewers (NB and SE) with conflict resolution by a third reviewer (TK). The main characteristics of the included studies and study outcomes are shown in Table 1. Table 2 to presents results of search for ongoing trials on covid-nma website.

Risk of bias for the included trial were obtained from the Covid-nma website (www.covid-nma.com website). We reported rate and risk ratios for dichotomous data and mean differences for continuous outcomes with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness (Guyatt et al). Table 3 is a GRADE summarises of findings table for the comparison aspirin compared to usual care.

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age or comorbidity, any disease severity.

Intervention: NSAID - No restriction on dose or frequency or route of administration.

Comparators: Standard of care/placebo.

Outcomes: Resolution of symptoms; time to resolution of symptoms; progression to hospitalisation; progression to requiring oxygen; mortality; duration of hospitalisation; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse reactions; adverse events.

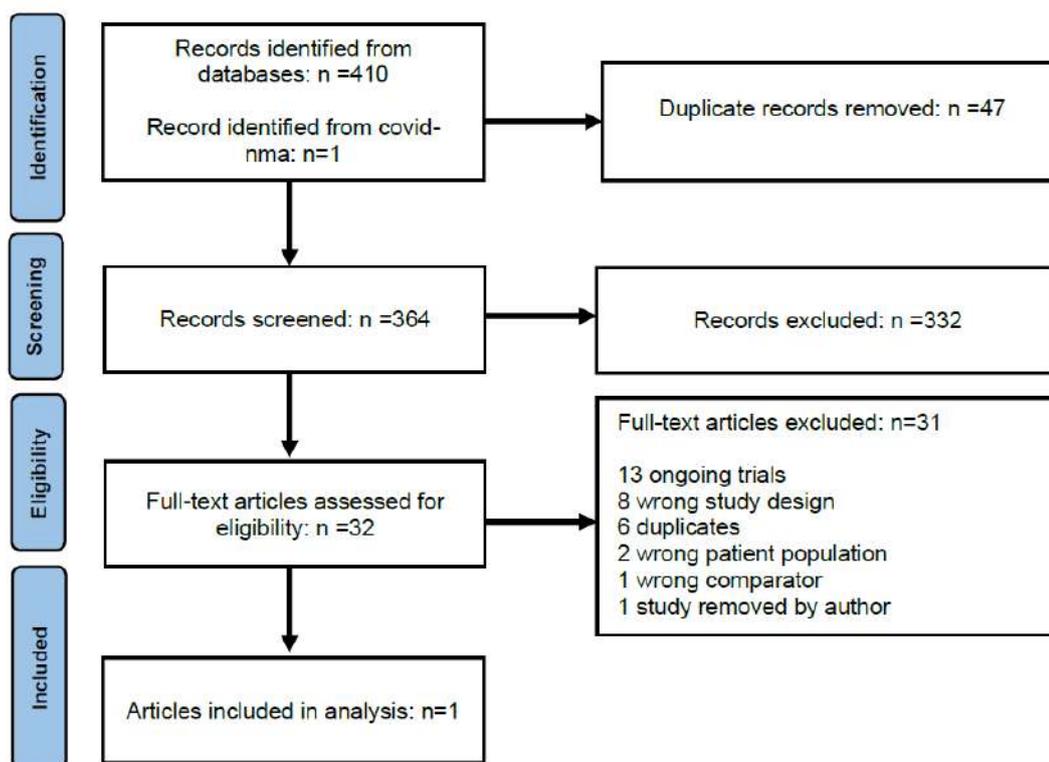
Study designs: Randomised controlled trials and, systematic reviews of randomised controlled trials.

