health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

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

TITLE: ANTIPLATELETS AS TREATMENT FOR COVID-19

DATE: 4 JULY 2022

KEY FINDINGS

- A rapid review of the evidence was conducted to evaluate the effectiveness of antiplatelet agents including aspirin and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) to treat adult patients with COVID-19.
- The Australian Task Force and the World Health Organisation (WHO) databases were searched for COVID-19 guidelines and recommendations on the 3 June 2022. Additionally, the Cochrane Library COVID-19 study register, and the COVID-nma.com living review database were searched for trials on 13 June 2022. We identified three eligible trials: REMAP-CAP 2022, RECOVERY 2021/2022 and ACTIV-4B COVID-19 Outpatient Thrombosis Prevention Trial.
- Overall, among inpatients, antiplatelet therapy may result in little or no difference in mortality [Risk Ratio (RR) 0.97 (95% CI 0.90 to 1.03], progression to mechanical ventilation [RR 0.95 (95% CI 0.87 to 1.05)] or number of thromboembolic events [RR 0.89 (95% CI 0.78 to 1.01)] compared to usual care. There was an increase in major bleeding with use of antiplatelet therapy [RR 2.47 (95% CI 0.93 to 6.60)].
- Overall, among outpatients, antiplatelet therapy may result in little or no difference in mortality [Risk Ratio (RR) 0.33 (95% CI 0.01 to 8.12] or number of thromboembolic events [RR 1.00 (95% CI 0.06 to 15.85)] compared to usual care. There was an increase in major bleeding with use of antiplatelet therapy [RR 2.33 (95% CI 0.61 to 8.87)].
- Adding antiplatelet therapy to the standard of care for hospitalised or ambulatory patients with COVID-19 did not improve clinically important outcomes, and the balance of benefit and harms of its use does not support inclusion in current guidelines.
- hospitalised

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

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

Recommendation & Rationale: Adding antiplatelet therapy to the standard of care for hospitalised or ambulatory patients with COVID-19 did not improve clinically important outcomes and the balance of benefit and harms of its use does not support inclusion in current guidelines. Evidence of harm was particularly noted in the in-patient setting. There is less clear evidence of harm in ambulatory care. Patients who are on regular antiplatelet agents for other indications should continue their use.

Level of Evidence: LoA II

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

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

PROSPERO registration: CRD42021286710

BACKGROUND

Antiplatelet drugs can be classified based on their mechanism of action into i) platelet aggregation inhibitors (aspirin and related cyclooxygenase inhibitors), ii) oral thienopyridines (clopidogrel, ticagrelor, ticlopidine, and prasugrel), iii) glycoprotein platelet inhibitors (abciximab, eptifibatide, tirofiban), iv) protease-activated receptor-1 antagonists (vorapaxar) and v) miscellaneous (dipyridamole - a nucleoside transport inhibitor and phosphodiesterase type 3 (PDE3) inhibitor, cilostazol - a PDE3 inhibitor) (1).

Aspirin is the most commonly used oral antiplatelet agent. It has antiplatelet and anti-inflammatory effects as an inhibitor of COX-1 and decreases thromboxane A_2 synthesis, platelet aggregation, and thrombus formation. Oral thienopyridines such as clopidogrel selectively inhibit adenosine diphosphate-induced (ADP-induced) platelet aggregation. These drugs are converted into the active drug by means of the hepatic CYP450 system that irreversibly inhibits the platelet P2Y12 receptor (1). Aspirin and oral thienopyridines are indicated in patients with arterial ischaemic events including coronary artery disease, cerebrovascular accidents and peripheral arterial disease, thrombotic disorders such as atrial fibrillation and in the primary prevention of venous thromboembolism (VTE) (1).

Platelet activation has been shown to play a role in the pathogenesis of COVID-19 with circulating biomarkers reflecting platelet activity such as soluble CD40 ligand, P-selectin and thromboxane B2 found to be independently associated with risk of severe disease, thrombosis, and death (2). Thus, activated platelets may represent a therapeutic target for improved clinical outcomes in patients with COVID-19 (3).

Observational studies have shown that hospitalised patients who received aspirin had lower risk-adjusted mortality (4-6). However, in a large randomised controlled trial (RCT) of 14,892 patients hospitalised with COVID-19 and allocated to either aspirin (n=7,351) or usual care alone (n=7,541); aspirin use was not associated with reductions in 28-day mortality (rate ratio 0.96, 95% CI 0.89–1.04; p=0.35), or in the risk of progressing to invasive mechanical ventilation or death. In this study, patients allocated to aspirin had a slightly shorter duration of hospitalisation (median 8 days, IQR 5 to >28, *vs* 9 days, IQR 5 to >28) and aspirin use was associated with a small increase in the rate of being discharged alive within 28 days 75% *vs* 74%; rate ratio 1.06, 95% CI 1.02–1.10; p=0.0062 (7).

The Australian National COVID-19 Clinical Evidence Task Force strongly recommends against the use of aspirin for the treatment of COVID-19 (with moderate certainty) (8), while the World Health Organization (WHO) guidelines (last updated 31 May 2022) report a strong expert opinion for the use of antiplatelet therapy in hospitalised patients with COVID-19 for their underlying medical conditions to continue use unless contraindications are present (9).

This review aimed to assess the effect of antiplatelets agents (aspirin and P2Y12 inhibitors such as clopidogrel, prasugrel, or ticagrelor) in patients with COVID-19 infection on mortality, duration of hospitalisation, progression to ICU admission, duration of ICU stay, progression to mechanical ventilation, duration of mechanical ventilation, number of thromboembolic events, bleeding events, adverse events, and adverse reactions.

RESEARCH QUESTION: what is the efficacy and safety of anti-platelets agents for managing those with COVID-19?

METHODS

The Australian Task Force and the World Health Organization (WHO) databases were searched for COVID-19 guidelines and recommendations on 3 and 7 June 2022. Additionally, the Cochrane Library COVID-19 study register, and the COVID-nma.com living review database were searched for trials on 3 and 13 June 2022, respectively. These databases systematically search PubMed, Embase, MedRxiv, WHO's ICTRP and clinicaltrials.gov. The search terms used can be found in Appendix 1 (currently only clopidogrel and ticagrelor are SAHPRA-registered). Screening of records, and selection of articles was done independently and in duplicate by two reviewers (NB and SE) with conflict resolution by a third reviewer (TK). Data extraction was done by one reviewer (SE) and checked by a second reviewer (NB). The main characteristics of the included study and study outcomes are shown in Table 1. Characteristics of excluded studies are described in Table 2. Table 3 presents the results of the search for planned/ongoing trials on the COVID-nma website.

Review Manager (Revman) 5 software was used to perform the analyses. Risk of bias (ROB) for the included trials was obtained from the COVID-nma website (www.covid-nma.com website), where available, and performed using the ROB 2.0 tool, as needed. We reported risk ratios for dichotomous data with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness (10). Table 4 is a GRADE evidence profile for the comparison of antiplatelets (aspirin and P2Y12 inhibitors) compared to usual care/placebo. Table 5 is a GRADE summary of findings table for this comparison. We carried out subgroup analyses to compare aspirin and placebo and P2Y12 inhibitors and placebo as well as the overall effect of antiplatelet therapy on outcomes. Unit of analysis consideration: where there was a shared control group, for example in the Bradbury *et al.* trial, this group was divided in half between the comparisons i.e., aspirin *vs*. placebo and P2Y12 inhibitor *vs*. placebo (both the number of events and total number of patients) in order to avoid 'double-counting' participants in the shared control group (11).

ELIGIBILITY CRITERIA FOR REVIEW

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

Intervention: Antiplatelet agents/therapy including aspirin and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) with no restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Placebo or standard of care.

Outcomes: Mortality; duration of hospitalisation; progression to ICU admission; duration of ICU stay; progression to mechanical ventilation; duration of mechanical ventilation; number of thromboembolic events; bleeding events; adverse events, and adverse reactions.

Study designs: Systematic review of randomized controlled trials, and randomized controlled trials.

RESULTS

RESULTS OF SEARCH

Four trials were identified from the COVID-nma.com living review database. Three trials were eligible for inclusion in the review, Bradbury *et al.* (12), Horby *et al* .(7) and Connors *et al.* (13). We excluded one study, the Berger *et al* 2022. The Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 Acute (ACTIV-4a) trial was an international, adaptive, randomised clinical trial (14). This study was ineligible as the standard of care included a therapeutic dose of heparin compared to therapeutic dose of heparin plus P2Y12 inhibitor thus not matching our standard of care and potentially confounding the outcomes of the review (see Characteristics of excluded studies Table 2). There are 23 planned/ongoing trials that will be monitored for publication (Table 3).

DESCRIPTION OF STUDIES

The three included trials are described in detail in the characteristics of included studies Table 1. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia)/Bradbury *et al.* trial was an adaptive, open-label, platform trial (11). Patients were enrolled from 105 sites in eight countries (Canada, France, Germany, India, Italy, Nepal, the Netherlands, and the United Kingdom). Patients admitted to the hospital, who were 18 years or older, with clinically suspected or microbiologically confirmed COVID-19 were eligible for enrolment. Patients admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support were classified as critically ill and all others as non–critically ill. "Respiratory organ support was defined as invasive or non-invasive mechanical ventilation including via high-flow nasal cannula if the flow rate was at least 30 L/min and the fraction of inspired oxygen was at least 0.4. Cardiovascular organ support was defined as receipt of vasopressors or inotropes". Exclusion criteria: "presumption that death was imminent with lack of commitment to full support, clinical or laboratory-based bleeding risk sufficient to contraindicate antiplatelet therapy, creatinine clearance less than 30 mL/min or receipt of kidney replacement therapy, enrolment in an external trial of anticoagulation or antiplatelet therapy, or enrolment in the anticoagulation domain of the trial platform for participants older than 75 years. Patients were also excluded if they were already receiving antiplatelet therapy or nonsteroidal anti-inflammatory drugs (NSAIDs), if a clinical decision had been made to commence antiplatelet or NSAID therapy, or if a treating clinician believed that participation would not be in the best interests of a patient". Critically ill patients had to be enrolled within 48 hours of admission to an ICU. Patients were randomized to receive either open-label aspirin orally (n = 655), a P2Y12 inhibitor orally (n = 522), or no antiplatelet therapy (control; n = 638). Interventions were continued in the hospital for a maximum of 14 days and were in addition to anticoagulation thromboprophylaxis. Gastric acid suppression was recommended for patients receiving antiplatelet therapy through co-administration of either proton pump inhibitor or H2 receptor antagonist. Other co-interventions patients received were steroids, remdesivir, tocilizumab and sarilumab.

