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"Rolling Collaborative Review" of Covid-19 treatments

ASPIRIN FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V 1.0	**17/02/2021**	First version
V 2.0	**16/03/2021**	Second version
V 3.0	**20/04/2021**	Third version
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V 5.0	**15/06/2021**	Fifth Version
V 6.0	**15/07/2021**	Sixth Version

Major changes from previous version

Chapter, page no.	Major changes from version 4.0
Table 4-1, 15 **Table 4-11, 35**	• The pool of evidence has changed • One randomised trial was added to the summary of findings table Table 4.1 (NCT04381936) • One ongoing two arm trial was added (n=200; NCT04937088)
Table 4-6, 26 to Table 4-13, 38	• Actual status of all ongoing trials listed in Tables 4 are verified and updated when indicated.
Appendix, 41	• The Appendix tables are updated.

Disclaimer

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
COVID-19	Coronavirus disease of 2019
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
ICU	Intensive Care Unit
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against COVID-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on COVID-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on COVID-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA COVID-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Aspirin, active substance: acetylsalicylic acid (ASA). Any generic equivalent of ASA. Oral intake. MESh terms: aspirin
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and a minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: randomised controlled trials and, optional, observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on two main mandatory sources and one optional source of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

In May 2021, the Swiss Network for Health Technology Assessment (SNHTA) created SoF tables, in which risk of bias assessments were used from covid-nma.com. From June 2021 the Austrian Institute for Health Technology Assessment (AIHTA) is responsible for the monthly updates. Whenever indicated the update of the SoF tables is done with the use of covid-nma.com (COVID-NMA initiative: find the living review protocol here). Multiple SoF tables are constructed by the type of comparison. Whenever feasible and sensible, data on efficacy outcomes will we depicted and assessed for the overall population and by disease severity.

From June 2021, the literature search is used from COVID-NMA initiative according living review protocol [1], [2], [3] or is conducted by authors of this RCR in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

The search results are screened, full texts of studies are assessed and study characteristics and outcome data are extracted according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [4] or reused from one living SR/MA source [2]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for RCTs [5].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [6]. Whenever feasible and sensible, stratified meta-analyses are performed by disease severity (mild to moderate versus severe to critical). For rating the certainty of the evidence, the GRADE approach is being used [7].

From June 2021, if new RCTs are published, certainty of evidence are reused from already published living systematic reviews/meta-analysis (SRs/MA) source from the international COVID-NMA initiative.

- Sources: https://covid-nma.com/ for SoF

2. Table(s) on published (peer reviewed) observational studies for safety results:

From June 2021, only RCTs are used for assessment of safety. Interested readers are referred to version 4.0 for the description of two observational studies.

3. Table(s) on ongoing trials :

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/
- WHO ICTRP through https://clinicaltrials.gov/ct2/who_table

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of AIHTA is searching and extracting the data for the eligible studies. At the drafting stage of each update, the authoring team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-1.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Aspirin with active substance acetylsalicylic acid belongs to the drug group non-steroidal anti-inflammatory drugs and is a nonselective cyclooxygenase inhibitor [8]. Salicylic acid is the most important active metabolite of aspirin. It is produced by plants upon infection with pathogens and in particular viruses [9, 10]. The production of salicylic acid in turn mediates resistance to viral replication, intercellular spread and systemic movement through so-called pathogenesis-related proteins including

the protein Coronatine Insensitive [9]. Aspirin is expected to stimulate cell-autonomous immunity against viral infection.

Apart from its capability to inhibit virus replication and its anti-inflammatory potential, acetylsalicylic acid has analgesic and antipyretic properties. The peripheral analgesic effect is due to the inhibition of cyclooxygenase. This inhibits the formation of prostaglandins (E2 and I2), which are involved in the development of pain [11]. The antipyretic effect is due to a central action on the hypothalamic temperature-regulating centre, resulting in peripheral dilatation of skin vessels with sweating and heat loss [11].

An additional mechanism of action is based on anti-platelet aggregation. Acetylsalicylic acid has an antithrombotic effect by inhibiting thromboxane A2 synthesis in platelets [12]. Accumulating data suggests COVID-19 to be profoundly prothrombotic. Microthrombosis due to a hypercoagulable state has been repeatedly reported in patients with COVID 19 [13]. Furthermore, the likelihood of progressing to severe disease and COVID-19 severity appears to be in part driven by direct injury to the cardiovascular system. Due to its anti-thrombotic effects, cardioprotective and lung-injury protective effects of aspirin in COVID-19 are expected.

3.2 Regulatory Status

Aspirin, produced by Bayer, is not currently approved for the treatment of COVID-19[14]. Beside the Brand-name “Aspirin” there are generic equivalents of acetylsalicylic acid on the market, but they have the same therapeutic indications and limitations as the original "Aspirin" (e.g. Alcacyl, Aspégic, Aspro, ASS Cardio Mepha). It is approved for the treatment of mild to moderately severe acute pain (headache, toothache, pain in the area of joints and ligaments, back pain) and for symptomatic treatment of fever and/or pain in colds. In adolescents aged 12 years and over, aspirin is indicated only after a doctor's prescription and only as a second-line treatment. Aspirin chewable tablets and granules are approved for self-medication for short-term treatment of a maximum of 3 days. Aspirin is marketed as Aspirin, Aspirin-C, Aspirin S, Aspirin Complex and Aspirin 500 Instant-tablets. In children aged 9 years and over and in adolescents, aspirin-C is approved only after a doctor's prescription and only as a second-line treatment (swissmedicinfo.ch).

Aspirin Cardio 100, Aspirin Cardio 300 of Bayer are approved for the following indication (swissmedicinfo.ch):

- Thrombosis prevention (reocclusion prophylaxis) after aortocoronary bypass, percutaneous transluminal coronary angioplasty (PTCA) and arteriovenous shunt in dialysis patients.
- Prophylaxis of cerebrovascular insults after precursor stages have occurred (transient ischaemic attacks, TIA).
- Reduction of the risk of further coronary thrombosis after a heart attack (reinfarction prophylaxis).
- Myocardial infarction prophylaxis in conjunction with other therapeutic measures in patients with a very high cardiovascular risk according to the benefit-risk assessment by the attending physician.
- Unstable angina pectoris.
- Prophylaxis of arterial thrombosis after vascular surgery.
- In acute myocardial infarction, as part of standard therapy.
- Prevention of vascular occlusion in arterial occlusive disease.

3.3 Level of Evidence

Randomised controlled trials

Our searches identified two completed randomised controlled trial (RCT), both reporting outcome data in preprint format. The 4-arm trial with acronym RESIST was conducted in a single centre in India, randomising 900 patients with mild to severe COVID-19. Of the 900 study participants, 724 (82.1%), 133 (15.1%) and 25 (2.8%) patients had baseline WHO Ordinal Scale for Clinical Improvement of 3, 4 and 5 respectively[15]. The average age in the study population was 53 year, 74% was male and the median number of days since symptom onset was 6 days (25%-75% interquartile range 4 to 8). Most frequent comorbid conditions were diabetes in 28% and hypertension in 29%. Aspirin was provided at a daily dose of 75 mg, on top of standard care. The open label trial used adequate methods with respect to concealment of allocation (sequentially numbered, sealed, opaque envelopes) and baseline characteristics of the study participants were similar across the study groups.[15] The trial authors randomised patients to aspirin, a statin (atorvastatin), a combination therapy with statin and aspirin or to no intervention. All four trial arms received standard care as well. Treatments received, other than those randomised, were hydroxychloroquine in 10%, azithromycin in 12%, remdesivir in 21%, favipiravir in 4%, doxycycline in 21%, anticoagulation in 28% and steroids in 27%. Plasma therapy or tocilizumab were given in 7 patients only (1%).

The comparisons of interest to this rolling review are:

- aspirin versus no intervention
- statin plus aspirin versus no intervention
- statin plus aspirin versus statin
- aspirin versus statin therapy

The trial authors aimed to evaluate all active treatment arms against the control arm where patients did not receive any intervention on top of standard care. The authors of this rolling review added the statin controlled comparisons. The comparison statin therapy versus no intervention falls outside the scope of this review but can be found in the preprint document [15], at https://www.deplazio.net/farmacicovid/ and https://covid-nma.com/.

The second trial with acronym RECOVERY concerned an investigator initiated multicenter open label adaptive platform trial conducted in the UK, Indonesia, and Nepal (NCT04381936; ISRCTN50189673). RECOVERY evaluates effects of potential treatments in patients hospitalized with COVID-19. One hundred seventy seven National Health Service (NHS) hospital organizations participated in the United Kingdom, whereas two hospitals in Indonesia and two hospitals in Nepal participated. In this report, we only considered the randomised comparison between aspirin (n=7351) and standard care (7541). Latter comparison was added to the RECOVERY protocol on November 27 2020. A daily dose of 150 mg aspirin was given orally or by nasogastric tube or rectally until discharge. Standard care was provided according to local treatment protocols and the treating physician's clinical judgment. A majority of participants had simple oxygen support or no oxygen support at baseline (9972, 67%). Twenty-eight percent had severe Covid-19 (n=4190) and 15% had critical COVID-19 (n=730). At randomisation, 5035 patients (34%) were receiving thromboprophylaxis with higher dose low molecular weight heparin (LMWH), 8878 (60%) with standard dose LMWH, and 979 (7%) were not receiving thromboprophylaxis. 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.