RESULTS

Results of search

The databases search identified 410 records and one trial from covid-nma. Following the removal of duplicates, 364 titles and abstracts and then 32 potentially eligible full-text records were screened against the PICO. Of the 32 full-text records, 31 were excluded. One trial (Horby et al., 2021) was eligible for inclusion in the review. An excluded trial, Ravichandran et al, evaluated indomethacin compared to standard of care in inpatients. The standard of care included doxycycline, ivermectin and a protein pump inhibitor – as this does not reflect current care in South Africa, this was not eligible for inclusion. An additional trial was identified after our search date on covid-nma.com – the trial was evaluating the use of aspirin in outpatients – the trialist aimed to recruit 7000 participants, but only managed to recruit under 10% of this (N= 657), as such it was not powered to answer the question and was not included to inform the current decision about NSAID use. There are 9 ongoing trials that will be monitored for publication (Table 2). Study selection is shown in the Prisma flow graphic Figure 1.

Figure 1: PRISMA flow diagram for the review



Description of studies

The Horby et al., 2021 trial investigated the effectiveness of aspirin compared to standard of care in 1:1 ratio. The trial enrolled 14892 participants from the United Kingdom, Indonesia and Nepal into a randomised, unblinded trial. Patients admitted to hospital with suspected or confirmed SARS-CoV-2 infection were eligible for inclusion in the trial. The

exclusion criteria included children under 18 years, patients with hypersensitivity to aspirin, a recent history of major bleeding, receiving aspirin or anti-platelets treatment. The disease severity ranged with most having mild to moderate disease as follows: None or simple oxygen: n=9,972, noninvasive ventilation: n=4,190 and invasive mechanical ventilation: n=730. Aspirin was administered at 150 mg orally, by nasogastric tube or rectally daily until discharge and to 1222 (17%) of patients for 28 days. Standard of care defined as *receiving usual care in participating hospital* was received by 1299 (17%) of patients in the control arm (Table 1 summarises the characteristics and results reported of the included trial). Additionally, patients could receive other co-interventions related to their treating site protocols, described in Figure 2. An intention-to-treat analysis was conducted of patients randomised to aspirin and usual standard of care but for whom aspirin was both available and suitable as a treatment.

Figure 2: Other co-interventions received

	Treatment allocation	
	Aspirin (n=7351)	Usual care (n=7541)
Compliance data available	7290	7457
Received aspirin	6587 (90%)	210 (3%)
Other treatments received		
Lopinavir-Ritonavir	5 (<1%)	4 (<1%)
Dexamethasone	6331 (87%)	6618 (89%)
Hydroxychloroquine	16 (<1%)	15 (<1%)
Azithromycin or other macrolide	1959 (27%)	2016 (27%)
Tocilizumab	946 (13%)	975 (13%)
Remdesivir	1869 (26%)	1952 (26%)
Convalescent plasma	1125 (15%)	1157 (16%)
REGN-COV2	1175 (16%)	1159 (16%)
Colchicine	1705 (23%)	1796 (24%)
Baricitinib	414 (6%)	423 (6%)
Dimethyl fumarate	5 (<1%)	4 (<1%)

Percentages are of those with a completed follow-up form. Of those allocated aspirin who received at least one dose, 77% received all (or nearly all) of their scheduled doses during their hospital stay (taken on at least 90% of the days from randomisation to time to discharge or 28 days after randomisation, whichever was earlier) while 89% received at least half of their scheduled doses (Horby et al)

Appraisal of the trial

Overall, the trial was judged to have a risk of bias with some concerns due to the *measurement of outcome domain*. A web-based simple randomization with concealed allocation sequenced was used. There was deviation from intervention due to the administration of co-interventions. This deviation was small, and the distribution of co-intervention was similar between intervention arms, thus warranting a low risk of bias for day 28 mortality and clinical improvement. There was a low risk of bias for missing outcomes as data available to analyse was of >99% of the enrolled participants, despite having 23 (aspirin) and 19 (standard of care) withdrawing consent. The risk of bias for measurement of outcomes was low for day 28 mortality. Ascertainment of clinical improvement (defined as discharge alive) requires clinical judgement and could be affected by knowledge of intervention receipt, but it not considered likely to in the context of a pandemic, therefore leading to risk assessed to be some concerns for clinical improvement at day 28. The risk of bias was low in the selection of reported results since the outcomes and analyses plan were pre-specified in a published protocol (Table 1).