The RECOVERY/Horby *et al.* trial (7) investigated the effectiveness of aspirin compared to standard of care in 1:1 ratio. The trial enrolled 14,892 participants from the United Kingdom, Indonesia and Nepal into a randomised, unblinded trial. Patients admitted to hospital with suspected or confirmed SARS-CoV-2 infection were eligible for inclusion in the trial. The exclusion criteria included children under 18 years, patients with hypersensitivity to aspirin, a recent history of major bleeding, receiving aspirin or anti-platelets treatment. The disease severity ranged with most having mild to moderate disease as follows: None or simple oxygen: n=9,972, non-invasive ventilation: n=4,190 and invasive mechanical ventilation: n=730. Aspirin was administered at 150mg orally, by nasogastric tube or rectally daily until discharge and to 1,222 (17%) of patients for 28 days. Standard of care, defined as receiving usual care in participating hospital, was received by 1,299 (17%) of patients in the control arm. Additionally, patients could receive other co-interventions related to their treating site protocols, such as lopinavir-ritonavir, dexamethasone, hydroxychloroquine, azithromycin or other macrolide, tocilizumab, remdesivir, convalescent plasma, casirivimab/imdevimab (REGN-COV2), colchicine or baricitinib. An intention-to-treat analysis was conducted of patients randomised to aspirin and usual standard of care but for whom aspirin was both available and suitable as a treatment.

ACTIV-4B COVID-19 Outpatient Thrombosis Prevention Trial/Connors *et al.* was an adaptive, randomized, double-blind, placebo-controlled trial of antiplatelet and anticoagulant agents with blinded adjudication of outcomes (13). Patients were enrolled from 52 centres in the United States (US). Ambulatory patients between the ages of 40 and 80 years with newly diagnosed symptomatic SARS-CoV-2 infection with positive polymerase chain reaction or antigen test results were eligible. Creatinine clearance was required to be greater than 30mL/min/1.73m^2 and platelet count greater than 100,000/mm^3. Exclusion criteria: patients who had been previously hospitalised for COVID-19, had acute leukaemia, recent major bleeding, a contraindication to or other indication for anticoagulation, need for single or dual antiplatelet therapy, or who were pregnant or lactating. 657 symptomatic but clinically stable outpatients with COVID-19 were randomized centrally in a 1:1:1:1 ratio (164 were randomized to receive aspirin 81mg once daily orally, 165 were randomized to receive apixaban 2.5mg twice daily orally, 164 were randomized to receive apixaban 5mg twice daily orally and 164 were randomized to receive placebo) for 45 days, with a 30-day safety follow-up evaluation. The trial was terminated early due to lower than anticipated event rates; thus, despite the adaptive clinical trial design, no additional agents underwent evaluation.

APPRAISAL OF THE TRIALS

Overall, the Horby *et al.* trial was judged to have low risk of bias. A web-based simple randomization with concealed allocation sequenced was used. There was deviation from intervention due to the administration of co-interventions. This deviation was small, and the distribution of co-intervention was similar between intervention arms, thus warranting a low risk of bias for day 28 mortality. There was a low risk of bias for missing outcomes as data available to analyse was of >99% of the enrolled participants, despite having 23 (aspirin) and 19 (standard of care) withdrawing consent. The risk of bias for measurement of outcomes was low for day 28 mortality. The risk of bias was low in the selection of reported results since the outcomes and analyses plan were pre-specified in a published protocol.

Similarly, the Connors *et al.* trial was also judged to have an overall risk of bias with some concerns. Some concerns were raised in how the trial deviated from intervention and missing outcome data. Specifically, the authors deviated from the intended intervention by failing to report on the method of analysis for the time-to-death outcome. Additionally, missing outcome data brought about some concerns due to the unavailability of data for all or nearly all randomized participants (657 participants randomized; 558 participants analyzed (Mortality D60 or more). 657 participants analyzed (mortality D28, hospitalisation or death, adverse events. serious adverse events).

Lastly, the Bradbury *et al.* trial had an overall risk of bias assessed as 'some concerns', based on missing outcome data and lack of blinding of outcome assessors and study participants. Mortality, bleeding events, and thrombotic events outcomes had missing data and therefore were not analyzed using the ITT method. The risk of bias was low for randomisation, measurement of outcomes, and selection of reported data. Randomisation was conducted using a centralized computer program where allocation concealment was maintained; mortality was not subjected to ascertainment bias, and bleeding and thrombotic events were centrally adjudicated in a blinded manner.

EFFECTS OF INTERVENTION

The GRADE Evidence Profile Table 4 and Summary of findings in Table 5 summarise the effects of the intervention for each of the following outcomes. The study outcomes are described in detail in Table 1.

COMPARISON 1: ANTIPLATELET THERAPY VERSUS NO ANTIPLATELET THERAPY IN INPATIENTS

Two studies; by Bradbury *et al.* (12) and Horby *et al.* (7) evaluated the effect of antiplatelet therapy (aspirin and/or P2Y12 inhibitors) in inpatients.

1. Mortality

Overall, antiplatelet agents compared to placebo may result in little or no difference in mortality, Risk Ratio (RR) 0.97 (95% CI 0.90 to 1.03), n = 16,707, high certainty evidence. Figure 1 shows the Forest plot for this comparison.

Aspirin: Both studies reported on the effect of aspirin on mortality, Bradbury *et al.** on in-hospital mortality and Horby *et al.* on mortality at day 28. Overall, aspirin compared to placebo may result in little or no difference in mortality, Risk Ratio (RR) 0.97 (95% CI 0.90 to 1.04), n = 15,866, high certainty evidence.

P2Y12 inhibitors: Bradbury *et al.* reported on the effect of P2Y12 inhibitors on mortality; P2Y12 inhibitors compared to placebo may result in little or no difference in mortality, Risk Ratio (RR) 0.94 (95% CI 0.74 to 1.19), n = 841, moderate certainty evidence.

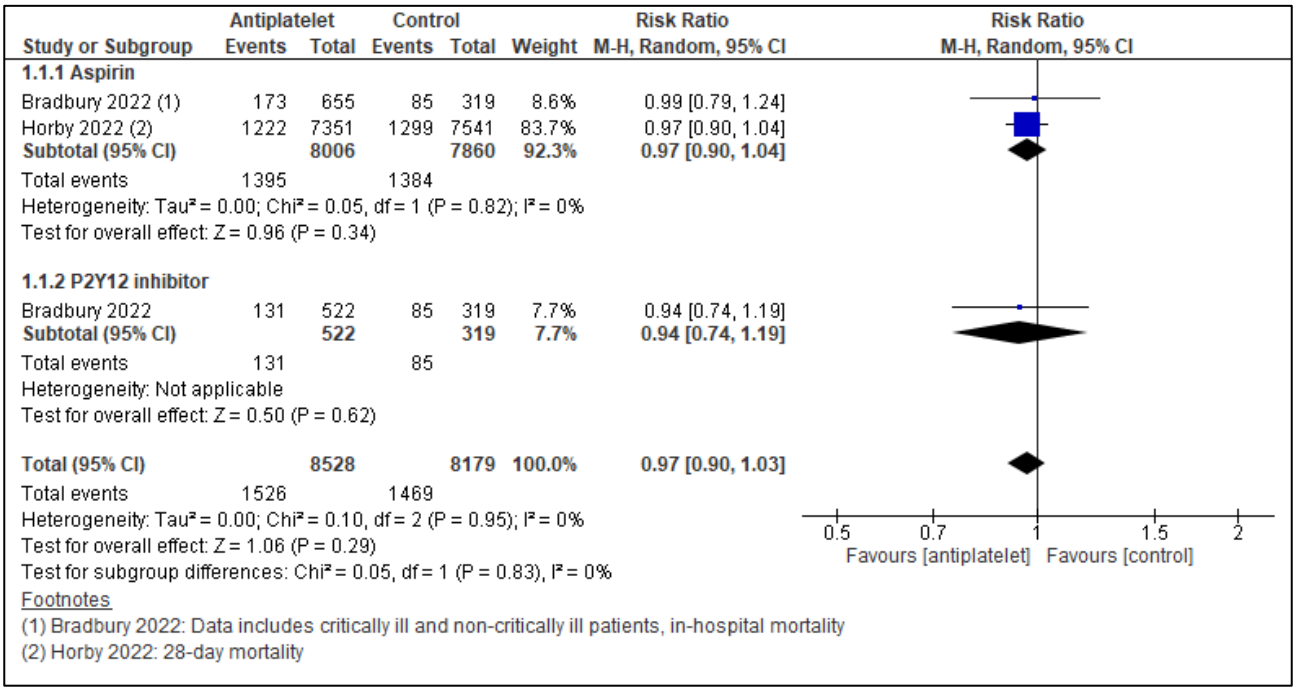

Figure 1: Forest plot of Comparison 1 Antiplatelet Therapy Versus No Antiplatelet Therapy in Inpatients, Mortality

2. Duration of hospitalisation

Bradbury *et al*. report this as a time-to-event endpoint of leaving the hospital alive analysed as dichotomous data with adjusted odds ratios (OR) provided for this outcome. Comparisons of pooled antiplatelet therapy *vs*. placebo are reported among non-critically ill (median OR 0.93 and 95% Credible Interval [CrI] 0.70, 1.24) and critically ill patients (median OR 1.05 and 95% CrI 0.92, 1.20). This outcome was not reported in the Horby study. This outcome is thus not reported in the review.

3. Progression to ICU admission

This outcome was not reported in either the Bradbury *et al.* or Horby *et al.* studies.

4. Duration of ICU stay

Bradbury *et al.* report this as a time-to-event endpoint of leaving the ICU alive analysed as dichotomous data with adjusted odds ratios (OR) provided for this outcome. Comparisons of pooled antiplatelet therapy *vs*. placebo are reported among critically ill patients (median OR 1.05 and 95% CrI 0.92, 1.20). This outcome was not reported in the Horby *et al.* study. This outcome is thus not reported in the review.