The trial authors performed prespecified subgroup analyses on the primary outcome all-cause mortality by age, sex, ethnicity, level of respiratory support, days since symptom onset, and use of corticosteroids. A sensitivity analysis restricting analysis of the primary outcome to patients with a positive PCR test for SARS-COV-2 was conducted. The follow-up form was completed for 7290 (99%) participants in the aspirin group and 215 7457 (99%) participants in the usual care group.

We did not find additional RCTs with published outcome data in any of the sources searched (Table 6-1).

Observational studies

As of June 2021, observational studies are no longer considered in the RCR on aspirin. Version 4.0 of this report can be consulted for the observational studies identified up to May 2021 (EUnetHTA JA3 rolling RCR 23).

Ongoing studies

We identified 35 reports to 22 ongoing studies in international clinical trial registries and through searching other sources (Table 6-1; Table 4-6 to Table 4-13).

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

In this section we describe outcome data from the RECOVERY trial and from four comparisons of the RESIST trial that are of interest to this report. With respect to the RESIST trial, outcome data from the modified intent-to-treat analyses were used, relating to 882 persons analysed from the 900 randomised (98%). Ninety-nine percent of those randomised in the RECOVERY trial had follow-up data available.

Aspirin & standard care versus standard care

The summary estimate for the effects of aspirin on mortality up to 28 days was a RR of 0.86 with 95% CI of 0.49 to 1.50 (2 studies, low certainty evidence, mild to critical COVID-19). Both studies reported the length of hospital stay as medians with interquartile ranges (IQR), so that these estimates were not pooled. RESIST did not find a difference in length of hospital stay, whereas RECOVERY reported a median difference of 1 day, without providing an indication of spread for the difference. High certainty evidence was reported for the outcome discharge from hospital within 28 days. In absolute terms 15 more patients per 1000 would be discharged within 28 days when compared to standard care without aspirin (0 fewer to 29 more, based on the RECOVERY trial). Clinical progression to mechanical ventilation was estimated to occur in six fewer patients per 1000, but according to the 95% CI this could be 15 fewer to 5 more (2 studies, moderate certainty evidence). Effects on other outcomes related to clinical progression were unclear as the estimates were based on the RESIST trial only and were of very low certainty. Similarly, effects on Major bleeding are unclear, as the RESIST trial was not powered to measure this outcome and because safety outcome data from the RECOVERY trial are not yet available. Full details are found in Table 4-1.

Aspirin and statin therapy versus no intervention

Outcome data was abstracted from RESIST. No difference was detected in the length of hospital stay when comparing the aspirin on top of standard care group with the group receiving standard care only (moderate certainty evidence). Effects of aspirin on in hospital mortality at 10 days, clinical progression or major bleeding were unclear (very low certainty evidence). Full details are found in Table 4-2.

Aspirin and statin therapy on top of standard of care versus statin therapy on top of standard of care

Outcome data was abstracted from RESIST. No difference was detected in the length of hospital stay when comparing the aspirin on top of standard care group with the group receiving standard care only (moderate certainty evidence). Effects of aspirin on in hospital mortality at 10 days, clinical progression or major bleeding were unclear (very low certainty evidence). Full details are found in Table 4-3.

Aspirin on top of standard of care versus statin therapy on top of standard of care

Outcome data was abstracted from RESIST. No difference was detected in the length of hospital stay when comparing the aspirin on top of standard care group with the group receiving standard care only (moderate certainty evidence). Effects of aspirin on in hospital mortality at 10 days, clinical progression or major bleeding were unclear (very low certainty evidence). Full details are found in Table 4-4.

In summary, the effects of combination treatment or effects of aspirin compared to statin treatment remain vastly unclear, due to the indirectness and serious imprecision. Only the outcome Length of hospital stay in days was judged of moderate certainty. The safety profile of aspirin in patients with COVID-19 remains unclear, as RESIST was not powered to measure such outcomes, and due to indirectness.

4.2 Safety evidence from observational studies

From June 2021, only RCTs are used for the assessment of safety. Previous evidence from prospective observational studies, can be found in the previous version of this report.

4.3 Ongoing studies

One hundred and eleven citations were identified by our searches. Sixty-four entries were found in the four trial registries searched. Twenty-six entries to 7 unique trials were identified in the Cochrane COVID-19 register and eighteen were identified in the covid-nma database (https://covid-nma.com/dataviz/). An additional two unique reports were found when using trial acronyms and clinical trial registration numbers in google.com, scholar.google.com and pubmed.gov. In this update, six citations were identified across all sources searched leading to the inclusion of one newly identified phase 2 RCT, planning to enrol 200 outpatients with newly diagnosed COVID-19 (NCT04937088).

After deduplication, 35 reports to 22 ongoing studies were considered in this report (Table 4-6 to Table 4-13). None of these is marked as completed with outcome data available. Two RCTs compared colchicine plus aspirin with aspirin alone. As the effect of aspirin cannot be distilled from such comparison, the trials were excluded CTRI ID 2021/03/032060; CTRI ID 2021/03/032059). Another ongoing RCT was excluded as aspirin was provided in all trial arms (LEAD COVID-19; NCT04363840). The LEAD COVID-19 trial evaluates aspirin and vitamin D in vitamin D deficient COVID-19 patients and will be addressed in EUnetHTA RCR20 [16]. The 21 included studies involved 5 platform adaptive RCTs (Table 4-6,Table 4-7); twelve studies evaluating aspirin as a single agent (Table 4-8 to Table 4-11) and four studies evaluating a combination therapy with aspirin (Table 4-12). Three platform randomized trials and two RCTs recruited (part of) the patients in Europe. Sixteen of the ongoing RCTs evaluated Aspirin in daily doses of 75 to 160mg. Latter doses are typically used to obtain antiplatelet effects and are used for cardioprotection. One RCT used a lower dose by using Aggrenox twice daily for a total daily dose of 400 mg Dipyridamole and 50mg aspirin (NCT04410328). One trial used a daily dose of 325 mg, a dosage used to elicit both antiplatelet and anti-inflammatory action (CTRI ID 2020/09/028088). The dose used in the ASCOT-ADAPT platform trial in Denmark remains unclear (EudraCT: 2020-005963-29-DK) but it likely the same as used in the ASCOT-ADAPT with recruitment in Australia, which is 100 mg (NCT04483960 / ACTRN12620000445976). The remaining trial did not describe the dose in detail, but it was clear that the Aspirin dose was to obtain anti-inflammatory effects (NCT04554433). The severity of COVID-19 in the study population varied between trials. The majority studied hospitalized patients with moderate to critical COVID-19, two RCTs focused on outpatients (NCT04498273, NCT04937088), another on both outpatients and hospitalized patients (NCT04324463) and another restricted inclusion to patient on the intensive care unit (NCT04466670).

4.4 Scientific conclusion about status of evidence generation

Aspirin versus standard care
Two RCTs conducted in the UK, Indonesia, Nepal and India provided both non-peer reviewed reports. Aspirin may reduce all-cause mortality, increased the number of patients discharged from hospital within 28 days and probably reduces progression to mechanical ventilation, whereas effects on other outcomes related to disease progression are unclear. The safety profile of aspirin in patients with mild to critical COVID-19 remains unclear, as the trial authors of RECOVERY have not yet published safety data in the public domain.

Aspirin and statin therapy on top of standard of care versus standard of care
Aspirin and statin therapy on top of standard of care versus statin therapy on top of standard of care
Aspirin on top of standard of care versus statin therapy on top of standard of care
The very low certainty of the evidence from RESIST hamper the interpretation of the efficacy and safety data. The direction of effects is favouring aspirin plus standard of care over standard of care with or without statin therapy, but this finding is over very low certainty. With respect to the combined use of aspirin and statin, the point estimates favour standard of care without such combination treatment (very low certainty evidence).

Overall, the evidence base has grown, and helps the interpretation of the magnitude of effects but there still is a paucity in data on the safety profile. There is no evidence supporting the use of combined aspirin plus statin therapy.