Effects of intervention

See Table 3 for the GRADE summary of findings table

The following outcomes were not reported in the trial report: Progression to hospitalization; progression to requiring oxygen; duration of hospitalization; progression to ICU admission; duration of ICU stay; duration of mechanical ventilation.

Primary outcome

1. Mortality (day 28)

Aspirin compared to standard of care does not decrease mortality (day 28), Rate Ratio (RR) 0.96 (95% CI 0.89 to 1.04), n = 14892, high certainty evidence.

Secondary outcomes

1. Resolution of symptoms (Discharge from hospital /Clinical improvement day 28)

Aspirin compared to standard of care does not result in improved resolution of symptoms (Discharge from hospital/Clinical improvement day 28), RR 1.02 (95% CI 1.00 to 1.04), n = 14892, high certainty evidence.

2. Time to discharge from hospital alive

Aspirin compared to standard of care does not reduce the time to discharge from hospital alive. Median (range) time to being discharged: Aspirin 8 days (5 to >28 days) compared to usual care 9 days (5 to >28 days), high certainty evidence.

3. Progression to mechanical ventilation

Aspirin compared to standard of care does not decrease progression to mechanical ventilation. RR 0.95 (95% CI 0.87 to 1.05), n =14162, high certainty evidence.

4. Adverse reactions - Thrombotic events

Aspirin compared to standard of care probably does not decrease thrombotic events. RR 0.88 (95% CI 0.76 to 1.01), n = 14892, high certainty evidence.

5. Adverse reactions - Major bleeding events

Aspirin compared to standard of care probably increases major bleeding events. RR 1.55 (95% CI 1.16 to 2.07), n = 14892, high certainty evidence.

6. Adverse reactions - Any major cardiac arrhythmia

Aspirin compared to standard of care did not increase major cardiac arrhythmia. RR 0.89 (95% CI 0.75 to 1.06), n = 14892, high certainty evidence.

7. Serious adverse events of bleeding attributed to aspirin

Aspirin compared to standard of care probably increases serious adverse events of bleeding attributed to aspirin slightly. 18 SAEs of major bleeding events attributed to aspirin use, 13 non-fatal and 5 fatal.

CONCLUSION

We identified one eligible trial for inclusion, Horby 2021. This is a randomised, controlled, open-label platform trial, which reports on the use of aspirin compared with usual care in patients hospitalised with COVID-19. Between November 2020 and March 2021, the trial recruited 14,892 participants hospitalized with COVID-19. Overall, there is no impact on mortality), time to discharge, progression to mechanical ventilation or resolution of symptoms/ discharge from hospital. Aspirin compared to standard of care may not decrease thrombotic events, but likely increases major bleeding events RR 1.55 (95% CI 1.16 to 2.07).

Adding aspirin to the standard of care for hospitalized patients with COVID-19 does not improve clinically important outcomes, and the balance of benefit and harms of its use do not support inclusion in current guidelines.

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Declaration of interests: TK (Cochrane South Africa, South African Medical Research Council (SAMRC) and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network and is partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.)

Acknowledgements:

Joy Oliver, Cochrane South Africa, SAMRC, for conducting the electronic searches.

Trudy Leong, Essential Drugs Programme, National Department of Health supported the review team.