5. Progression to mechanical ventilation

Data from the Horby *et al.* study was used to report this outcome in the review. 11% (772/6,993) of patients in the aspirin group progressed to requiring mechanical ventilation *vs*. 12% (829/7,169) in the usual care group. Aspirin compared to standard of care does not decrease progression to mechanical ventilation. RR 0.95 (95% CI 0.87 to 1.05), n =14162, high certainty evidence. Analyses exclude those on invasive mechanical ventilation at randomisation.

In the Bradbury *et al.* study, for their outcome of progression to intubation and extracorporeal membrane oxygenation (ECMO), comparisons of pooled antiplatelet therapy *vs*. placebo are reported for critically ill patients. 36.2% (230/636) patients in the pooled antiplatelet group progressed to requiring intubation/ventilation and 0.6% (4/636) to ECMO *vs*. 40.8% (133/326) intubated and 0.3% (1/326) requiring ECMO in the placebo group.

6. Duration of mechanical ventilation

This outcome was not reported in either the Bradbury *et al.* or Horby *et al.* studies.

7. Number of thromboembolic events (Venous thromboembolism: deep vein thrombosis [DVT], pulmonary embolism [PE], and other venous thromboembolism, arterial thrombosis: cerebrovascular event, myocardial infarction, and other arterial thrombotic event). Thrombotic outcomes and major bleeding events below were centrally adjudicated in a blinded manner.

   Overall, antiplatelet therapy compared to placebo may result in little or no difference the number of thromboembolic events, Risk Ratio (RR) 0.89 (95% CI 0.78 to 1.01), n = 16,707, moderate certainty evidence. Figure 2 shows the Forest plot for this comparison.

   Aspirin: Both studies reported on the effect of aspirin on the number of thromboembolic events. Aspirin compared to placebo may result in little or no difference in the number of thromboembolic events, Risk Ratio (RR) 0.89 (95% CI 0.78 to 1.02), n = 15,866, moderate certainty evidence.

   P2Y12 inhibitors: Bradbury *et al.* reported on the effect of P2Y12 inhibitors on thromboembolic events; P2Y12 inhibitors compared to placebo may result in little or no difference the number of thromboembolic events, Risk Ratio (RR) 0.84 (95% CI 0.56 to 1.28), n = 841, low certainty evidence.

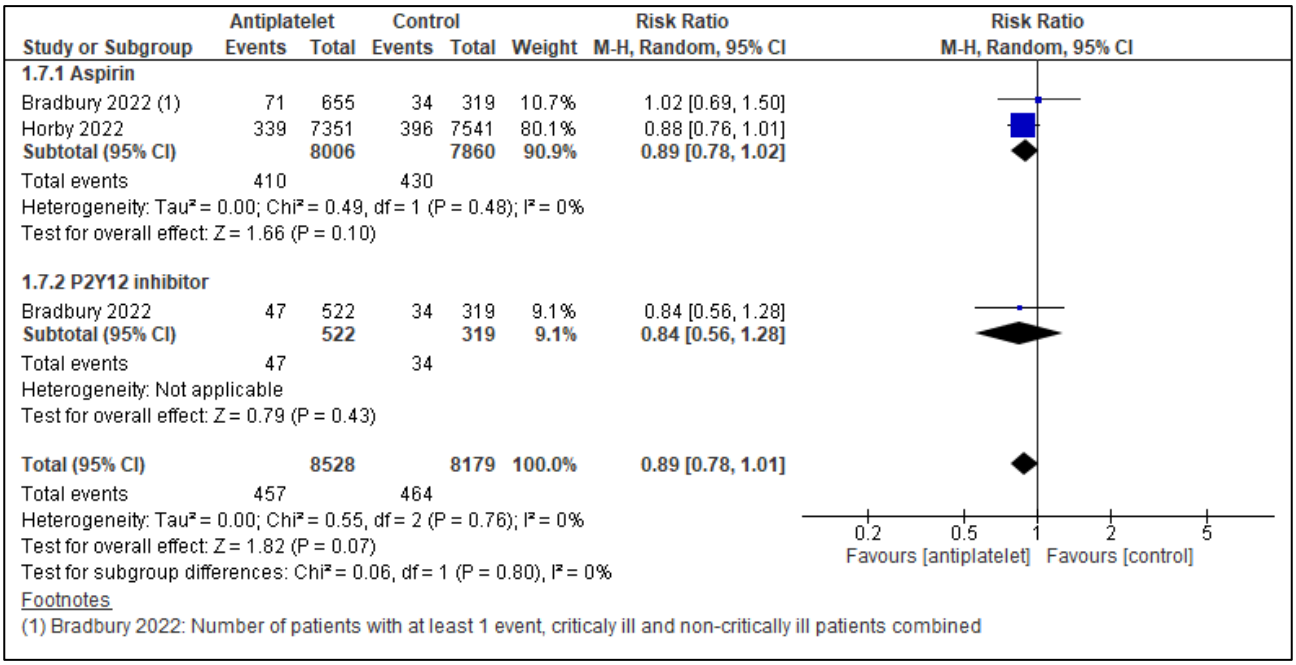

Figure 2: Forest plot of Comparison 1 Antiplatelet Therapy Versus No Antiplatelet Therapy in Inpatients, Number of thromboembolic events

8. Major bleeding events: Major bleeding (according to International Society of Hemostasis and Thrombosis definition) is defined as fatal bleeding, symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a decrease in haemoglobin of 2 g/dL or greater or leading to transfusion of 2 or more whole blood or red blood cell units.

   Overall, antiplatelet therapy compared to placebo may result in an increase in the number of major bleeding events, Risk Ratio (RR) 2.47 (95% CI 0.93 to 6.60), n = 16,707, moderate certainty evidence. Figure 3 shows the forest plot for this comparison.

   Aspirin: Both studies reported on the effect of aspirin on major bleeding events. Aspirin compared to placebo may result in an increase in the number of bleeding events, Risk Ratio (RR) 2.03 (95% CI 0.71 to 5.83), n = 15,866, moderate certainty evidence.

P2Y12 inhibitors: Bradbury *et al.* reported on the effect of P2Y12 inhibitors on major bleeding events; P2Y12 inhibitors compared to placebo may result in an increase in the number of bleeding events, Risk Ratio (RR) 6.11 (95% CI 0.79 to 47.51), n = 841, moderate certainty evidence.

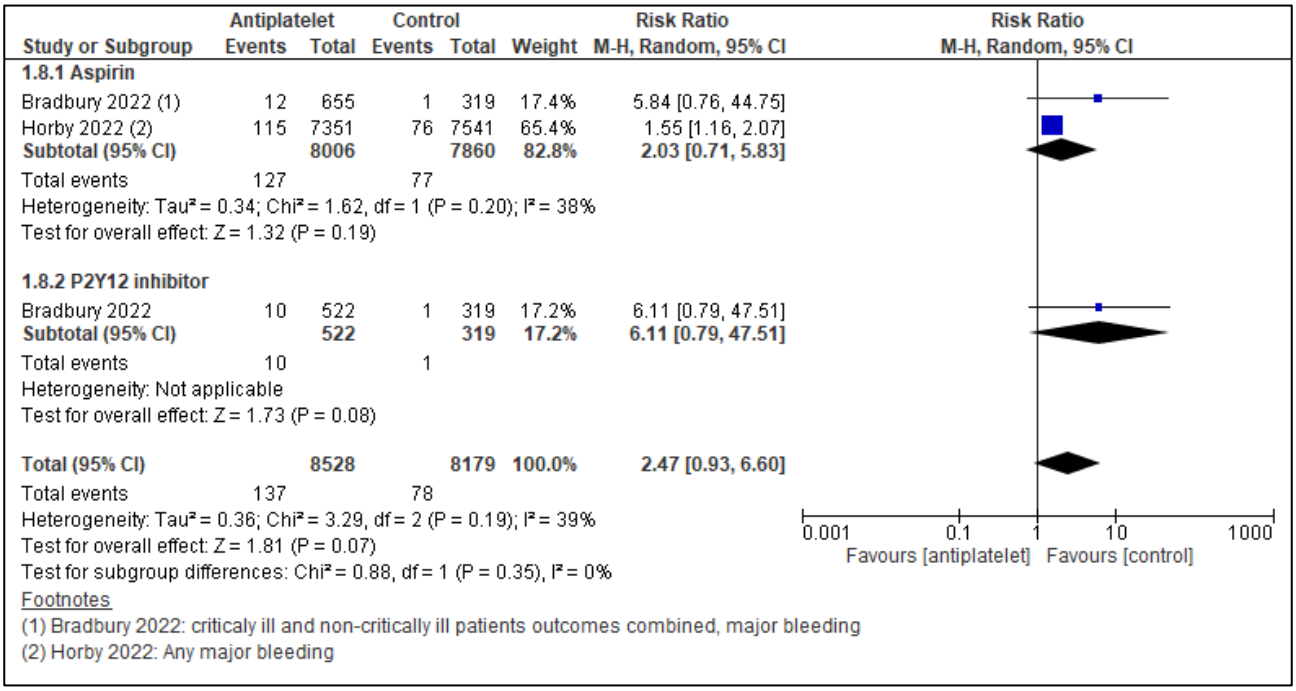

Figure 3: Forest plot of Comparison 1 Antiplatelet Therapy Versus No Antiplatelet Therapy in Inpatients, Number of bleeding events

9. Adverse events (Serious adverse events [SAE]: In accordance with accepted standards a SAE is defined as an event that is fatal, life-threatening, results in/may result in disability that is long-lasting and significant, or results in a birth defect or congenital anomaly)

   Overall, antiplatelet therapy compared to placebo may result in an increase in SAEs, low certainty evidence.

   Bradbury *et al*.: Serious adverse events were reported in five of 565 (0.9%), four of 455 (0.9%), and three of 529 (0.6%) participants in the aspirin, P2Y12 inhibitor, and control groups, respectively (critically ill patients).

   Horby *et al*.: There were 18 events of SAEs of bleeding related to aspirin, 13 non-fatal and five fatal.