Table 4-1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of aspirin

Patient or population: mild to critical COVID-19 infection
Setting: Hospital, worldwide
Intervention: aspirin 75mg to 150 mg daily on top of standard care
Comparison: standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[b]	Risk with aspirin					
All-cause mortality at 10 to 28 days	168 per 1000	145 per 1000 (82 to 252)	RR 0.86 (0.49 to 1.50)[c]	24 fewer per 1000 (from 86 fewer to 84 more)	15343 (2)[17, 18]	low[d]	
Length of hospital stay in days	RECOVERY: median 9 days IQR 5 to >28 days RESIST: median 9 (IQR 8 to 11)	RECOVERY: median 8 days IQR 5 to >28 days RESIST: median 9 (IQR 8 to 11)	RECOVERY: not reported RESIST: not reported, p-value=0.85[e]	RECOVERY: Median 1 day RESIST: -	RECOVERY: 15332 (2)[17, 18][f]	moderate[g,h]	It was not considered appropriate to pool medians. The study estimates are displayed separately instead.
Discharged from hospital within 28 days	736 per 1000	750 per 1000 (736 to 765)	RR 1.02 (1.00 to 1.04)	15 more per 1000 (from 0 fewer to 29 more)	14892(1) [18]	high[g]	
Clinical progression WHO progression score level 6 or above on Day 10	32 per 1000	13 per 1000 (4 to 52)	RR 0.42 (0.11 to 1.62)[i]	19 fewer per 1000 (from 28 fewer to 20 more)	440 (1)[17]	very low[j,k]	At covid-nma.com, a HR of 0.40 (0.10 to 1.57) was reported for the outcome Time to WHO progression score level 7 or above (10 days of follow-up). HR below 1 favoured aspirin over control.
Clinical progression: Mechanical ventilation	116 per 1000	110 per 1000 (101 to 120)	RR 0.95 (0.87 to 1.04 [i]	6 fewer per 1000 (from 15 fewer to 5 more)	14602 (2)[17, 18]	moderate[g,l]	Patients on mechanical ventilation at trial entry are not considered in this analyses.
Clinical progression: shock	27 per 1000	5 per 1000 (1 to 37)	RR 0.17 (0.02 to 1.36) [i]	23 fewer per 1000 (from 27 fewer to 10 more)	440 (1)[17]	very low[j,k]	
Clinical progression ≥ 1 level increase on WHO clinical improvement ordinal scale[l]	100 per 1000	118 per 1000 (69 to 201)	RR 1.17 (0.69 to 2.00) [i]	17 more per 1000 (from 31 fewer to 100 more)	440 (1)[17]	very low[j,k]	

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[b]	Risk with aspirin					
SAE: Major bleeding	0 per 1000	0 per 1000	Not estimable		440 (1)[17]	very low[k,m]	No events occurred in either trial arm. Safety data from RECOVERY are not yet in the public domain.

Source: based on publication by Ghati et al, 2021[17]; CTRI/2020/07/026791 (RESIST trial) and preprint of Horby et al, 2021 [18]; ISRCTN 50189673 and clinicaltrials.gov NCT04381936. GRADE assessments adapted from covid-nma.com for all-cause mortality; outcome data, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: RR=relative risk; IQR=interquartile range from 25th to 75th percentile; HR=hazard ratio; SAEs=serious adverse events.
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
Explanations

a. Standard care consisted of conventional medical therapy according to the institute's COVID-19 treatment protocol and the treating physician's clinical judgment.
b. Background risk as observed in the trial in the standard care control groups. The risk with aspirin is calculated from the relative risk from own calculations and the background risk.
c. RR from covid-nma.com
d. Downgraded by two levels for imprecision: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm
e. P-value from Wilcoxon rank sum test evaluating differences across the original four trial arms[15]
f. Number of patients contributing to the analyses in RESIST (440 out of 451 randomised) [17]
g. Not downgraded for indirectness: multicentre study conducted across several countries, therefore not downgraded for indirectness
h. Downgraded by one level for imprecision: the confidence interval is consistent with the possibility for benefit and the possibility for harm
i. RR from own calculations, using the raw data as reported by the trial authors[17, 18]
j. Downgraded by two levels for imprecision: the optimal information size is not met, the wide confidence interval is consistent with the possibility for benefit and the possibility for harm
k. Downgraded by one level for indirectness: single study from a single institution in India, therefore results in this population might not be generalizable to European settings
l. WHO progression score level 6 or above referring to intubation and mechanical ventilation (score 6); ventilation + additional organ support – pressors, renal replacement therapy RRT, extracorporeal membrane oxygenation ECMO (score 7) or death (score 8)
m. Downgraded by two levels for imprecision: the optimal information size is not met

Table 4-2. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of statin plus aspirin

Patient or population: mild to severe COVID-19 infection
Setting: Hospital
Intervention: combined treatment with statin 40mg and aspirin 75mg (once daily) on top of standard care
Comparison: standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)[c]	Certainty of evidence	Comments
	Risk with standard care[b]	Risk with statin plus aspirin					
In hospital mortality at 10 days	32 per 1000	36 per 1000 (13 to 98)	RR 1.13 (0.42 to 3.07)[d]	4 more per 1000 (from 19 fewer to 66 more)	440 (1)[17]	very low[e,f,g]	
Length of hospital stay in days	Median 9 (IQR 8 to 11)	Median 9 (IQR 8 to 12)	Not reported, p-value[h]=0.85	-	440 (1)[17]	moderate[g]	
Clinical progression WHO progression score level 6 or above[i] on Day 10	32 per 1000	36 per 1000 (13 to 98)	RR 1.13 (0.42 to 3.07)[d]	4 more per 1000 (from 19 fewer to 66 more)	440 (1)[17]	very low[e,f,g]	At covid-nma.com, a HR of 1.00 (0.36 to 2.77) was reported for the outcome Time to WHO progression score level 7 or above (10 days of follow-up). HR below 1 favoured aspirin over control.
Clinical progression: Mechanical ventilation	27 per 1000	36 per 1000 (13 to 103)	RR 1.32 (0.47 to 3.75)[d]	9 more per 1000 (from 15 fewer to 75 more)	440 (1)[17]	very low[e,f,g]	
Clinical progression: shock	27 per 1000	27 per 1000 (9 to 83)	RR 0.99 (0.32 to 3.03)[d]	0 fewer per 1000 (from 19 fewer to 56 more)	440 (1)[17]	very low[e,f,g]	
Clinical progression: ≥ 1 level increase on WHO clinical improvement ordinal scale	100 per 1000	90 per 1000 (51 to 161)	RR 0.90 (0.51 to 1.61)[d]	10 fewer per 1000 (from 49 fewer to 60 more)	440 (1)[17]	very low[e,f,g]	
SAE: Major bleeding	0 per 1000	0 per 1000	Not estimable	-	440 (1)[17]	very low[e,g,j]	No events occurred in either trial arm

Source: based on publication by Ghati et al, 2021[17] & CTRI/2020/07/026791 (RESIST trial). Risk of bias assessments from covid-nma.com; outcome data, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: RR=relative risk; IQR=interquartile range from 25th to 75th percentile; RDS=respiratory distress syndrome; HR=hazard ratio; SAEs=serious adverse events.
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

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)[c]	Certainty of evidence	Comments
	Risk with standard care[b]	Risk with statin plus aspirin					

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

Explanations

a. Standard care consisted of conventional medical therapy according to the institute's COVID-19 treatment protocol and the treating physician's clinical judgment.
b. Background risk as observed in the trial in the standard care control group. The risk with the combined statin plus aspirin treatment is calculated from the relative risk from own calculations and the background risk.
c. Number of patients contributing to the analyses (440 out of 451 randomised)
d. RR from own calculations, using the raw data as reported by the trial authors [17]
e. Not downgraded for risk of bias: some concerns regarding deviation from intended intervention. Participants and personnel/carers were not blinded. Deviations from intended intervention arising because of the study context: 3 (Atorvastatin group) vs 2 (Aspirin group) participants received both drugs. 5 participants (Aspirin group) received Atorvastatin only. 7 received only Atorvastatin and 4 only Aspirin (Atorvastatin+Aspirin group). This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Administration of co-interventions of interest, antivirals, biologics and corticosteroids, were reported and balanced among arms (adapted from covid-nma.com).
f. Downgraded by two levels for imprecision: the optimal information size is not met, the wide confidence interval is consistent with the possibility for benefit and the possibility for harm
g. Downgraded by one level for indirectness: single study from a single institution in India, therefore results in this population might not be generalizable to European settings
h. P-value from Wilcoxon rank sum test evaluating differences across the original four trial arms [15]
i. WHO progression score level 6 or above referring to intubation and mechanical ventilation (score 6); ventilation + additional organ support – pressors, renal replacement therapy RRT, extracorporeal membrane oxygenation ECMO (score 7) or death (score 8)
j. Downgraded by two levels for imprecision: the optimal information size is not met

Table 4-3. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of statin plus aspirin versus statin treatment