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4. NIH COVID-19 Treatment Guidelines.
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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias (covid-nma)
<p>Landray M, Horby P, Pessoa-Amorim G, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021. https://www.medrxiv.org/content/10.1101/2021.06.08.21258132v1 NCT04381936; ISRCTN50189673 Horby P, medRxiv, 2021</p>	<p><u>Design</u> Parallel, open-label, platform RCT – multi-centre: United Kingdom, Indonesia and Nepal</p> <p><u>Study phase</u> Main randomisation, Part C factorial (from 1 November 2021). Protocol available at: https://www.recoverytrial.net/files/recovery-protocol-v17-1-2021-08-10-1.pdf</p> <p><u>Follow-up duration (days)</u> 28</p> <p><u>Funding</u> UK Research and Innovation (Medical Research Council), National Institute of Health Research (Grant ref: MC_PC_19056), and the Wellcome Trust (Grant Ref: 222406/Z/20/Z) through the COVID-19 Therapeutics Accelerator</p> <p><u>Declarations</u> No conflicts of interest declared</p> <p><u>Informed Consent</u> "Written informed consent was obtained from all patients, or a legal representative if they were too unwell or unable to provide consent"</p>	<p><u>Sample size</u> N=14,892 (7,351 patients were randomly allocated to usual care plus aspirin and 7,541 were randomly allocated to usual care alone)</p> <p><u>Oxygen supplementation</u> None/simple oxygen: n=9,972 / Noninvasive ventilation: n=4,190 Invasive mechanical ventilation: n=730</p> <p><u>Inclusion criteria</u> "Patients admitted to hospital were eligible for the trial if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial."</p> <ul style="list-style-type: none"> • Gender: Men 9,201 (62%), Women 5,691 (38%) • Mean age: 59.2 years (SD 14.2) • Median time since symptom onset was 9 days (IQR 6 to 12 days) • Comorbidities: Diabetes, heart disease, Chronic lung disease, TB, HIV, severe liver disease and severe kidney impairment <p><u>Exclusion criteria</u></p>	<p><u>Intervention</u> Aspirin 150 mg orally or by nasogastric tube or rectally once per day until discharge</p> <p><u>Control</u> Usual standard of care <i>Definition of Standard care: All patients will receive usual care in the participating hospital.</i></p> <p>"At randomization, 5,035 patients (34%) were receiving thromboprophylaxis with higher dose low molecular weight heparin (LMWH), 8,878 (60%) with standard dose LMWH, and 979 (7%) were not receiving thromboprophylaxis."</p> <p>"Use of other treatments for COVID-19 was similar among participants allocated aspirin and among those allocated usual care, with nearly 90% receiving a corticosteroid, about one-quarter receiving remdesivir, and one-eighth receiving tocilizumab."</p> <p>As a platform trial, and in a factorial design, patients could be simultaneously randomised to other treatment groups: i) azithromycin or colchicine or dimethyl fumarate versus usual care, ii) convalescent plasma or monoclonal antibody (REGN-CoV2) versus usual care, and iii) baricitinib versus usual care</p>	<p><u>Primary Outcome</u> All-cause mortality, reported at 28-days</p> <p><u>Secondary Outcomes</u></p> <ul style="list-style-type: none"> • Time to discharge from hospital • Among patients not on invasive mechanical ventilation at randomization progression to invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death <p><u>Subsidiary Clinical Outcomes</u></p> <ul style="list-style-type: none"> • Use of non-invasive respiratory support • Time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days) • Use of renal dialysis or haemofiltration • Cause-specific mortality • Major bleeding events (defined as intracranial bleeding or bleeding requiring transfusion, endoscopy, surgery or vasoactive drugs) • Thrombotic events (defined as acute pulmonary embolism, deep vein thrombosis, ischaemic stroke, myocardial infarction or systemic arterial embolism) • Major cardiac arrhythmias • Serious adverse reactions <p><i>Results</i></p>	<p><u>Randomisation</u> "Eligible and consenting adult patients were assigned in a 1:1 ratio to either usual standard of care or usual standard of care plus aspirin using web-based simple (unstratified) randomisation with allocation concealed until after randomization." Comment: Allocation sequence random. Allocation sequence concealed. Imbalances in baseline characteristics appear to be compatible with chance Low risk</p> <p><u>Deviations from Intervention</u> "Participants and local study staff were not masked to the allocated treatment. The trial steering committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial." Comment: Unblinded study (participants and personnel/carers) Deviations from intended intervention arising because of the study context: Administration of co-interventions of interest, biologics, antivirals and corticosteroids, reported and balanced between groups. 210 of 7,457 (3%) usual care patients who completed follow-up received aspirin. 6,587 of 7,290 (90%) patients with completed follow-up at time of analysis allocated to aspirin received aspirin. Overall, the deviation was</p>