10. Adverse reactions

    This outcome was not reported in the Bradbury *et al.* study. Data from the Horby *et al.* study was used to report this outcome in the review. 3.1% (231/7,351) of patients in the aspirin group had major cardiac arrythmia *vs*. 3.5% (267/7,541) in the usual care group. Aspirin compared to standard of care did not increase major cardiac arrhythmia. RR 0.89 (95% CI 0.75 to 1.06), n = 14,892, high certainty evidence.

COMPARISON 2: ANTIPLATELET THERAPY VERSUS NO ANTIPLATELET THERAPY IN OUTPATIENTS

One study by Connors *et al.* (13) evaluated the effect of antiplatelet therapy (aspirin) in outpatients.

1. Mortality**

   There was one death (0.61%) in the control group (n = 164) and none in the aspirin group (n = 164). Aspirin compared to placebo may result in little or no difference in mortality (day 45), Risk Ratio (RR) 0.33 (95% CI 0.01 to 8.12), n = 328, low certainty evidence.

2. Duration of hospitalisation

   This outcome was not reported in the study.

3. Progression to ICU admission

   This outcome was not reported in the study.

4. Duration of ICU stay

   This outcome was not reported in the study.

5. Progression to mechanical ventilation

   This outcome was not reported in the study.

6. Duration of mechanical ventilation

   This outcome was not reported in the study.

7. Number of thromboembolic events

   There was one (0.61%) thromboembolic event of either a deep vein thrombosis (DVT) or pulmonary embolism (PE) in in the control group (n = 164) and one (0.61%) in the aspirin group (n = 164). Aspirin compared to placebo may result in little or no difference in thromboembolic events (day 45), Risk Ratio (RR) 1.00 (95% CI 0.06 to 15.85), n = 328, low certainty evidence.

8. Bleeding events**

   Principal safety outcomes were major bleeding and clinically relevant non-major bleeding (CRNMB) as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria: Non-major clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study intervention, or associated with discomfort for the participant such as pain or impairment of activities of daily life. Suspected major and clinically relevant non-major bleeding events were reported by the trial medical monitor, and minor bleeding events were identified through follow-up with the research pharmacists. All suspected major and clinically relevant non-major bleeding events were adjudicated by the Clinical Events Committee; minor bleeding events were not adjudicated.

   Regarding any bleeding event (suspected haemorrhagic events), there were seven (4.3%) reported in the aspirin group (four CRNMB and three minor bleeding events) (n = 164) and three (1.8%) in the placebo group (minor bleeding events) (n = 164). Aspirin compared to no placebo may result in an increase in bleeding events (day 45), Risk Ratio (RR) 2.33 (95% CI 0.61 to 8.87), n = 328, low certainty evidence.

Adjudicated outcomes: Aspirin may result in little to no difference in major bleeding; there were no major or non-major clinically relevant bleeding events in either arm, n = 328, low certainty evidence.

9. Adverse events

   This outcome was not reported in the study.

10. Adverse reactions

    This outcome was not reported in the study.

*Data from critically ill and non-critically ill patients combined
**Data taken from eTable 2 in supplementary material

CONCLUSION

Antiplatelet therapy in addition to current standard of care for those with COVID-19 did not improve clinically important outcomes and the balance of benefit and harms of its use does not support inclusion in current guidelines, for either hospitalised or ambulatory patients.

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

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TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS ASSESSMENT
REMAP-CAP Writing Committee for the REMAP-CAP Investigators. Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2022; 327(13):1247–1259. doi:10.1001/jama.2022.2910 (Bradbury *et al.*)	Design Ongoing, adaptive, open-label, platform trial REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Patients were enrolled from 105 sites in 8 countries (Canada, France, Germany, India, Italy, Nepal, the Netherlands, and the United Kingdom). Follow-up duration (days) 90 Funding "This study was funded by the following: the Platform for European Preparedness Against (Re-)Emerging Epidemics (PREPARE) consortium of the European Union, FP7-HEALTH-2013-INNOVATION-1 (grant 602525), the Rapid European COVID-19 Emergency Research Response (RECOVER) consortium of the European Union's Horizon 2020 Research and Innovation Programme (grant 101003589), the Australian National Health and Medical Research Council (grant APP1101719), the Health Research Council of New Zealand (grant 16/631), the Canadian Institute of Health Research Strategy for Patient-Oriented	Sample size N=1,549 critically ill patients. Patients were randomized to receive either open-label aspirin (n = 565), a P2Y12 inhibitor (n = 455), or no antiplatelet therapy (control; n = 529). N=266 non-critically ill patients. 90 were randomized to receive aspirin, 67 to P2Y12 inhibitor and 109 to no antiplatelet therapy (control). Inclusion criteria • Patients admitted to the hospital, aged 18 years or older, with clinically suspected or microbiologically confirmed COVID-19 were eligible for enrollment • Patients admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support were classified as critically ill and all others as non–critically ill	Intervention Aspirin or P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor according to availability and local preference). "All antiplatelet interventions were administered enterally until study day 14 or hospital discharge, whichever occurred first. After 14 days, decisions regarding antiplatelet therapy were at the discretion of treating clinicians. Antiplatelet dosing was as follows: aspirin, 75 to 100mg once daily; clopidogrel, 75mg once daily without a loading dose; ticagrelor, 60mg twice daily with-out a loading dose; prasugrel, a 60-mg loading dose followed by 10mg daily (if aged <75 years and weight ≥60 kg) or 5mg daily (if aged ≥75 years or weight <60 kg). Gastric acid suppression was recommended for patients receiving antiplatelet therapy through co-administration of either proton pump inhibitor or H2 receptor antagonist. Antiplatelet therapy could be discontinued if there was	Primary outcome(s) The primary outcome was respiratory and cardiovascular organ support–free days to day 21 Secondary outcomes • Survival to day 90 • Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death among those not receiving that support at baseline • Vasopressor-/inotrope-free days, respiratory support–free days • Duration of ICU stay • Duration of hospital stay • Serious adverse events (SAE): In accordance with accepted standards a SAE is defined as an event that is fatal, life-threatening, results in (or may result) in disability that is long-lasting and significant, or results in a birth defect or congenital anomaly • World Health Organization ordinal score for clinical improvement (ranging from 0 [no evidence of infection] to 8 [death]) • Major bleeding up to day 14 defined according to International Society of Hemostasis and Thrombosis criteria including fatal and intracranial bleeding: Fatal bleeding, symptomatic or clinically manifest bleeding in a critical are or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a fall in hemoglobin of ≥2g/dL, or leading to the transfusion of 2 or more whole blood or red cell units	Overall risk of bias Some Concerns Based on missing outcome data and lack of blinding of outcome assessors and study participants

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	Research Innovative Clinical Trials Program (grant 158584), the NIHR and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (grant CTN 2014-012), the University of Pittsburgh Medical Center (UPMC) Learning While Doing Program, the Translational Breast Cancer Research Consortium, the French Ministry of Health (grant PHRC-20-0147), the Minderoo Foundation, and the Wellcome Trust Innovations Project (grant 215522). Dr Shankar-Hari is funded by an NIHR clinician scientist fellowship (grant CS-2016-16-011) and Dr Gordon is funded by an NIHR research professorship (grant RP-2015-06-18). The study funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The platform trial has 4 regional nonprofit sponsors: Monash University, Melbourne, Victoria, Australia (Australasian sponsor); Utrecht Medical Center, Utrecht, the Netherlands (European sponsor); St Michael's Hospital, Toronto, Ontario, Canada (Canadian sponsor); and the Global Coalition for Adaptive Research, San Francisco, California (US	• Admitted to an ICU with the following features suggestive of COVID-19-related pneumonia within 48 hours of hospital admission: ○ Symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND ○ Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate) • Respiratory organ support was defined as invasive or noninvasive mechanical ventilation including via high-flow nasal cannula if the flow rate was at least 30 L/min and the fraction of inspired oxygen was at least 0.4. Cardio-vascular	an adverse event or commenced in the control group if clinically warranted for a standard indication other than COVID-19. Patients received concurrent anticoagulation thromboprophylaxis according to standard care if not randomised in the anticoagulation domain of the trial". <u>Control</u> No antiplatelet therapy	• Venous thromboembolism (deep vein thrombosis, pulmonary embolism, and other venous thromboembolism), arterial thrombosis (cerebrovascular event, myocardial infarction, and other arterial thrombotic event), as well as a composite of thrombosis or death * Thrombotic outcomes and major bleeding events were centrally adjudicated in a blinded manner. *Results* <u>Critically ill patients (N=1,549)</u> • Baseline characteristics were comparable between the intervention groups. Median age was 57 years in all groups, interquartile range (IQR): 48-64 years in aspirin group, 49-65 years in P2Y12 inhibitors group and 48-63 years in the control group. There were 521 women (34%) and 1,028 men (66%) • Co-morbidities: Diabetes, respiratory disease, kidney disease, severe cardiovascular disease and any immunosuppressive condition • The median duration of antiplatelet therapy for critically ill patients randomized to receive aspirin was 12 (IQR, 7-14) days (data available for 560/565), and for those receiving a P2Y12 inhibitor the median duration was 11 (IQR, 6-14) days (data available for 433/455) • Among 455 participants allocated to receive a P2Y12 inhibitor, 403 (88.5%) received clopidogrel, 6 (1.3%) received ticagrelor, 6 (1.3%) received prasugrel, and in 40 (8.8%) the P2Y12 inhibitor administered was unknown (for these remaining patients, site choice was clopidogrel for 13, ticagrelor for 17, prasugrel for 4, and unknown for 6) • All patients with data available (n = 1419) received concurrent thromboprophylaxis according to usual care at the site or were concomitantly enrolled in the platform	