Patient or population: mild to severe COVID-19 infection
Setting: Hospital
Intervention: combined treatment with aspirin 75mg and statin 40mg once daily on top of standard care
Comparison: statin 40mg once daily on top of standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)[c]	Certainty of evidence	Comments
	Risk with statin[b]	Risk with statin plus aspirin					
In hospital mortality at 10 days	32 per 1000	36 per 1000 (13 to 98)	RR 1.14 (0.42 to 3.10)[d]	4 more per 1000 (from 18 fewer to 67 more)	442 (1)[17]	very low[e,f,g]	
Length of hospital stay in days	Median 9 (IQR 8 to 11)	Median 9 (IQR 8 to 12)	Not reported, p-value[h]=0.85	-	442 (1)[17]	moderate[g]	
Clinical progression WHO progression score level 6 or above on Day 10	32 per 1000	36 per 1000 (13 to 98)	RR 1.14 (0.42 to 3.10)[d]	4 more per 1000 (from 18 fewer to 67 more)	442 (1)[17]	very low[e,f,g]	
Clinical progression Mechanical ventilation	32 per 1000	36 per 1000 (13 to 98)	RR 1.14 (0.42 to 3.10)[d]	4 more per 1000 (from 18 fewer to 67 more)	442 (1)[17]	very low[e,f,g]	
Clinical progression shock	23 per 1000	27 per 1000 (8 to 88)	RR 1.20 (0.37 to 3.87)[d]	5 more per 1000 (from 14 fewer to 65 more)	442 (1)[17]	very low[e,f,g]	
Clinical progression ≥ 1 level increase on WHO clinical improvement ordinal scale	122 per 1000	90 per 1000 (53 to 156)	RR 0.74 (0.43 to 1.28)[d]	32 fewer per 1000 (from 70 fewer to 34 more)	442 (1)[17]	very low[e,f,g]	
SAE: Major bleeding	0 per 1000	0 per 1000	Not estimable	-	442 (1)[17]	very low[e,g,j]	No events occurred in either trial arm

Source: based on publication by Ghati et al, 2021[17] & CTRI/2020/07/026791 (RESIST trial). Risk of bias assessments from covid-nma.com; outcome data, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: RR=relative risk; IQR=interquartile range from 25th to 75th percentile; HR=hazard ratio; SAEs=serious adverse events.
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
Explanations

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)[c]	Certainty of evidence	Comments
	Risk with statin[b]	Risk with statin plus aspirin					

a. Standard care consisted of conventional medical therapy according to the institute's COVID-19 treatment protocol and the treating physician's clinical judgment.
b. Background risk as observed in the trial in the statin group. The risk with the combined aspirin and statin treatment is calculated from the relative risk from own calculations and the background risk.
c. Number of patients contributing to the analyses (442 out of 449 randomised)
d. RR from own calculations, using the raw data as reported by the trial authors [17]
e. Not downgraded for risk of bias: some concerns regarding deviation from intended intervention. Participants and personnel/carers were not blinded. Deviations from intended intervention arising because of the study context: 3 (Atorvastatin group) vs 2 (Aspirin group) participants received both drugs. 5 participants (Aspirin group) received Atorvastatin only. 7 received only Atorvastatin and 4 only Aspirin (Atorvastatin+Aspirin group). This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Administration of co-interventions of interest, antivirals, biologics and corticosteroids, were reported and balanced among arms.
f. Downgraded by two levels for imprecision: the optimal information size is not met, the wide confidence interval is consistent with the possibility for benefit and the possibility for harm
g. Downgraded by one level for indirectness: single study from a single institution in India, therefore results in this population might not be generalizable to European settings
h. P-value from Wilcoxon rank sum test evaluating differences across the original four trial arms [15]
i. WHO progression score level 6 or above referring to intubation and mechanical ventilation (score 6); ventilation + additional organ support – pressors, renal replacement therapy RRT, extracorporeal membrane oxygenation ECMO (score 7) or death (score 8)
j. Downgraded by two levels for imprecision: the optimal information size is not met

Table 4-4. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of aspirin versus statin treatment

Patient or population: mild to severe COVID-19 infection
Setting: Hospital
Intervention: aspirin 75mg daily on top of standard care
Comparison: statin (atorvastatin) on top of standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)[c]	Certainty of evidence	Comments
	Risk with statin[b]	Risk with aspirin					
In hospital mortality at 10 days	32 per 1000	14 per 1000 (3 to 52)	RR 0.43 (0.11 to 1.64)[d]	18 fewer per 1000 (from 28 fewer to 20 more)	442 (1)[17]	very low[e,f,g]	
Length of hospital stay in days	Median 9 (IQR 8 to 11)	Median 9 (IQR 8 to 11)	Not reported, p-value=0.85[h]	-	442 (1)[17]	moderate[g]	
Clinical progression WHO progression score level 6 or above on Day 10	32 per 1000	14 per 1000 (3 to 52)	RR 0.43 (0.11 to 1.64)[d]	18 fewer per 1000 (from 28 fewer to 20 more)	442 (1)[17]	very low[e,f,g]	
Clinical progression Mechanical ventilation	32 per 1000	14 per 1000 (3 to 52)	RR 0.43 (0.11 to 1.64)[d]	18 fewer per 1000 (from 28 fewer to 20 more)	442 (1)[17]	very low[e,f,g]	
Clinical progression shock	23 per 1000	5 per 1000 (0 to 38)	RR 0.20 (0.02 to 1.70)[d]	18 fewer per 1000 (from 22 fewer to 16 more)	442 (1)[17]	very low[e,f,g]	
Clinical progression ≥ 1 level increase on WHO clinical improvement ordinal scale	122 per 1000	117 per 1000 (71 to 195)	RR 0.96 (0.58 to 1.60)[d]	5 fewer per 1000 (from 51 fewer to 73 more)	442 (1)[17]	very low[e,f,g]	
SAE: Major bleeding	0 per 1000	0 per 1000	Not estimable		442 (1)[17]	very low[e,g,j]	No events occurred in either trial arm

Source: based on publication by Ghati et al, 2021[17] & CTRI/2020/07/026791 (RESIST trial). Risk of bias assessments from covid-nma.com; outcome data, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: RR=relative risk; IQR=interquartile range from 25th to 75th percentile; HR=hazard ratio; SAEs=serious adverse events.
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

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)[c]	Certainty of evidence	Comments
	Risk with statin[b]	Risk with aspirin					

Explanations

a. Standard care consisted of conventional medical therapy according to the institute's COVID-19 treatment protocol and the treating physician's clinical judgment.
b. Background risk as observed in the trial in the statin group. The risk with aspirin is calculated from the relative risk from own calculations and the background risk.
c. Number of patients contributing to the analyses (442 out of 449 randomised)
d. RR from own calculations, using the raw data as reported by the trial authors [17]
e. Not downgraded for risk of bias: some concerns regarding deviation from intended intervention. Participants and personnel/carers were not blinded. Deviations from intended intervention arising because of the study context: 3 (Atorvastatin group) vs 2 (Aspirin group) participants received both drugs. 5 participants (Aspirin group) received Atorvastatin only. 7 received only Atorvastatin and 4 only Aspirin (Atorvastatin+Aspirin group). This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Administration of co-interventions of interest, antivirals, biologics and corticosteroids, were reported and balanced among arms.
f. Downgraded by two levels for imprecision: the optimal information size is not met, the wide confidence interval is consistent with the possibility for benefit and the possibility for harm
g. Downgraded by one level for indirectness: single study from a single institution in India, therefore results in this population might not be generalizable to European settings
h. P-value from Wilcoxon rank sum test evaluating differences across the original four trial arms [15]
i. WHO progression score level 6 or above referring to intubation and mechanical ventilation (score 6); ventilation + additional organ support – pressors, renal replacement therapy RRT, extracorporeal membrane oxygenation ECMO (score 7) or death (score 8)
j. Downgraded by two levels for imprecision: the optimal information size is not met

Table 4-5 Study characteristics of included RCT

Author, year, reference number/Study name/Study ID	**Ghati 2021[17]** **Clinical Trials Registry - India Identifier: CTRI/2020/07/026791** **Acronym: RESIST**	**Horby 2021** **NCT04381936 / ISRCTN50189673** **Acronym: RECOVERY**
Study design, study phase	Phase 2/3 RCT. Single center 4-arm open label trial with parallel group assignment Randomisation: computer-generated permuted block randomization with mixed block size Concealment: Sequentially numbered, sealed, opaque envelopes Blinding: none	Phase 3 RCT. Multicenter adaptive platform open label trial Randomisation: on patient level, web-based simple (unstratified) randomisation with allocation concealment. Concealment: web-based, randomisation code is given once all details of both the patient and the caregiver are submitted Blinding: none
Centres (single centre or multicentre), country, setting	Single center / India / Hospital	Multicenter / UK, Indonesia, Nepal / Hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	N=900 randomised, 882 analysed at baseline Mean age: 53.1 overall 650 / 882 males (73.7%) Severity: Mild: n=724; Moderate: n=133; Severe: n=25; Critical: n=0 Severity as defined by the WHO Ordinal Scale for Improvement, scores 3 (mild) to 5 (severe)	N=14892 randomised, 14892 analysed at baseline Mean age: 59.2 overall 9201 / 14892 (61.8%) males Severity: Mild n=0; Moderate n=0; Severe n=4190; Critical n=730 Median time since symptom onset was 9 days (IQR 6 to 12 days)
Inclusion criteria	All RT-PCR positive Covid-19 patients, ≥ 40 years and < 75 years of age, requiring hospitalisation due to symptoms [World Health Organization (WHO) Ordinal Scale for Clinical Improvement 3 to 5]	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
Exclusion criteria	• critical illness (WHO Ordinal Scale for Clinical Improvement > 5) • documented significant liver disease/dysfunction (aspartate transaminase [AST] / alanine aminotransferase [19] > 240 IU/L) • myopathy and rhabdomyolysis (creatine phosphokinase [CPK] > 5x normal) • known allergy or intolerance to statins or aspirin • prior statin or aspirin use in last 30 days • history of active gastrointestinal bleeding in past three months • coagulopathy, thrombocytopenia (platelet count < 100000/ dL) • pregnancy, active breastfeeding • inability to take oral or nasogastric medications • refusing consent	• Children aged <18 years; • known hypersensitivity to aspirin; • a recent history of major bleeding; • currently receiving aspirin or another antiplatelet treatment; • aspirin unavailable at the hospital at the time of enrolment