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias (covid-nma)
		<p>“Children aged <18 years were not eligible for randomisation to aspirin; Patients with known hypersensitivity to aspirin, a recent history of major bleeding, or currently receiving aspirin or another antiplatelet treatment; aspirin unavailable at the hospital at the time of enrolment.”</p>		<ul style="list-style-type: none"> • No significant difference was observed in the proportion of patients who met the primary outcome of 28-day mortality between the two randomised groups (1,222 [17%] patients in the aspirin group vs. 1,299 [17%] patients in the usual care group; rate ratio 0.96; 95% confidence interval [CI], 0.89 to 1.04; p=0.35 • Allocation to aspirin was associated with a reduction of 1 day in median time until discharge alive from hospital compared to usual care (median 8 days vs. 9 days [IQR for each 5 to >28 days]) • Allocation to aspirin was associated with an increased rate of discharge alive within 28 days (75% vs. 74%, rate ratio 1.06, 95% CI 1.02 to 1.10, p=0.0062) • Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death among those allocated to aspirin was similar to that among those allocated to usual care (21% vs. 22%, risk ratio 0.96, 95% CI 0.90 to 1.03, p=0.23) • There were no observed significant differences in the pre-specified subsidiary clinical outcomes of cause-specific mortality (Supplementary Webtable 3), use of ventilation (23% vs. 24%, risk ratio 0.96, 	<p>too small to affect the outcome. Low risk</p> <p>Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Risk assessed to be low for the outcomes: Mortality (D28). Clinical improvement (D28). Low risk</p> <p><u>Missing outcome data</u> Comment: 14,892 participants randomised; 14,892 participants analysed (with completed follow up data for 14,747). Data available for all or nearly all participants randomised (99%). Of note, 23 vs. 19 participants withdrew consent. Risk assessed to be low for the outcomes: Mortality (D28). Clinical improvement (D28). Low risk</p> <p><u>Measurement of the outcome</u> Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) or “The trial steering committee, investigators, and all other individuals involved in the trial were masked to aggregated outcome data during the trial.”</p> <p><i>Clinical improvement</i> Clinical improvement (defined as discharge alive) requires clinical</p>

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias (covid-nma)
				<p>95% CI 0.90 to 1.03, p=0.30), successful cessation of invasive mechanical ventilation (38% vs. 36%, risk ratio 1.08, 95% CI 0.85 to 1.37, p=0.54), or receipt of renal dialysis or haemofiltration (4% in both groups, risk ratio 0.99, 95% CI 0.84 to 1.17, p=0.93)</p> <ul style="list-style-type: none"> • With aspirin use, the incidence of thrombotic events was lower (4.6% vs. 5.3%; absolute difference 0.6%, SE 0.4%) and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%, SE 0.2%) in the aspirin group • The incidence of new cardiac arrhythmias was similar in the two groups (3.1% vs. 3.5%) • There were 18 reports of a serious adverse event believed related to aspirin, all of which were due to haemorrhagic events 	<p>judgement and could be affected by knowledge of intervention receipt, but it not considered likely to in the context of a pandemic. Risk assessed to be some concerns clinical improvement (D28).</p> <p><i>Mortality</i> Mortality is an observer-reported outcome not involving judgement. Risk assessed to be low for the outcome: Mortality (D28). Low risk</p> <p><u>Selection of the reported results</u> Comment: The protocol and statistical analysis plan (prospective, dated November 1st, 2021) and registry (prospective, dated May 11th, 2020) were available. Outcomes were pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Trial analysed as pre-specified. Risk assessed to be low for the outcomes: Mortality (D28). Clinical improvement (D28). Low risk</p> <p><u>Overall risk of bias</u> Some concerns</p>