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	sponsor). Several authors are employees of these organizations. However, beyond the declared author contributions, the sponsors had no additional role". Declarations Listed in the paper Informed Consent "The trial was approved by relevant regional ethics committees and conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written or oral informed consent, in accordance with regional legislation, was obtained from all patients or their surrogates".	organ support was defined as receipt of vasopressors or inotropes Exclusion criteria • Presumption that death was imminent with lack of commitment to full support • Clinical or laboratory-based bleeding risk sufficient to contraindicate antiplatelet therapy • Creatinine clearance less than 30 mL/min or receipt of kidney replacement therapy • Enrollment in an external trial of anticoagulation or antiplatelet therapy, or enrollment in the anticoagulation domain of the trial platform for participants older than 75 years • Patients were also excluded if they were already receiving antiplatelet therapy or nonsteroidal anti-inflammatory drugs (NSAIDs), if a clinical decision had been made to commence		anticoagulation study. The most frequent concurrent anticoagulant at baseline was low-molecular weight heparin (97.7%), and the most frequent dose was an intermediate dose (59%) (see eTable 1 in Supplement 2 for anticoagulation dose classification). • *Primary outcome*: Among critically ill participants, the median number of organ support-free days was 7 (IQR, –1 to 16) in both the pooled antiplatelet (aspirin: 8 days, P2Y12: 7 days) and control groups. Number of patients with known outcome: aspirin (563/565), P2Y12 (448/455) and control (521/529). The median adjusted odds ratio (OR) for the effect of antiplatelet therapy compared with control was 1.02 (95% Credible interval [CrI], 0.86-1.23), aspirin: OR 1.05 (95% CrI 0.85-1.30), P2Y12: OR 1.00 (95% CrI 0.80-1.27) • *Secondary outcomes*: ○ The proportions of patients surviving to hospital discharge were 71.5% (723/1011) and 67.9% (354/521) in the antiplatelet and control groups, respectively, yielding a median adjusted odds ratio for hospital survival of 1.27 (95% CrI, 0.99-1.62) for antiplatelet therapy compared with control, aspirin (402/563): OR 1.30 (95% CrI 0.97, 1.72), P2Y12 (321/448): OR 1.18 (95% CrI 0.86, 1.62). OR >1 indicates a benefit of treatment ○ Mortality: the effect of antiplatelet therapy on survival over 90 days is shown in Figure 3, with a median adjusted hazard ratio (HR) of 1.22 (95% CrI, 1.06-1.40) of improved survival of the pooled antiplatelet group compared with control, aspirin: HR 1.19 (95% CrI 1.00, 1.42), P2Y12: HR 1.23 (95% CrI 1.02, 1.49). Five patients were censored	

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		antiplatelet or NSAID therapy • Or if a treating clinician believed that participation in the domain would not be in the best interests of a patient		before 90 days (1 in the control group, 1 in the aspirin group, and 3 in the P2Y12 inhibitor group). The estimated mortality rate at 90 days for the control group was 32.7% (95% CI, 28.5%-36.6%) and for the pooled antiplatelet group was 29.5% (95% CI, 26.6%-32.2%). HR >1 represents improved survival ○ Duration of hospitalisation: pooled antiplatelet *vs*. no antiplatelet OR 1.05 (95% CrI 0.92, 1.20) ○ Duration of ICU stay: pooled antiplatelet (265/636) *vs*. no antiplatelet (148/326) OR 1.05 (95% CrI 0.92, 1.20) ○ Progression to intubation, ECMO or death: pooled antiplatelet (265/636) *vs*. no antiplatelet (148/326) OR 1.14 (95% CrI 0.86, 1.51) ○ Serious adverse events: reported in 5 of 565 (0.9%), 4 of 455 (0.9%), and 3 of 529 (0.6%) participants in the aspirin, P2Y12 inhibitor, and control groups, respectively. Aspirin: OR 1.26 (95% CrI 0.42, 3.90) and P2Y12: OR 1.11 (95% CrI 0.35, 3.53) ○ Major bleeding: occurred in 21 of 1002 participants (2.1%) in the pooled antiplatelet group and in 2 of 517 participants (0.4%) in the control group. An analysis of major bleeding comparing the pooled antiplatelet group with control showed an adjusted OR of 2.97 (95% CrI, 1.23-8.28) and an adjusted absolute risk difference of 0.8% (95% CrI, 0.1%-2.7%). Aspirin: OR 2.34 (95% CrI 0.93, 5.93) and P2Y12: OR 2.50 (95% CrI 0.95, 6.56) ○ No. of thromboembolic events (at least 1): aspirin (69/556) OR: 1.07 (95% CrI 0.71, 1.59) and P2Y12 (43/440) OR: 0.75 (95% CrI	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS ASSESSMENT
				0.47, 1.21) and in the control group (65/513) <u>Non-critically ill patients (N=266)</u> • Baseline characteristics were comparable between the intervention groups. Mean age (standard deviation, SD): 52 (12.8) years in aspirin group, 53.9 (12.1) years in P2Y12 inhibitors group and 53.4 (13.4) years in the control group. There were 91 women (34%) and 175 men (66%) • Co-morbidities: Diabetes, respiratory disease, kidney disease, severe cardiovascular disease and any immunosuppressive condition • *Primary outcome*: Among non-critically ill participants, the median number of organ support-free days was 22 in all 3 groups (aspirin IQR: 18-22 days, P2Y12: 22-22 days and control 18.5-22). Number of patients with known outcome: aspirin (90/90), P2Y12 (67/67) and control (106/109). The median adjusted odds ratio (OR) for the effect of antiplatelet therapy compared with control for aspirin was: OR 0.94 (95% CrI 0.56, 1.35), P2Y12: OR 0.97 (95% CrI 0.59, 1.50) • *Secondary outcomes:* ○ Survival to hospital discharge: aspirin (78/90): OR 1.23 (95% CrI 0.70, 2.04), P2Y12 (63/64): OR 1.29 (95% CrI 0.77, 2.52). OR >1 indicates a benefit of treatment ○ 90-day mortality: pooled antiplatelet group *vs*. control adjusted HR 1.13 (95% CrI 0.57, 2.27) ○ Duration of hospitalisation: pooled antiplatelet *vs*. no antiplatelet OR 0.93 (95% CrI 0.70, 1.24)	

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				○ Progression to intubation, ECMO or death: pooled antiplatelet (11/76) *vs*. no antiplatelet (19/66) OR 1.15 (95% CrI 0.87, 1.53) ○ Serious adverse events: nil per group ○ Major bleeding: 1 in aspirin group, nil in the other 2 groups ○ No. of thromboembolic events (at least 1): aspirin (2/90) OR: 0.82 (95% CrI 0.21, 3.66) and P2Y12 (4/67) OR: 0.46 (95% CrI 0.12, 1.79), control (2/106)	
RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022 Jan 8; 399(10320):143-151. doi: 10.1016/S0140-6736(21)01825-0. Epub 2021 Nov 17. PMID: 34800427; PMCID: PMC8598213. (Horby *et al.*)	Design Parallel, open-label, platform RCT – multi-centre: United Kingdom, Indonesia and Nepal Follow-up duration (days) 28 Funding UK Research and Innovation (Medical Research Council), National Institute of Health Research (Grant ref: MC_PC_19056), and the Wellcome Trust (Grant Ref: 222406/Z/20/Z) through the COVID-19 Therapeutics Accelerator Declarations "The authors declare no competing interests or financial relationships relevant to the submitted work. No form of payment was given to anyone to produce the manuscript. The Nuffield Department of Population Health at the University of Oxford has a staff	Sample size N=14,892 (7,351 patients were randomly allocated to usual care plus aspirin and 7,541 were randomly allocated to usual care alone) Inclusion criteria "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 "Children aged <18 years were not eligible for randomisation to aspirin; Patients with known	Intervention Aspirin 150 mg orally or by nasogastric tube or rectally once per day until discharge Control Usual standard of care *Definition of Standard care: All patients will receive usual care in the participating hospital.* "At randomization, 5,035 patients (34%) were receiving thromboprophylaxis with higher dose low molecular weight heparin (LMWH), 8,878 (60%) with standard dose LMWH, and 979 (7%) were not receiving thromboprophylaxis." "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,	Primary Outcome All-cause mortality, reported at 28-days Secondary Outcomes • Time to discharge from hospital • Among patients not on invasive mechanical ventilation at randomization progression to invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death Subsidiary Clinical Outcomes • Use of non-invasive respiratory support • Time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days) • Use of renal dialysis or haemofiltration • Cause-specific mortality • Major bleeding events (defined as intracranial bleeding or bleeding requiring transfusion, endoscopy, surgery or vasoactive drugs) • Thrombotic events (defined as acute pulmonary embolism, deep vein thrombosis, ischaemic stroke, myocardial infarction or systemic arterial embolism) • Major cardiac arrhythmias • Serious adverse reactions	Overall risk of bias **Low**

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	policy of not accepting honoraria or consultancy fees directly or indirectly from industry". Informed Consent "The trial was done in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (reference 20/EE/0101). Written informed consent was obtained from all patients, or a legal representative if they were too unwell or unable to provide consent."	hypersensitivity to aspirin, a recent history of major bleeding, or currently receiving aspirin or another antiplatelet treatment; aspirin unavailable at the hospital at the time of enrolment."	about one-quarter receiving remdesivir, and one-eighth receiving tocilizumab." As a platform trial, and in a factorial design, patients could be simultaneously randomised to other treatment groups: i) azithromycin or colchicine or dimethyl fumarate versus usual care, ii) convalescent plasma or monoclonal antibody (REGN-CoV2) versus usual care, and iii) baricitinib versus usual care	*Results* • Baseline characteristics were comparable between the groups: Mean age: 59.2 years (SD 14.2). Gender: Men 9,201 (62%), Women 5,691 (38%) • Median time since symptom onset was 9 days (IQR 6 to 12 days) • Comorbidities: Diabetes, heart disease, Chronic lung disease, TB, HIV, severe liver disease and severe kidney impairment • No significant difference was observed in the proportion of patients who met the primary outcome of 28-day mortality between the two randomised groups (1,222 [17%] patients in the aspirin group *vs*. 1,299 [17%] patients in the usual care group; rate ratio 0.96; 95% confidence interval [CI], 0.89 to 1.04; p=0.35 • Allocation to aspirin was associated with a reduction of 1 day in median time until discharge alive from hospital compared to usual care (median 8 days vs. 9 days [IQR for each 5 to >28 days]) • Allocation to aspirin was associated with an increased rate of discharge alive within 28 days (75% *vs*. 74%, rate ratio 1.06, 95% CI 1.02 to 1.10, p=0.0062) • Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death among those allocated to aspirin was similar to that among those allocated to usual care (21% *vs*. 22%, risk ratio 0.96, 95% CI 0.90 to 1.03, p=0.23) • There were no observed significant differences in the pre-specified subsidiary clinical outcomes of cause-specific mortality (Supplementary Webtable 3), use of ventilation (23% *vs*. 24%, risk ratio 0.96, 95% CI 0.90 to 1.03, p=0.30), successful cessation of invasive mechanical	