	• taking medicines known to have a significant drug interaction with statin or aspirin	
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Trial arm: Aspirin - n=225 randomised Aspirin tablet 75mg once daily for ten days or till discharge whichever is later. N= 221 analysed. Trial arm Atorvastatin – n=224 Atorvastatin (Statin): atorvastatin 40mg tablet once daily for ten days or till discharge whichever is later. N= 221 analysed. Trial arm aspirin + atorvastatin, n=225 randomised Aspirin + atorvastatin with dose as described above. N= 221 analysed. Co-Intervention in all trial arms: standard of care, all participants received conventional medical therapy according to the institute's COVID-19 treatment protocol and the treating physician's clinical judgment. Duration : 10 days	Trial arm: Aspirin – n=7351 randomised 150 mg orally or by nasogastric tube or rectally once per day until discharge
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	N=226 Standard of care: all participants received conventional medical therapy according to the institute's COVID-19 treatment protocol and the treating physician's clinical judgment. N= 219 reported at baseline	Trial arm: Standard care – n=7541 randomised Definition of Standard care: all patients will receive usual care in the participating hospital
Primary Outcome(s)	Primary outcome described in the trial registry and preprint document: • Clinical deterioration characterised by progression to WHO clinical improvement ordinal score more than or equal to 6 (i.e., endotracheal intubation, non-invasive mechanical ventilation, pressor agents, RRT, ECMO, and mortality). Timepoint: 10 days or until discharge whichever is longer	Primary outcome described in the trial registry, protocol and preprint document: • All-cause mortality. Time Frame: Within 28 days after randomisation Pre-specified analyses of the primary outcome were performed in five subgroups defined by characteristics at randomization: age, sex, level of respiratory support, days since symptom onset, and use of corticosteroids.
Patient-relevant secondary outcome(s)	• change in serum inflammatory markers (C-reactive protein and Interleukin-6), and Troponin I from baseline (time zero) to 5th day of study enrolment or 7th day after symptom onset, whichever was later. (as indicated in the preprint). "Other" outcomes: • clinical deterioration (≥1 increase in baseline WHO Ordinal Scale for Clinical Improvement)	• time to discharge from hospital and among patients not on invasive mechanical ventilation at randomisation, progression to invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death Prespecified subsidiary clinical outcomes: • use of non-invasive respiratory support

	• progression to shock • requirement of mechanical ventilation • length of hospital stay • in-hospital mortality Safety outcomes • Adverse drug effects like ○ myalgia [severe muscle pain or aches (CPK < Upper limit of normal)], ○ myopathy (unexplained muscle pain or weakness accompanied by CPK >10 x ULN), ○ rhabdomyolysis (severe myopathy with CPK >40 x ULN and myoglobinuria ± acute renal failure), ○ hepatotoxicity (ALT/AST > 3 x ULN) ○ minor bleeding (BARC bleeding type 1 and 2 i.e., bleeding that is not actionable and does not cause the patient to seek treatment, bleeding requiring a healthcare assessment or less invasive treatment such as heavy menstrual bleeding, ecchymosis, or epistaxis etc.) ○ major bleeding [BARC bleeding type ≥ 3 i.e., significant blood loss requiring blood transfusion, bleeding into a critical closed space (e.g., intracranial bleeding, compartment syndrome) ○ bleeding requiring an intervention for management (e.g., surgery, interventional radiology procedures, endoscopic treatments) ○ fatal bleeding	• 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
Follow-up (days, months)	Up to 10 days	
Sponsor/ lead institution	All India Institute of Medical Sciences (AIIMS), New Delhi, India	

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
**The duration and dose of empiric antibiotics will be determined by the treating clinician and local guidelines or practice.
Abbreviations: see list of abbreviation on page 5. REMAP-COVID=sub-platform of REMAP-CAP evaluating treatments specific for COVID-19; REMAP-CAP=Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia

Table 4-6 Ongoing platform RCTs involving Aspirin

Trial Identifier/registry ID(s)/contact	**NCT04381936 / EudraCT2020-001113-21-GB / ISRCTN50189673** **RECOVERY** **Contact: Contact: Richard Haynes; +44 (0)1865 743743; recoverytrial@ndph.ox.ac.uk**	**NCT04498273** **ACTIV4-Outpatient** **Contact: Frank Sciurba, University of Pittsburgh**	**NCT02735707 / EudraCT: 2015-002340-14-IT** **REMAP—COVID** **Contact: Cameron Green; info@remapcap.org**
Study design, study phase	Phase 2/3 RCT, multicentre open label adaptive platform trial with factorial assignment	Phase 3 RCT, multicentre quadruple blinded adaptive platform trial with parallel assignment Pharmacological and standard of care comparators Masing: Participant, Care Provider, Investigator, Outcomes Assessor	Phase 4 Randomized, Embedded, Multifactorial Adaptive Platform Trial Masking: none
Recruitment status	Recruiting, randomisation to no additional treatment versus aspirin has finished recruitment (last update at trial registry on 5 May 2021).	Active, not recruiting (last update at trial registry on 22 June 2021)	Recruiting (last update at trial registry at 12 Oct. 2020)
Number of Patients, Disease severity*	40'000 Disease severity: not specified	7'000 planned, 657 actual Mild-Moderate	N=7100 in main trial, N=unclear in COVID-19 sub-platform Severe to critical
Setting (hospital, ambulatory,..)	Hospital	Outpatient	Hospital, ICU
Intervention (generic drug name and dosage)**	• Lopinavir-Ritonavir • Corticosteroid • Hydroxychloroquine • Azithromycin • Biological: Convalescent plasma • Tocilizumab • Biological: Immunoglobulin • Synthetic neutralising antibodies • **Aspirin**: 150 mg by mouth (or nasogastric tube) or per rectum once daily until discharge, for adults ≥18 years old. • Colchicine • Baricitinib • Infliximab (added in registry on may 2021) • Anakinra	Apixaban 2.5 MG Apixaban 5MG • Aspirin: low dose aspirin 81mg oral, twice daily for 45 days	• Aspirin administered at either 75mg or 100mg once per day for 14 days or until hospital discharge, whichever occurs first Other active trial arms • Fixed-duration Hydrocortisone • Shock-dependent hydrocortisone • Ceftriaxone • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam • Ceftaroline • Amoxicillin-clavulanate • Macrolide administered for 3-5 days • Macrolide administered for up to 14 days • Five-days oseltamivir • Ten-days oseltamivir • Lopinavir/ritonavir

Trial Identifier/registry ID(s)/contact	**NCT04381936 / EudraCT2020-001113-21-GB / ISRCTN50189673** **RECOVERY** **Contact: Contact: Richard Haynes; +44 (0)1865 743743; recoverytrial@ndph.ox.ac.uk**	**NCT04498273** **ACTIV4-Outpatient** **Contact: Frank Sciurba, University of Pittsburgh**	**NCT02735707 / EudraCT: 2015-002340-14-IT** **REMAP—COVID** **Contact: Cameron Green; info@remapcap.org**
	• dimethyl fumarate (UK adults only; early phase assessment)		• Hydroxychloroquine • Hydroxychloroquine + lopinavir/ritonavir • Interferon-β1a • Anakinra • Fixed-duration higher dose Hydrocortisone • Tocilizumab • Sarilumab • Vitamin C • Therapeutic anticoagulation • Simvastatin • Biological: Convalescent plasma • Other: Protocolised mechanical ventilation strategy • Eritoran • Apremilast • Clopidogrel, Prasugrel or Ticagrelor
Comparator (standard care or generic drug name and dosage)	Standard care: usual hospital care	• Placebo	• No intervention: patients will not receive any antiplatelet agent or NSAID for 14 days while patient remains in hospital • Active comparator: P2Y12 inhibitor, patients will receive either clopidogrel, prasugrel, or ticagrelor (as per site preference).
Primary Outcome(s)	All-cause mortality [Time Frame: Within 28 days after randomisation]	Composite endpoint of need for hospitalization for cardiovascular/pulmonary events, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, and all-cause mortality for up to 45 days after initiation of assigned treatment.	• All-cause mortality [Time Frame: Day 90] Days alive and not receiving organ support in ICU [Time Frame: Day 21]