Table 2. Characteristics of planned and ongoing studies (source: www.covid-nma.com 20 October 2021) (N=9)

Treatment (per arm)	Sample size	Severity at enrollment	Sponsor/Funder	Reg. number
(1) Naproxen vs (2) Standard of care	584	Moderate/severe/critical	Assistance Publique - Hôpital de Paris	EUCTR2020-001301-23-FR
(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Ibuprofen	132	Mild/moderate	Instituto Investigaci3n Sanitario Biocruces Bizkaia	EUCTR2020-001606-33-ES
(1) Enoxaparin + paracetamol vs (2) Celecoxib + paracetamol vs (3) Paracetamol	810	Mild/moderate	FONDAZIONE RICERCA TRASLAZIONALE (FORT)	EUCTR2020-005890-29-IT
(1) Naproxen vs (2) Placebo	40	Moderate/severe/critical	Abadan University of Medical Sciences	IRCT20200324046850N3
(1) Naproxen + lansoprazole vs (2) Standard of care	584	Critical	Assistance Publique - Hôpital de Paris	NCT04325633
(1) Mefenamic acid vs (2) Placebo	40	Mild/moderate	Medical School of the University of Colima; Mexico	RPCEC00000388
(1) Ibuprofen vs (2) Standard of care	230	Severe	King's College London	NCT04334629
(1) Remdesivir vs (2) Remdesivir + dornase alfa vs (3) Remdesivir + atibucimab vs (4) Remdesivir + celecoxib + famotidine vs (5) Remdesivir + narsoplimab vs (6) Remdesivir + aripridil (vasoactive intestinal peptide) vs (7) Remdesivir + ciclosporin	1500	Critical	QuantumLeap Healthcare Collaborative	NCT04488081
(1) Naproxen vs (2) Placebo	192	Moderate/severe	Faculdade de Medicina de S3o Jose do Rio Preto - FUNFARME/FAMERP - S3o Jos3 do Rio Preto; SP; Brazil	RBR-3rywwg

Table 3: Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SOC	Risk with NSAIDs				
Mortality (day 28)	172 per 1,000	165 per 1,000 (153 to 179)	RR 0.96 (0.89 to 1.04)	14892 (1 RCT)	⊕⊕⊕⊕ High	Aspirin does not reduce mortality (day 28).
Resolution of symptoms (Discharge from hospital /Clinical improvement day 28)	736 per 1,000	750 per 1,000 (736 to 765)	RR 1.02 (1.00 to 1.04)	14892 (1 RCT)	⊕⊕⊕⊕ High	Aspirin does not result in an increased proportion of those with resolution of symptoms (Discharge from hospital /Clinical improvement day 28).
Time to discharge from hospital alive	<ul style="list-style-type: none"> Median time to being discharged: Aspirin 8 days (5 to >28 days) Usual care 9 days (5 - >28 days) 			14892 (1 RCT)	⊕⊕⊕⊕ High	Aspirin does not reduce time to discharge from hospital.
Progression to mechanical ventilation ^c	116 per 1,000	110 per 1,000 (101 to 121)	RR 0.95 (0.87 to 1.05)	14162 (1 RCT)	⊕⊕⊕⊕ High	Aspirin does not reduce progression to mechanical ventilation.
Adverse reactions/Thrombotic events	53 per 1,000	46 per 1,000 (40 to 53)	RR 0.88 (0.76 to 1.01)	14892 (1 RCT)	⊕⊕⊕⊕ High	Aspirin may have little or no effect on thrombotic adverse events.
Adverse reactions/Major bleeding events	10 per 1,000	16 per 1,000 (12 to 21)	RR 1.55 (1.16 to 2.07)	14892 (1 RCT)	⊕⊕⊕⊕ High	Aspirin increases major bleeding events.
Adverse reactions/Any major cardiac arrhythmia	35 per 1,000	32 per 1,000 (27 to 38)	RR 0.89 (0.75 to 1.06)	14892 (1 RCT)	⊕⊕⊕⊕ High	Aspirin does not increase major cardiac arrhythmic adverse reactions.
Serious adverse events of bleeding attributed to aspirin	There were 18 events of SAEs of bleeding related to aspirin, 13 non-fatal and 5 fatal. Not comparative data, only the aspirin group reported.			7541 (1 RCT)		Aspirin may increase serious adverse events of bleeding.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; 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.