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				ventilation (38% *vs*. 36%, risk ratio 1.08, 95% CI 0.85to 1.37, p=0.54), or receipt of renal dialysis or haemofiltration (4% in both groups, risk ratio 0.99, 95% CI 0.84 to 1.17, p=0.93) • With aspirin use, the incidence of thrombotic events was lower (4.6% *vs*. 5.3%; absolute difference 0.6%, SE 0.4%) and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%, SE 0.2%) in the aspirin group • The incidence of new cardiac arrhythmias was similar in the two groups (3.1% *vs*. 3.5%) • There were 18 reports of a serious adverse event believed related to aspirin, all of which were due to haemorrhagic events	

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Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, Baucom AL, Kirwan BA, Eng H, Martin D, Zaharris E. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA. 2021 Nov 2; 326 (17):1703-12.	Design ACTIV-4B COVID-19 Outpatient Thrombosis Prevention Trial is an adaptive, randomized, double-blind, placebo controlled trial of antiplatelet and anticoagulant agents with blinded adjudication of outcomes Patients were enrolled from 52 US centres Follow-up duration (days) 45 Funding "This study was, in part, funded by National Institutes of Health (NIH) Agreement 1OT2HL156812-01. Specifically, the ACTIV-4B trial was supported by Other Transition Authorities from the National Heart, Lung, and Blood Institute (NHLBI). Grantee institutions included the University of Pittsburgh,the University of Illinois Chicago, and the Brigham and Women's Hospital. The trial drugs and matching placebo were donated by the Bristol Myers Squibb Pfizer Alliance. *Role of the Funder/Sponsor*: The NHLBI funded the ACTIV-4B trial and had a collaborative role in the trial design. The NHLBI had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the	Sample size N=657 symptomatic but clinically stable outpatients with COVID-19 (164 were randomized to receive aspirin 81mg once daily, 165 were randomized to receive apixaban 2.5mg twice daily, 164 were randomized to receive apixaban 5mg twice daily and 164 were randomized to receive placebo). However, 558 participants initiated randomized trial treatments as follows: 144 initiated therapy as randomized in the aspirin group, 135 in the apixaban 2.5mg daily group, 143 in the apixaban 5mg twice daily group and 136 in the placebo group Inclusion criteria • Ambulatory patients between the ages of 40 and 80 years • With newly diagnosed symptomatic SARS-CoV-2 infection with positive polymerase chain reaction or antigen test results • Creatinine clearance was required to be greater than 30mL/min/1.73m^2	Intervention Participants were randomized centrally in a 1:1:1:1 ratio to receive aspirin (81 mg once daily), prophylactic-dose apixaban (2.5 mg twice daily), apixaban at therapeutic dose (5mg twice daily) for 45 days, with a 30-day safety follow-up evaluation. Control Matching placebo	Primary outcome(s) • Composite of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, hospitalisation for cardiovascular or pulmonary events, and all-cause mortality for up to 45 days after treatment initiation • Principal safety outcomes were major bleeding and clinically relevant non-major bleeding (CRNMB) as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria: Non-major clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study intervention, or associated with discomfort for the participant such as pain or impairment of activities of daily life • Any events of disseminated intravascular coagulation (DIC) Secondary outcomes • Pre-specified secondary outcomes included the individual components of the primary study end point as well as mortality without antecedent hospitalisation *Results* "Between September 1, 2020, through June 17, 2021, 775 potential participants provided informed consent and were screened, of whom 657 met preliminary eligibility criteria and were randomized. On June 18, 2021, the NHLBI accepted a recommendation from the independent data and safety monitoring board to terminate the trial early because of lower than anticipated event rates; for this reason, despite the adaptive clinical trial design, no additional agents underwent evaluation".	Overall risk of bias **Some Concerns** Some concerns were raised in how the trial deviated from intervention and missing outcome data

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS ASSESSMENT
	decision to submit the manuscript for publication". <u>Declarations</u> Listed in the paper <u>Informed consent</u> Informed consent was obtained from trial participants	and platelet count greater than 100 000/mm^3 • Be able to be contacted by telephone and, optionally, other electronic methods of communication <u>Exclusion criteria</u> • Previously hospitalised for COVID-19 • Had acute leukemia • Recent major bleeding • A contraindication to or other indication for anticoagulation • Need for single or dual antiplatelet therapy • Pregnant or lactating		• Baseline characteristics were balanced among treatment groups in all randomised participants and among those who initiated treatment. The median age of randomized participants was 54 years (IQR, 46-59), 59.1% were women (n=388) and 40.9% men (n=269) • Comorbidities: hypertension, diabetes, history of smoking • The median time from diagnosis to randomisation was 7 days (IQR, 3-10 days) • Median time from randomisation to initiation of study treatment was 3 days (IQR, 2-5 days) • *Primary outcome*: During the period that transpired between the time of randomization and initiation of study drug, 22 randomized participants (3.3%) became acutely unstable and were hospitalised for worsening symptoms of pneumonia prior to initiating study treatment. In this group, there were two pneumonia-related deaths during the 45-day observation period (one of which was attributable to pulmonary embolism [PE]) and one case of non-fatal deep vein thrombosis (DVT). There was an additional death in this group secondary to respiratory failure that occurred after the 45-day observation period but during the 30-day subsequent safety period • Among the 558 participants who initiated randomized trial treatment, 556 (99.6%) had complete follow-up at 45 days after drug initiation or at the time of trial termination, whichever came earlier, and 544 (97.5%) were followed-up through day 45 ○ There were five suspected primary end points and no deaths accrued during the trial treatment period ○ There were no major bleeding events, no episodes of DIC in any of the 4 groups and one case of DVT or PE in the aspirin group	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS ASSESSMENT
				• Among the ITT population, N=657: ○ There were 26 suspected primary end points 7 in the aspirin group (4.3%) 5 (3.0%) in the apixaban 2.5mg daily group, 5 (3.1%) in the apixaban 5mg twice daily group and 9 (5.5%) in the placebo group ○ There was 1 case each of DVT or PE in the aspirin, apixaban 5mg twice daily and placebo groups ○ There were 2 deaths, 1 each in the apixaban 5mg twice daily and placebo groups ○ There were no major bleeding events in any of the 4 groups	

TABLE 2: CHARACTERISTICS OF EXCLUDED STUDIES

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Berger JS, Kornblith LZ, Gong MN, Reynolds HR, Cushman M, Cheng Y, McVerry BJ, Kim KS, Lopes RD, Atassi B, Berry S. Effect of P2Y12 Inhibitors on Survival Free of Organ Support Among Non–Critically Ill Hospitalised Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2022 Jan 18; 327(3):227-36.	Design Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 Acute (ACTIV-4a) is an international, adaptive, randomised clinical trial Patients were enrolled from 400 sites in 4 countries (Brazil, Italy, Spain and the United States). Follow-up duration (days) 28 Funding "This research was funded by Agreement 1OT2HL156812-01 with the National Institutes of Health. The ACTIV-4a platform was sponsored by the National Heart, Lung, and Blood Institute and administered through another transactions authority (OTA-20-011). *Role of the Funder/Sponsor*: The National Institutes of Health professional staff and peer reviewers participated in the trial protocol design and review of the manuscript. The National Institutes of Health did not have a role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication". Declarations	Sample size N=562 non-critically ill patients hospitalised for COVID-19. (293 patients were randomly allocated to receive a therapeutic dose of heparin and P2Y12 inhibitor and 269 were randomly allocated to receive a therapeutic dose of heparin [usual care] alone) Inclusion criteria "In order to be eligible to participate in this study, an individual must meet all of the following criteria: • ≥ 18 years of age • Hospitalised for COVID-19 • Enrolled within 72 hours of hospital admittance or 72 hours of positive COVID test • Expected to require hospitalisation for > 72 hours • D-dimer level that was 2-fold or greater than the upper limit of normal (determined at each hospital site) or were 60 to 84 years of age • If a patient was younger than 60 years of age, he or she could be enrolled if at least 1 of the following criteria were met: had an oxygen requirement greater than 2L per minute or had hypertension, diabetes, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m2), cardiovascular disease, or a body mass index (calculated as weight in kilograms divided by height in meters squared) of 35 or greater". Exclusion criteria "Patients were ineligible for enrollment if 72 hours or more had elapsed from the hospital admission for COVID-19 or SARS-CoV-2 infection confirmation, if hospital discharge was expected within 72 hours, or if they had a contraindication	Intervention Therapeutic dose of heparin plus a P2Y12 inhibitor. Ticagrelor was the preferred P2Y12 inhibitor; however, clopidogrel and prasugrel were allowed. When clopidogrel was used, a loading dose of 300 mg was encouraged. Control Therapeutic dose of heparin only (usual care)	Primary outcome(s) • 21 Day Organ Support Free Days, which is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry. Organ Support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support, with death at any time (including beyond 21 days) during the index hospitalisation assigned -1 days • Primary safety outcome: major bleeding (as defined by the ISTH)-see above for definition Secondary outcomes • Major thrombotic events or death by 28 days (a composite outcome of myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death) • Secondary efficacy outcomes included all thrombotic events (major thrombotic events plus deep venous thrombosis) or death by 28 days • The secondary safety outcome was a composite of major bleeding or death by 28 days *All reported bleeding and thrombotic events were adjudicated in a blinded fashion by the clinical end point committee using consensus definitions