Trial Identifier/registry ID(s)/contact	**NCT04381936 / EudraCT2020-001113-21-GB / ISRCTN50189673** **RECOVERY** **Contact: Contact: Richard Haynes; +44 (0)1865 743743; recoverytrial@ndph.ox.ac.uk**	**NCT04498273** **ACTIV4-Outpatient** **Contact: Frank Sciurba, University of Pittsburgh**	**NCT02735707 / EudraCT: 2015-002340-14-IT** **REMAP—COVID** **Contact: Cameron Green; info@remapcap.org**
Sponsor/ lead institution, country (also country of recruitment if different)	University of Oxford, UK Recruitment in Indonesia, Nepal, United Kingdom	University of Pittsburgh, USA	MJM Bonten, , UMC Utrecht, the Netherlands Recruitment in USA, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, the Netherlands; New Zealand, Portugal, Romania, Spain, United Kingdom

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
** Description on dose and route of administration for interventions other than aspirin are found on the trial registration site.
Abbreviations: see list of abbreviation on page 5.

Table 4-7 Ongoing platform RCTs involving Aspirin, continued

Trial Identifier/registry ID(s)/contact	**NCT04483960 / ACTRN12620000445976** **ASCOT-ADAPT** **Contact: Naomi Perry ;+61 3 83442647; naomi.perry@unimelb.edu.au**	**EudraCT: 2020-005963-29-DK** **ASCOT-ADAPT (in Denmark)** **Contact: Charlotte Kastberg Levin; +4530477341; charlotte.kastberg.levin.01@regionh.dk**
Study design, study phase	Phase 3 RCT, multicentre open label adaptive platform trial with factorial assignment Pharmacological and standard of care comparators.	Phase 3 RCT. Current: Randomised single center national multistage adaptive platform Trial with 3 arms. Planned: center involvement of Ausralia, India a d New Zealand
Recruitment status	Recruiting (last update at trial registry on 25 Jan. 2021)	Ongoing (trial registry assessed at 20 April 2021)
Number of Patients, Disease severity*	2'400 Non critical	N=20 in Denmark N=2400 overall Not described, but non-critical
Setting (hospital, ambulatory,..)	Hospital	Acute Care Hospital
Intervention (generic drug name and dosage)**	• Nafamostat Mesilate • Biological: Convalescent plasma • Enoxaparin • Dalteparin • Tinzaparin • Aspirin: In addition to standard dose thromboprophylaxis, patients randomised to this arm will also receive 100mg aspirin daily.	• Standard dose thromboprophylaxis + Aspirin. Standard dose thromboprophylaxis not described but involving Tinzeparin, Enoxaparin, Dalteparin. In the platform trial, the addition of Acetylsalicylic Acid is described as comparator.
Comparator (standard care or generic drug name and dosage)	• Anticoagulation - standard dose thromboprophylaxis: low molecular weight heparin, choice of agent according to availability and local practice at the participating site. • Other pharmacological interventions and standard of care as listed above	• Standard dose thromboprophylaxis • Intermediate dose thromboprophylaxis
Primary Outcome(s)	• Proportion of participants alive and not having required new intensive respiratory support (invasive or non-invasive ventilation) or vasopressors/inotropic support [Time Frame: 28 days]	• The primary endpoint for this trial is death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation.
Sponsor/ lead institution, country (also country of recruitment if different)	University of Melbourne/ The Peter Doherty Institute for Infection and Immunity; Australasian Society for Infectious Diseases	University of Melbourne, Australia, recruitment in Denmark. Planned future recruitment in Australia, India and New Zealand

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
**Description on dose and route of administration for interventions other than aspirin are found on the trial registration site.
Abbreviations: see list of abbreviation on page 5.

Table 4-8 Ongoing trials of single agent: Aspirin

Trial Identifier/registry ID(s)/contact	**CTRI/2020/07/026791[15]** **RESIST** **Deepti Siddharthan; 9968774019; deeptikailath@gmail.com**	**NCT04365309** **PEAC** **Contact: Cai Yue; the first affiliated hospital of the Air force medical university**	**NCT04324463** **ACT COVID-19** **Contact: ACT COVID-19 Study Coordinator; 905-297-3479; ACT.ProjectTeam@PHRI.ca**
Study design, study phase	Phase 2/3 RCT. Single center 4-arm open label trial with parallel group assignment Randomisation: computer-generated permuted block randomization with mixed block size Concealment: Sequentially numbered, sealed, opaque envelopes	Phase 2-3 Randomized controlled trial with parallel group assignment Masking: none	Two parallel randomised controlled trials Outpatient trial: 2x2 factorial design Inpatient trial: up to Nov. 2020 a 2x2x2 factorial design, thereafter 2x2 design Masking: none
Recruitment status	Open to recruitment (last update at trial registry at 11 Oct. 2020)	Enrolling by invitation (last update at trial registry at 28 April 2020)	Recruiting (last update at trial registry at 4 May 2020)
Number of Patients, Disease severity*	N=800 Non-critical	N=128 Moderate to severe COVID-19	N= 4000 overall Outpatient study: symptomatic severity not described, symptomatic with COVID-19 in the community who are at high risk of disease progression Inpatient study: severity not described, symptomatic with COVID-19
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital and Outpatients
Intervention (generic drug name and dosage)	• Aspirin with standard of care: Aspirin tablet 75mg once daily for ten days or till discharge whichever is later. • Atorvastatin (Statin) with standard of care: Atorvastatin 40mg tablet once daily for ten days or till discharge whichever is later • Aspirin + atorvastatin with standard of care	Aspirin administered orally with 100 mg per day on top of standard of care for COVID-19 at admission until 14 days after discharge	Outpatient study: • Trial arm Colchicine: 0.5 or 0.6 mg twice daily for 3 days, then o.5 or 0.6 mg once daily for 25 days (total 28 days). • Trial arm ASA: 75 to 100 mg once daily for 28 days. For inpatients: • Up to Nov. 2020 - trial arm Interferon-β: 0.25 mg by subcutaneous injection on days 1, 3, 5 & 7** • Trial arm Colchicine: 1 or 1.2 mg followed by 0.5 or 0.6 mg 2 hours later, then 0.5 or 0.6 mg twice daily for 28 days.

Trial Identifier/registry ID(s)/contact	**CTRI/2020/07/026791[15]** **RESIST** **Deepti Siddharthan; 9968774019; deeptikailath@gmail.com**	**NCT04365309** **PEAC** **Contact: Cai Yue; the first affiliated hospital of the Air force medical university**	**NCT04324463** **ACT COVID-19** **Contact: ACT COVID-19 Study Coordinator; 905-297-3479; ACT.ProjectTeam@PHRI.ca**
			• Trial am combination of ASA and rivaroxaban: ASA 75 to 100 mg once daily for 28 days; 2.5 mg twice daily for 28 days.
Comparator (standard care or generic drug name and dosage)	Standard of care: conventional therapy for COVID-19 infected patients	Standard of care without aspirin	No Intervention: Usual Care (Control) Outpatients and Inpatients: No constraints for treating physicians on the therapies within the standard of care arm. All key co-interventions will be documented.
Primary Outcome(s)	• Clinical deterioration characterised by progression to WHO clinical improvement ordinal score more than or equal to 6 (i.e., endotracheal intubation, non-invasive mechanical ventilation, pressor agents, RRT, ECMO, and mortality). Time frame: 10 days or until discharge whichever is longer	• clinical recovery time (TTCR) defined as the study treatment (oral aspirin enteric-coated tablet) began to fever, breathing rate, blood oxygen saturation recovery, and cough relieving for at least 72 hours. [Time Frame: not more than 14 days] • the time of SARS-CoV2 overcasting defined as Time of SARS-CoV2 in upper respiratory tract specimens overcasting detected by RT-PCR. [Time Frame: not more than 37 days]	Outpatient trial Colchicine vs. control & ASA vs. control At registration in March 2020 • composite of hospitalization or death. [Time Frame: 45 days post randomization] added in registry during recruitment: • disease progression of 2 points on a 7 point Scale • composite of major adverse cardiovascular events (myocardial infarction [MI], stroke, acute limb ischemia [18], VTE, death) Inpatient trial Interferon-β vs. control & Colchicine vs. control & ASA and rivaroxaban vs. control At registration in March 2020 • composite of invasive mechanical ventilation or death. [Time Frame: 45 days post randomization] Added in registry during recruitment • disease progression of 2 points on a 7 point Scale [Time Frame: 45 days post randomization].