Appendix 1: Search strategy

Database: Cochrane COVID-19 Study Register (<https://covid-19.cochrane.org/>)

Search strategy: Ibuprofen or naproxen or diclofenac or celecoxib or "mefenamic acid" or etoricoxib or indomethacin or Aspirin or rofecoxib or lumiracoxib or valdecoxib or NSAID or NSAIDS or "nonsteroidal anti-inflammatory agent" or "nonsteroidal anti-inflammatory agents" or "non-steroidal anti-inflammatory agent" or "non-steroidal anti-inflammatory agents" or "anti-inflammatory analgesics"

Filtered by: Study type – interventional; Study Aim – treatment and management; Intervention Assignment - randomised

Output: 46 studies with 58 references (2 duplicates)

Date: 1 October 2021

Database: LOVE Platform (<https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=aiel>)

Search strategy: (NSAID OR NSAIDS OR "nonsteroidal anti-inflammatory agent" OR "nonsteroidal anti-inflammatory agents" OR "nonsteroidal antiinflammatory agent" OR "nonsteroidal antiinflammatory agents" OR "non steroidal antiinflammatory agent" OR "non steroidal antiinflammatory agents" OR "non-steroidal anti-inflammatory agent" OR "non-steroidal anti-inflammatory agents" OR "anti-inflammatory analgesics") OR (Ibuprofen OR naproxen OR diclofenac OR celecoxib OR "mefenamic acid" OR etoricoxib OR indomethacin OR Aspirin OR rofecoxib OR lumiracoxib OR valdecoxib)

Filtered by: Systematic reviews and Primary studies (RCTs and Pending)

Output: 69 studies (18 duplicates)

Date: 1 October 2021

The screenshot shows the LOVE Platform search interface. At the top, there are tabs for "COVID-19 Evidence" and "COVID-19 News". Below this is the "Advanced search" section with a "Help" button and "Edit" and "Clear" buttons. The search query is displayed in a text box: "(NSAID OR NSAIDS OR "nonsteroidal anti-inflammatory agent" OR "nonsteroidal anti-inflammatory agents" OR "nonsteroidal antiinflammatory agent" OR "nonsteroidal antiinflammatory agents" OR "non steroidal antiinflammatory agent" OR "non steroidal antiinflammatory agents" OR "non-steroidal anti-inflammatory agent" OR "non-steroidal anti-inflammatory agents" OR "anti-inflammatory analgesics") OR (Ibuprofen OR naproxen OR diclofenac OR celecoxib OR "mefenamic acid" OR etoricoxib OR indomethacin OR Aspirin OR rofecoxib OR lumiracoxib OR valdecoxib)". To the right of the query box are several filter menus: "Broad synthesis" (set to Broad synthesis), "Systematic review" (checked), "Primary study" (checked) with sub-options for "RCT" (checked), "Non RCT", and "Pending" (checked), and "Other articles". Below these are "Other filters" including "Type of publication", "Publication year" (set to "YYYY" to "Present"), and "Epistemonikos date" (set to "From" to "To"). At the bottom, it shows "Total results: 69" and a legend for "Primary study / RCT" and "No data reported". A snippet of a result is visible at the bottom: "A randomized open-label trial to evaluate the efficacy and safety of".