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	Listed in the paper Informed consent "The study received central institutional review board approval for the US sites coordinated by the University of Pittsburgh and central ethics committee approvals in Brazil, Italy, and Spain. Written informed consent was obtained from the patient or legal representative if the patient was unable to provide consent. The trial was conducted in accordance with the principles of the Good Clinical Practice guidelines of the International Conference on Harmonization".	to P2Y12 inhibitors or a clinical requirement for dual antiplatelet therapy."		*Results* • On June 18, 2021, the trial data and safety monitoring board recommended early termination because of lower than anticipated event rates • Baseline characteristics were comparable between the groups: Mean age: 52.7 years (SD 13.5). Gender: Men 329 (58.5%), Women 233 (41.5%) • Concomitant baseline therapies included corticosteroids (64.1%), remdesivir (52.0%), and IL-6 receptor antagonists (2.8%). Aspirin use at baseline was comparable between groups (15.0% in the P2Y12 inhibitor group *vs.* 13.4% in the usual care group) • Comorbidities: cardiovascular disease, diabetes, chronic kidney disease, liver disease and respiratory disease. A lower percentage of patients (42.7%, n=125) in the P2Y12 inhibitor group than in the usual care group had a history of hypertension (54.9%, n=147) • Among the 562 patients, the median number of organ support-free days was 21 days (IQR, 20-21 days) in the P2Y12 inhibitor group and 21 days (IQR, 21-21days) in the usual care group • *Primary outcomes:* The adjusted OR for the effect of a P2Y12 inhibitor on organ support-free days was 0.83 (95% CrI 0.55-1.25) ○ Overall, 75 patients (26%) in the P2Y12 inhibitor group and 58 patients (22%) in the usual care

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				group died or required respiratory or cardiovascular organ support during the first 28 days (adjusted hazard ratio, 1.19 [95%CI,0.84-1.68],P = 0.34 ○ The primary safety outcome of major bleeding occurred in 6 patients (2.0%) in the P2Y12 inhibitor group and in 2 patients (0.7%) in the usual care group (adjusted OR, 3.31 [95% CI, 0.64-17.2], P = 0.15 • *Secondary outcomes:* The key secondary outcome of major thrombotic events or in hospital death was not significantly different between randomized groups and occurred in 18 patients (6.1%) in the P2Y12 inhibitor group and in 12 patients (4.5%) in the usual care group (adjusted OR, 1.42 [95% CI, 0.64-3.13] ○ Major bleeding events or in hospital death occurred in 18 patients (6.1%) in the P2Y12 inhibitor group and in 10 patients (3.7%) in the usual care group (adjusted OR, 1.80 [95% CI, 0.79-4.10]

TABLE 3: CHARACTERISTICS OF PLANNED AND ONGOING STUDIES (SOURCE: www.covid-nma.com 13 JUNE 2022)

TREATMENT (PER ARM)	SAMPLE SIZE	SEVERITY	SPONSOR/FUNDER	REG. NUMBER
(1) Dalteparin + enoxaparin + tinzaparin vs (2) Dalteparin + enoxaparin + tinzaparin vs (3) Aspirin + dalteparin + enoxaparin + tinzaparin vs (4) Convalescent plasma vs (5) Nafamostat mesilate vs (6) Standard of care	2400	Mild/moderate	University of Melbourne	NCT04483960
(1) Aspirin + atorvastatin + clopidogrel + omeprazole + rivaroxaban vs (2) Standard of care	320	No restriction on type of patients	Imperial College London	NCT04333407
(1) Anakinra vs (2) Aspirin vs (3) Azithromycin vs (4) Baricitinib vs (5) Colchicine vs (6) Convalescent plasma vs (7) Corticosteroid vs (8) Dimethyl fumarate vs (9) Empagliflozin vs (10) Corticosteroid vs (11) Hydroxychloroquine vs (12) Immunoglobulin vs (13) Lopinavir + ritonavir vs (14) Molnupiravir vs (15) Nirmatrelvir + ritonavir vs (16) Sotrovimab vs (17) Standard of care vs (18) Synthetic neutralising antibodies vs (19) Tocilizumab	50000	Moderate/severe/critical	University of Oxford	NCT04381936
(1) Colchicine vs (2) Interferon beta vs (3) Aspirin vs (4) Rivaroxaban vs (5) Standard of care	6667	Mild	Population Health Research Institute	NCT04324463
(1) Aspirin vs (2) Standard of care	128	Moderate/severe	Xijing Hospital	NCT04365309
(1) Apixaban vs (2) Apixaban vs (3) Aspirin vs (4) Placebo	657	No restriction on type of patients	Frank C Sciurba	NCT04498273
(1) Aspirin + dipyridamole vs (2) Standard of care	99	Severe/critical	Rutgers, The State University of New Jersey	NCT04410328
(1) Liquid aspirin vs (2) Placebo	200	Mild/moderate	Louisiana State University Health Sciences Center in New Orleans	NCT04937088
(1) Aspirin vs (2) Aspirin + vitamin d vs (3) Standard of care	0	Mild	Louisiana State University Health Sciences Center in New Orleans	NCT04363840
(1) Hydrocortisone vs (2) Hydrocortisone vs (3) Hydrocortisone vs (4) Unfractioned heparin or low molecular weight heparin (lmwh) vs (5) Hydroxychloroquine vs (6) Hydroxychloroquine + lopinavir + ritonavir vs (7) Oseltamivir vs (8) Oseltamivir vs (9) Lopinavir + ritonavir vs (10) Interferon beta 1a vs (11) Convalescent plasma vs (12) Simvastatin vs (13) Anakinra vs (14) Tocilizumab vs (15) Sarilumab vs (16) Vitamin c vs (17) Ceftriaxone + macrolide vs (18) Levofloxacin or moxifloxacin vs (19) Macrolide + piperacillin-tazobactam vs (20) Ceftaroline + macrolide vs (21) Amoxicillin-clavulanate + macrolide vs (22) Macrolide vs (23) Macrolide vs (24) Mechanical ventilation vs (25) Eritoran vs (26) Apremilast vs	10000	No restriction on type of patients	UMC Utrecht	NCT02735707

(27) Aspirin vs (28) Clopidogrel vs (29) Prasugrel vs (30) Ticagrelor vs (31) Standard of care				
(1) Aspirin + multimineral + multivitamin + promethazine vs (2) Standard of care	60	Mild/moderate	Meyer Organics Pvt Ltd	CTRI/2021/06/034254
(1) Aspirin + atorvastatin + nicorandil vs (2) Standard of care	300	Moderate	Dr Ambudhar Sharma	CTRI/2021/04/032648
(1) Aspirin + colchicine + montelukast vs (2) Standard of care	34	Severe/critical	Vivek Chauhan	CTRI/2020/09/028088
(1) Aspirin vs (2) Atorvastatin vs (3) Standard of care vs (4) Standard of care	800	Moderate/severe	Dr Deepti Siddharthan	CTRI/2020/07/026791
(1) Aspirin vs (2) Standard of care	60	Moderate/severe	Dr Souvik Maitra	CTRI/2020/08/027503
(1) Aspirin vs (2) Ivermectin vs (3) Placebo	1200	Moderate/severe	London School of Hygiene and Tropical Medicine	NCT04703608
(1) Losartan vs (2) Aspirin vs (3) Simvastatin vs (4) Aspirin + simvastatin vs (5) Aspirin + losartan vs (6) Losartan + simvastatin vs (7) Aspirin + losartan + simvastatin vs (8) Standard of care	10000	Moderate/severe	London School of Hygiene and Tropical Medicine	PACTR202006473370201
(1) Aspirin vs (2) Standard of care	36	Moderate/severe	Rasht University of Medical Sciences	IRCT20180205038626N7
(1) Aspirin + ivermectin vs (2) Aspirin + ivermectin vs (3) Standard of care	490	Moderate	Makerere University	NCT04768179
(1) Aspirin + ethanol vs (2) Standard of care	80	Mild/moderate	Mansoura University	NCT04554433
(1) Ivermectin vs (2) Ivermectin vs (3) Aspirin	1200	Moderate/severe	Medical Research Council Unit The Gambia at LSHTM	PACTR202101544570971
(1) Unfractioned heparin vs (2) Unfractioned heparin vs (3) P2Y12 inhibitor + unfractioned heparin vs (4) P2y12 inhibitor + unfractioned heparin vs (5) Crizanlizumab vs (6) Sglt2 inhibitor	3000	Mild	Matthew Neal MD	NCT04505774
(1) Hydrocortisone vs (2) Hydrocortisone vs (3) Hydrocortisone vs (4) Unfractioned heparin or low molecular weight heparin (lmwh) vs (5) Hydroxychloroquine vs (6) Hydroxychloroquine + lopinavir + ritonavir vs (7) Oseltamivir vs (8) Oseltamivir vs (9) Lopinavir + ritonavir vs (10) Interferon beta 1a vs (11) Convalescent plasma vs (12) Simvastatin vs (13) Anakinra vs (14) Tocilizumab vs (15) Sarilumab vs (16) Vitamin c vs (17) Ceftriaxone + macrolide vs (18) Levofloxacin or moxifloxacin vs (19) Macrolide + piperacillin-tazobactam vs (20) Ceftaroline + macrolide vs (21) Amoxicillin-clavulanate + macrolide vs (22) Macrolide vs (23) Macrolide vs (24) Mechanical ventilation vs (25) Eritoran vs (26) Apremilast vs (27) Aspirin vs (28) **Clopidogrel** vs (29) **Prasugrel** vs (30) **Ticagrelor** vs (31) Standard of care	10000	No restriction on type of patients	UMC Utrecht	NCT02735707