Trial Identifier/registry ID(s)/contact	**CTRI/2020/07/026791[15]** **RESIST** **Deepti Siddharthan; 9968774019; deeptikailath@gmail.com**	**NCT04365309** **PEAC** **Contact: Cai Yue; the first affiliated hospital of the Air force medical university**	**NCT04324463** **ACT COVID-19** **Contact: ACT COVID-19 Study Coordinator; 905-297-3479; ACT.ProjectTeam@PHRI.ca**
			• composite of major adverse cardiovascular events (myocardial infarction [MI], stroke, acute limb ischemia [18], VTE, death) [Time Frame: 45 days post randomization].
Sponsor/ lead institution, country (also country of recruitment if different)	All India Institute of Medical Sciences (AIIMS), New Delhi, India	Xijing Hospital, China	Sponsor: Population Health Research Institute, Canada Collaborator: Bayer Countries of recruitment: Brazil, Canada, Chile, Colombia, Ecuador, Egypt, India, Pakistan, Philippines, Russian Federation, Saudi Arabia, United Arab Emirates

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
**The duration and dose of empiric antibiotics will be determined by the treating clinician and local guidelines or practice. **The Inpatient study previously also included a comparison of Interferon-β with control in a 2x2x2 design. The Interferon-β arm was closed to recruitment in November 2020.
Abbreviations: see list of abbreviation on page 5. REMAP-COVID=sub-platform of REMAP-CAP evaluating treatments specific for COVID-19; REMAP-CAP=Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia

Table 4-9 Ongoing trials of single agent: Aspirin, continued

Trial Identifier/registry ID(s)/contact	**NCT04703608 / PACTR202101544570971 PaTS-COVID Contact: Anna Roca; +220 4495442 Ext. 2305; aroca@mrc.gm**	**NCT04333407 C-19-ACS Contact: Alena Marynina; 07776 224520; alena.marynina@nhs.net**	**CTRI/2020/08/027503 Contact: Souvik Maitra; souvikmaitra@live.com**
Study design, study phase	RCT. Multicenter single blinded trial with parallel group assignment Permuted block randomization; central allocation; masking: participant, blinding with non-identical placebo	Multicenter RCT with parallel group assignment Masking: none	RCT. Two-arm single center pilot trial with parallel group assignment Stratified block randomization Concealment: sequentially numbered, sealed, opaque envelopes Masking: outcome assessor
Recruitment status	Recruiting (last update at trial registry 4 June 2021)	Recruiting (last update at trial registry 9 April 2020)	Not yet recruiting (last update at trial registry 31 Aug. 2020)
Number of Patients, Disease severity*	Unclear, 1'200 for both cohorts defined by mild/moderate versus severe COVID-19** Severe	N= 3170 Not reported	N=60; moderate to severe
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)**	Aspirin: 150 mg daily for 28 days or until hospital discharge (whichever is sooner)	• Aspirin 75mg once daily unless contraindicated • Clopidogrel 75mg, once daily unless contraindicated • Rivaroxaban 2.5 mg twice daily unless contraindicated. If patient on DOAC then change to rivaroxaban 2.5mg unless contraindicated • Atorvastatin 40mg once daily unless contraindicated • Omeprazole, if patient not on a proton pump inhibitor, add omeprazole 20mg once daily	Aspirin: Low dose aspirin (75 mg OD) for 10 days along with standard of care
Comparator (standard care or generic drug name and dosage)	Non identical placebo; doses as per above	• No intervention (supportive care)	Standard of care: standard practice of the institute at that time
Primary Outcome(s)	• Cohort 1 index case: Percentage of patients with COVID-19 associated mild disease/moderate pneumonia progressing to severe pneumonia [Time frame 14 days] • Cohort 1, Household contacts: Percentage of HH members that get	All-cause mortality at 30 days after admission	SpO2/ FiO2 ratio in day 1- 7 post randomization

	infected with SARS-CoV-2 [Time frame 14 days] • Cohort 2: Percentage of COVID-19 associated severe pneumonia patients worsening their condition [Time frame at discharge or day 28]		
Sponsor/ lead institution, country (also country of recruitment if different)	London School of Hygiene and Tropical Medicine, Great Britain; Recruitment in Gambia	Imperial College London, UK	All India Institute of Medical Sciences, New Delhi, India

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
**RCT with two cohorts, descriptions only apply to cohort 2, cohort 1 is described in EUNETHTA RCR 22 on Ivermectin[20].
Abbreviations: see list of abbreviation on page 5.

Table 4-10 Ongoing trials of single agent: Aspirin, continued

Trial Identifier/registry ID(s)/contact	**IRCT20180205038626N7 zahra ahmadnia; gums.icrc@gmail.com**	**PACTR202006473370201 CRASH-19 Ian Roberts; crash19@lshtm.ac.uk**	**NCT04554433 Ragab; +201099323347; Dr.ezz2712@gmail.com**
Study design, study phase	RCT. Single center two-arm trial with parallel group assignment Permutation block randomisation (block size 6); Concealment: sealed envelopes; Masking: outcome assessor	RCT. Multinational open label trial with factorial group assignment Permuted block randomisation Concealment: central randomisation by phone/fax	RCT. Open label trial with parallel group assignment
Recruitment status	Recruitment complete (last update at trial registry 4 April. 2021)	Not yet recruiting (last update at trial registry 17 June 2020)	Not yet recruiting (last update at trial registry 28 October 2020)
Number of Patients, Disease severity*	N=36; non-critical	N=10'000, non-critical	N=80, COVID-19 with mild to severe ARDS
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)**	Aspirin 80 mg for three months.	• Aspirin: 150mg once daily, up to 28 days (n=1250) • Losartan: 100mg once daily, up to 28 days (n=1250) • Simvastatin: 80mg once daily, up to 28 days (n=1250) • Aspirin & Losartan, up to 28 days (n=1250) • Aspirin and Simvastatin, up to 28 days (n=1250) • Losartan and Simvastatin, up to 28 days (n=1250)	combination of Asprin in anti - inflammatory dose and controlled ethanol vapor inhalation in concentrations and technique according to their medical condition

		• Aspirin & Losartan & Simvastatin, up to 28 days (n=1250)	
Comparator (standard care or generic drug name and dosage)	Standard treatment for three months, not further described	• Usual standard of care at the study hospital, up to 28 days (n=1250)	standard protocol
Primary Outcome(s)	Thromboembolic events at the beginning of the study and 3 and 6 months later	In-hospital death up to 28 days	Disinfection of COVID-19 in human respiratory tract. [Time Frame: Negative PCR test within 7 days from starting the protocol]
Sponsor/ lead institution, country (also country of recruitment if different)	Rasht University of Medical Sciences, Rasht, Iran	London School of Hygiene and Tropical Medicine, UK Recruitment in Nigeria and Pakistan	Ragab, Resident of anesthesia and surgical ICU, Mansoura University, Egypt

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviation on page 5.

Table 4-11 Ongoing trials of single agent: Aspirin, continued

Trial Identifier/registry ID(s)/contact	**ClinicalTrials.gov Identifier: NCT04808895 / Eudract ID 2020-006130-12-IT ASPERUM Pietro Minuz;+39 045-8124414; pietro.minuz@univr.it**	**NCT04466670 Contact: Vanderson Rocha; +55-11-26617575; vanderson.rocha@hc.fm.usp.br**	**NCT04937088 (new) OLA COVID Frank Lau; 504-412-1240; flau@lsuhsc.edu**
Study design, study phase	Phase 3 RCT: multicentre national two arm double blind placebo controlled trial with parallel group assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Phase 1 and Phase 2 Adaptive clinical trial. Phase 1 concerns an observational arm. Phase 2 concern RCT with adaptive design and sequential group assignment¨ Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Phase 2 RCT: two arm placebo controlled single center randomised trial with parallel group assignment Masking: patients, outcome assessors, study staff, healthcare providers, the principle investigator and one biostatistician will remain blinded.
Recruitment status	Not yet recruiting (last update at trial registry at 22 March 2021)	Recruiting (last update at trial registry at 9 June 2021)	Not yet recruiting (last update at trial registry at 23 June 2021)
Number of Patients, Disease severity*	N=204 Moderate COVID-19 with pneumonia	N=379 Phase 2: ICU patients with PaO2 to FiO2 ratio < 200	N=200 New (within 24 hours) COVID-19 diagnosis, severity not defined
Setting (hospital, ambulatory,..)	hospital	Hospital (ICU for phase 2)	outpatients
Intervention (generic drug name and dosage)**	Aspirin: tablets of 100 mg acetylsalicylic acid. Loading dose of 300 mg on day 1 followed by 100mg once daily on day 2 to 15	• Trial arm Unfractionated heparin: "unfractionated heparin - 25,000 U/ 5 ml nebulized inhalation every 6 hours up to 14 days.	liquid aspirin 150 mg daily (ASA 150)