Database: PubMed

Search strategy: see table below

Output: Systematic review (17 duplicates) and RCTs (10 duplicates)

Date: 1 October 2021

Search	Query	Results
#8	Search: #3 AND #4 Filters: Systematic Review Sort by: Most Recent	14
#7	Search: #5 AND #6 Sort by: Most Recent	269
#6	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	4,533,839
#5	Search: #3 AND #4 Sort by: Most Recent	559

#4	Search: Coronavirus[mh:noexp] OR coronavirus*[tiab] OR corona virus*[tiab] OR COVID-19[mh] OR covid-19[tiab] OR covid19[tiab] OR covid 2019[tiab] OR SARS-Cov-2[mh] OR SARS-CoV-2[tiab] OR SARS-CoV2[tiab] OR SARSCoV2[tiab] OR SARsCov-2[tiab] OR SARS-coronavirus*[tiab] OR severe acute respiratory syndrome coronavirus 2[nm] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR nCov2019[tiab] OR nCOV-2019[tiab] OR hCOV*[tiab] OR n-cov[tiab] OR ncov*[tiab] Sort by: Most Recent	192,818
#3	Search: #1 OR #2 Sort by: Most Recent	208,310
#2	Search: Ibuprofen OR naproxen OR diclofenac OR celecoxib OR "mefenamic acid" OR etoricoxib OR indomethacin OR Aspirin OR rofecoxib OR lumiracoxib OR valdecoxib Sort by: Most Recent	148,608
#1	Search: anti-inflammatory agents, non-steroidal[mh] OR NSAID[tiab] OR NSAIDS[tiab] OR nonsteroidal anti-inflammatory agent*[tiab] OR nonsteroidal antiinflammatory agent*[tiab] OR non steroidal antiinflammatory agent*[tiab] OR non-steroidal anti-inflammatory agent*[tiab] OR anti-inflammatory analgesics[tiab] Sort by: Most Recent	98,045
<p>Database: Living mapping and living systematic review of Covid-19 studies (www.covid-nma.com) Reviewed ongoing trials and living SR data, https://covid-nma.com/networks/ Output: 8 ongoing studies Date: 8 October 2021</p>		

Appendix 2: Evidence to decision framework

Desirable Effects		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<p>X Trivial</p> <ul style="list-style-type: none"> <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>See table 3. Summary of findings. No decrease on mortality or other clinical outcomes (RR 0.96 (95% CI 0.89 to 1.04)</p>	
Undesirable Effects		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large <input type="radio"/> Moderate X Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>See table 3. Summary of findings. Increase in bleeding reported RR 1.55 (95% CI 1.16 to 2.07. That is six more bleeds per 1000 people who received aspirin (from 10 to 16 bleeds / 1000 comparing standard of care to aspirin).</p>	
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate X High <input type="radio"/> No included studies 	<p>High certainty evidence.</p>	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability X No important uncertainty or variability 	<p>No research evidence available.</p>	<p>The committee was of the opinion that there is no important uncertainty or variability in how much people value the outcomes that were presented and reviewed as part of this decision.</p>
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<p>X Favors the comparison</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>The balance of effects probably favours the standard of care rather than aspirin.</p>	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know X Not applicable 	<p>Costs are considered negligible in addition to other care provided in hospitalized patients.</p>	<p>The committee discussed that as aspirin is not favoured that further in depth discussion on the following items was not necessary.</p>

Cost-effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies X Not applicable	No research commissioned for this decision.	

Equity: What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know X Not applicable	Not applicable.	

Acceptability: Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know X Not applicable	Not applicable.	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know X Not applicable	Not applicable.	

Research priorities

Other NSAIDs; Other sub-groups: Pregnant women, children

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	19 Nov 2021	HD, TK, NB, SE	Aspirin not recommended for the treatment of COVID-19, as aspirin shown to be no more effective than standard care. No other RCTs investigating other NSAIDs (other than aspirin) were identified.

For internal NDoH use:
 WHO INN: Acetylsalicylic acid
 ATC: B01AC06
 ICD10: U07.1/ U07.2