		• Trial arm acetylsalicylic acid: Aspirin (ASA) "acetylsalicylic acid (ASA) 100 mg daily PO up to 14 days In all intervention and placebo arms: arterial oxygen saturation greater than or equal to 92% or PaO2 to FiO2 ratio greater than 200 for 2 consecutive days associated to thromboprophylaxis institutional protocol	
Comparator (standard care or generic drug name and dosage)	Placebo: tablets of placebo, identical to active comparator (one tablet daily dose. On the first day 3 tablets will be administered)	Phase 1: Standard of care (observational arm) Phase 2: placebo acetylsalicylic acid	placebo
Primary Outcome(s)	Occurrence of the first of the following events: • Prevention of clinical worsening, defined as transfer to ICU [Time Frame: day 15] • Prevention of lung function worsening, defined as PaO2/FiO2 lower than 150 mm Hg [Time Frame: day 15] • Prevention of death, defined as death of any cause [Time Frame: day 15]	Hospital discharge - alive / death: number of COVID-19 positive patients who are alive within 30 days of symptoms onset	Reduced COVID-19 related hospitalizations [Time Frame: 6 months]
Sponsor/ lead institution, country (also country of recruitment if different)	Azienda Ospedaliera Universitaria Integrata Verona, Italy	University of Sao Paulo General Hospital, Brazil	Louisiana State University Health Sciences Center in New Orleans, USA

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviation on page 5; OLA = Outpatient Liquid Aspirin (OLA).

Table 4-12 Ongoing trials of combination therapies including Aspirin

Trial Identifier/registry ID(s)/contact	**NCT04410328 ATTAC-19 Amit Singla; 3195123558; as3321@njms.rutgers.edu**	**CTRI/2020/09/028088 CAM-Covid-19 Vivek Chauhan; drvivekshimla@yahoo.com**	**NCT04768179 IVCOM Jackson Mukonzo; 256758113468; mukojack@yahoo.co.uk**
Study design, study phase	RCT. Single center open label two arm pilot trial with parallel group assignment	RCT. Single center open label two arm pilot trial with parallel group assignment Computer generated randomization Concealment: central randomisation	RCT. Single center open label three arm pilot trial with parallel group assignment
Recruitment status	Recruiting (last update at trial registry 23 Oct. 2020)	Not yet recruiting (last update at trial registry 25 Sept. 2020)	Not yet recruiting (last update at trial registry 24 Feb. 2021)

Trial Identifier/registry ID(s)/contact	**NCT04410328** **ATTAC-19** **Amit Singla; 3195123558; as3321@njms.rutgers.edu**	**CTRI/2020/09/028088** **CAM-Covid-19** **Vivek Chauhan; drvivekshimla@yahoo.com**	**NCT04768179** **IVCOM** **Jackson Mukonzo; 256758113468; mukojack@yahoo.co.uk**
Number of Patients, Disease severity*	N=132 Not reported	N=34 Severe	N=490 moderate
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Dipyridamole and Aspirin (Aggrenox): • Dipyridamole ER 200mg/ Aspirin 25mg orally/enterally 2 times daily plus standard care starting on the day of enrollment for a total of 2 weeks.	Colchicine, Aspirin and Montelukast: • Colchicine - 0.6 mg per oral, 12 hourly till discharge Aspirin - 325 mg per oral 6 hourly till discharge Montelukast - 10 mg per oral once a day till discharge	low dose aspirin and ivermectin combination therapy • Trial arm: 3-day ivermectin (IVM) 200 mcg/kg/day plus 14-day of 75mg ASA/day + standard of care (intervention 1) • Trial arm: 3-day IVM 600 mcg/kg/day plus 14-day of 75mg ASA/day + standard of care (Intervention 2)
Comparator (standard care or generic drug name and dosage)	Standard of care: standard care starting on the day of enrolment for a total of 2 weeks.	Standard of care	Standard of care
Primary Outcome(s)	Covid Ordinal Scale: Change in composite COVID ordinal scale at day 15. Ordinal scale Ranging from 1) not hospitalized with resumption of normal activities to 8) death. [Time Frame: 15 days]	Change in the marker of Adult Multi-system Inflammatory Syndrome i.e. C-reactive Protein up to 4 months	• SARS COV 2 Viral clearance [Time Frame: Day 14] • World Health Organization COVID-19 ordinal improvement score [Time Frame: Day 14]. Minimum score is 0 (un infected, no clinical or virological evidence of infection) Maximum sore is 8 (death) Higher scores mean a worse outcome, low scores mean a better outcome
Sponsor/ lead institution, country (also country of recruitment if different)	Rutgers, The State University of New Jersey, USA	Indira Gandhi Medical College, Shimla, India	Makerere University, Uganda

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviation on page 5

Table 4-13 Ongoing trials of combination therapies including Aspirin

Trial Identifier/registry ID(s)/contact	**CTRI/2021/04/032648** **NAAC** **Ambudhar sharma: ambudhar1984@gmail.com; tel 09418048268**
Study design, study phase	RCT, single center open label two arm trial with parallel group assignment phase 3
Recruitment status	Recruiting (last update at trial registry 11 May 2021)
Number of Patients, Disease severity*	N=300 - Moderate and severe, requiring hospitalisation
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	triple therapy with nicorandil, aspirin and atorvastatin: • Aspirin 325 mg stat f/b 75 mg od plus • atorvastatin 80 mg stat f/b 40 mg od hs plus • nicorandil 10 mg stat f/b 5 mg bd for 10 days or till hospital discharge whichever is later
Comparator (standard care or generic drug name and dosage)	standard therapy as per guidelines of ministry of health and family welfare new delhi india: HCQS 400 mg bd on day 1 f/b 400 mg od for 4 days i/v methylprednisolone 0.5 -1 mg /kg for 3 days LMWH/UFH prophylactic dose
Primary Outcome(s)	Progression to any of following: In-hospital mortality, moderate and severe ARDS , shock ,Occurrence of thrombotic events(VTE, ACS, ischemic stroke),Cardiac injury (acute heart failure,dysrythmia), Acute kidney injury, Impaired counciousness, Length of hospital stay, Length of mechanical ventilation (invasive plus noninvasive). Timepoint: up to 10 days.
Sponsor/ lead institution, country (also country of recruitment if different)	Dr Ambudhar Sharma, Dr. RPGMCTanda India1

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy has been responsible till May 2021 for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020. The search has been done in medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with COVID-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence. We refer to versions of this report for detailed descriptions of the search strategies performed up to May 2021, including search terms.

From June 2021, literature search strategy and results from COVID-NMA initiative were used, according living review protocol [1, 3]. Randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with COVID-19 were included. Early-phase clinical trials, single-arm trials, non-randomized studies or modelling studies of interventions for COVID-19 were excluded, as well as studies about prognosis, systematic reviews and meta-analyses and diagnostic test accuracy studies. We applied no restriction on language of publication. Details can be found in COVID-NMA Protocol[2].

In addition, AIHTA search the Cochrane COVID-19 register through https://covid-19.cochrane.org/, filtered by Aspirin on a monthly basis.

6.2 Search strategy to identify ongoing studies

AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Aspirin are described in Appendix Table 6-1.

As of June 2021, AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Aspirin are described in Appendix Table 6-1.

Table 6-1 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" [adapt if you used "Advanced search mode"] Terms used at Condition or disease: • covid-19 Terms used at "other terms": • aspirin clinicaltrials.gov automatically searches relevant synonyms of aspirin and COVID-19	13/07/2021	22 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and aspirin 2. covid-19 and Acetylsalicylic Acid 3. covid-19 and ASA 4. SARS-CoV-2 and aspirin 5. SARS-CoV-2 and Acetylsalicylic Acid 6. SARS-CoV-2 and ASA	13/07/2021	6 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and aspirin 2. covid-19 and Acetylsalicylic Acid 3. covid-19 and ASA 4. SARS-CoV-2 and aspirin 5. SARS-CoV-2 and Acetylsalicylic Acid 6. SARS-CoV-2 and ASA	13/07/2021	6 0 new
ICTRP COVID-19 collection accessed through search platform of clincaltrials.gov	https://clinicaltrials.gov/ct2/who_table	Basic search mode Terms used: aspirin acetylsalicylic acid	13/07/2021	30** 2 new
COVID-NMA	https://covid-nma.com/dataviz/	Basic search mode Terms used: aspirin	13/07/2021	18 1 new
Cochrane COVID-19 register	https://covid-19.cochrane.org/	Filtered by aspirin	13.07.2021	26 (7 studies) 2 new citations, 0 new studies
Google Scholar / Google/ PubMed	Google.com Scholar.google.com Pubmed.org	Basic search mode Terms used: trial acronyms and clinical trial registration numbers of included ongoing studies (both randomized and non-randomized studies)	12/02/2021	3

* In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms"; ** some hits previously included in the register at https://clinicaltrials.gov/ct2/who_table are no longer present, the current total is 30.