TABLE 4: GRADE EVIDENCE PROFILES

COMPARISON 1: ANTIPLATELET THERAPY VERSUS NO ANTIPLATELET THERAPY IN INPATIENTS

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet therapy (Aspirin and P2Y12 inhibitors)	Standard of care/placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality											
2	randomised trials	not serious	not serious	not serious	not serious	none	1526/8528 (17.9%)	1469/8179 (18.0%)	**RR 0.97** (0.90 to 1.03)	**5 fewer per 1,000** (from 18 fewer to 5 more)	⊕⊕⊕⊕ High
Progression to mechanical ventilation											
1	randomised trials	not serious	not serious	not serious	not serious	none	772/6993 (11.0%)	829/7169 (11.6%)	**RR 0.95** (0.87 to 1.05)	**6 fewer per 1,000** (from 15 fewer to 6 more)	⊕⊕⊕⊕ High
Thromboembolic events											
2	randomised trials	not serious	not serious	serious[a]	not serious	none	457/8528 (5.4%)	464/8179 (5.7%)	**RR 0.89** (0.78 to 1.01)	**6 fewer per 1,000** (from 12 fewer to 1 more)	⊕⊕⊕◯ Moderate
Major bleeding events											
2	randomised trials	not serious	not serious	not serious[b]	serious[c]	none	137/8528 (1.6%)	78/8179 (1.0%)	**RR 2.47** (0.93 to 6.60)	**14 more per 1,000** (from 1 fewer to 53 more)	⊕⊕⊕◯ Moderate
Serious adverse events											
2	randomised trials	not serious	not serious	not serious	very serious[d]	none	REMAP-CAP: Serious adverse events were reported in 5 of 565 (0.9%), 4 of 455 (0.9%), and 3 of 529 (0.6%) participants in the aspirin, P2Y12 inhibitor, and control groups, respectively (critically ill) RECOVERY: There were 18 events of SAEs of bleeding related to aspirin, 13 non-fatal and 5 fatal.				⊕⊕◯◯ Low
Adverse reactions											
1	randomised trials	not serious	not serious	not serious[e]	not serious	none	231/7351 (3.1%)	267/7541 (3.5%)	**RR 0.89** (0.75 to 1.06)	**4 fewer per 1,000** (from 9 fewer to 2 more)	⊕⊕⊕⊕ High

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by one level for indirectness: This outcome includes a variety of thromboembolic events such as pulmonary embolism, myocardial infarction, ischemic cerebrovascular event, systemic arterial thromboembolism, and deep venous thrombosis

b. Major bleeding (according to International Society of Hemostasis and Thrombosis definition) is defined as fatal bleeding, symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a decrease in hemoglobin of 2 g/dL or greater or leading to transfusion of 2 or more whole blood or red blood cell units

c. Downgraded by one level for imprecision: Wide confidence interval ranging from a 7% reduction in risk to a 6.6-fold increase in risk

d. Downgraded by two levels for imprecision: Low number of events in both included trials

e. Any major cardiac arrhythmia

COMPARISON 2: ANTIPLATELET THERAPY VERSUS NO ANTIPLATELET THERAPY IN OUTPATIENTS

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet therapy (Aspirin)	Standard of care/placebo	Relative (95% CI)	Absolute (95% CI)	
Mortality											
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	0/164 (0.0%)	1/164 (0.6%)	**RR 0.33** (0.01 to 8.12)	**4 fewer per 1,000** (from 6 fewer to 43 more)	⨁⨁◯◯ Low
Thromboembolic events											
1	randomised trials	not serious	not serious	not serious[b]	very serious[c]	none	1/164 (0.6%)	1/164 (0.6%)	**RR 1.00** (0.06 to 15.85)	**0 fewer per 1,000** (from 6 fewer to 91 more)	⨁⨁◯◯ Low
Bleeding events											
1	randomised trials	not serious	not serious	not serious[d]	very serious[e]	none	7/164 (4.3%)	3/164 (1.8%)	**RR 2.33** (0.61 to 8.87)	**24 more per 1,000** (from 7 fewer to 144 more)	⨁⨁◯◯ Low
Major bleeding											
1	randomised trials	not serious	not serious	not serious[f]	very serious[g]	none	There no major bleeding events in either arm				⨁⨁◯◯ Low

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by two levels for imprecision: ACTIV-4B trial had a small sample size, low number of events and wide confidence interval ranging from a 99% reduction in risk to a 8-fold increase in risk

b. Thromboembolic events: DVT or PE

c. Downgraded by two levels for imprecision: ACTIV-4B trial had a small sample size, low number of events and wide confidence interval ranging from a 94% reduction in risk to a 15-fold increase in risk

d. Clinically relevant non-major bleeding (CRNMB) as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria and minor bleeding

e. Downgraded by two levels for imprecision: ACTIV-4B trial had a small sample size, low number of events and wide confidence interval ranging from a 39% reduction in risk to a 8-fold increase in risk

f. Major bleeding is defined as fatal bleeding, symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a decrease in hemoglobin of 2 g/dL or greater or leading to transfusion of 2 or more whole blood or red blood cell units.

g. Downgraded by two levels for imprecision: Small sample size and no events occurred

TABLE 5: SUMMARY OF FINDINGS TABLES

ANTIPLATELET THERAPY (ASPIRIN AND P2Y12 INHIBITORS) COMPARED TO STANDARD OF CARE/PLACEBO FOR INPATIENTS WITH COVID-19

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care/placebo	Risk with Antiplatelet therapy (Aspirin and P2Y12 inhibitors)				
Mortality	180 per 1,000	**174 per 1,000** (162 to 185)	**RR 0.97** (0.90 to 1.03)	16707 (2 RCTs)	⨁⨁⨁⨁ High	
Progression to mechanical ventilation	116 per 1,000	**110 per 1,000** (101 to 121)	**RR 0.95** (0.87 to 1.05)	14162 (1 RCT)	⨁⨁⨁⨁ High	
Thromboembolic events	57 per 1,000	**50 per 1,000** (44 to 57)	**RR 0.89** (0.78 to 1.01)	16707 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	
Major bleeding events	10 per 1,000	**24 per 1,000** (9 to 63)	**RR 2.47** (0.93 to 6.60)	16707 (2 RCTs)	⨁⨁⨁◯ Moderate[b,c]	
Serious adverse events	REMAP-CAP: Serious adverse events were reported in 5 of 565 (0.9%), 4 of 455 (0.9%), and 3 of 529 (0.6%) participants in the aspirin, P2Y12 inhibitor, and control groups, respectively (critically ill) RECOVERY: There were 18 events of SAEs of bleeding related to aspirin, 13 non-fatal and 5 fatal.			16707 (2 RCTs)	⨁⨁◯◯ Low[d]	
Adverse reactions	35 per 1,000	**32 per 1,000** (27 to 38)	**RR 0.89** (0.75 to 1.06)	14892 (1 RCT)	⨁⨁⨁⨁ High[e]	

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

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

Explanations
a. Downgraded by one level for indirectness: This outcome includes a variety of thromboembolic events such as pulmonary embolism, myocardial infarction, ischemic cerebrovascular event, systemic arterial thromboembolism, and deep venous thrombosis
b. Major bleeding (according to International Society of Hemostasis and Thrombosis definition) is defined as fatal bleeding, symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a decrease in hemoglobin of 2 g/dL or greater or leading to transfusion of 2 or more whole blood or red blood cell units
c. Downgraded by one level for imprecision: Wide confidence interval ranging from a 7% reduction in risk to a 6.6-fold increase in risk
d. Downgraded by two levels for imprecision: Low number of events in both included trials
e. Any major cardiac arrhythmia

ANTIPLATELET THERAPY (ASPIRIN AND P2Y12 INHIBITORS) COMPARED TO STANDARD OF CARE/PLACEBO FOR OUTPATIENTS WITH COVID-19

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care/placebo	Risk with Antiplatelet therapy (Aspirin and P2Y12 inhibitors)				
Mortality	6 per 1,000	**2 per 1,000** (0 to 50)	**RR 0.33** (0.01 to 8.12)	328 (1 RCT)	⨁⨁◯◯ Low[a]	
Thromboembolic events	6 per 1,000	**6 per 1,000** (0 to 97)	**RR 1.00** (0.06 to 15.85)	328 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Bleeding events	18 per 1,000	**43 per 1,000** (11 to 162)	**RR 2.33** (0.61 to 8.87)	328 (1 RCT)	⨁⨁◯◯ Low[d,e]	
Major bleeding	There no major bleeding events in either arm			(1 RCT)	⨁⨁◯◯ Low[f,g]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

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

Explanations
a. Downgraded by two levels for imprecision: ACTIV-4B trial had a small sample size, low number of events and wide confidence interval ranging from a 99% reduction in risk to a 8-fold increase in risk
b. Thromboembolic events: DVT or PE
c. Downgraded by two levels for imprecision: ACTIV-4B trial had a small sample size, low number of events and wide confidence interval ranging from a 94% reduction in risk to a 15-fold increase in risk
d. Clinically relevant non-major bleeding (CRNMB) as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria and minor bleeding
e. Downgraded by two levels for imprecision: ACTIV-4B trial had a small sample size, low number of events and wide confidence interval ranging from a 39% reduction in risk to a 8-fold increase in risk
f. Major bleeding is defined as fatal bleeding, symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a decrease in hemoglobin of 2 g/dL or greater or leading to transfusion of 2 or more whole blood or red blood cell units.
g. Downgraded by two levels for imprecision: Small sample size and no events occurred

APPENDIX 1: SEARCH STRATEGY

World Health Organisation [7 June 2022] *Search terms: Antiplatelets, aspirin, clopidogrel, prasugrel, and ticagrelor*
Australian Task Force (https://covid19.recmap.org/) [3 June 2022] *Search strategy terms: Aspirin, clopidogrel, prasugrel, and ticagrelor*
COVID NMA (https://covid-nma.com/) [3 June 2022] *Search terms: Aspirin, P2Y12, antiplatelets, clopidogrel, prasugrel, and ticagrelor*
COCHRANE Study COVID Register (https://covid-19.cochrane.org/) [13 June 2022] *Search terms: Aspirin, P2Y12, antiplatelets, clopidogrel, prasugrel, and ticagrelor*

APPENDIX 2: EVIDENCE TO DECISION FRAMEWORK

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Trivial (*In- and out-patient populations*) o Small o Moderate o Large o Varies o Don't know	**Desirable effects: Mortality, progression ro mechanical ventilation and thromboembolic events** **Inpatients**	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care/placebo	Risk with Antiplatelet therapy (Aspirin and P2Y12 inhibitors)				
Mortality	180 per 1,000	**174 per 1,000** (162 to 185)	**RR 0.97** (0.90 to 1.03)	16707 (2 RCTs)	⊕⊕⊕⊕ High	
Progression to mechanical ventilation	116 per 1,000	**110 per 1,000** (101 to 121)	**RR 0.95** (0.87 to 1.05)	14162 (1 RCT)	⊕⊕⊕⊕ High	
Thromboembolic events	57 per 1,000	**50 per 1,000** (44 to 57)	**RR 0.89** (0.78 to 1.01)	16707 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	
Major bleeding events	10 per 1,000	**24 per 1,000** (9 to 63)	**RR 2.47** (0.93 to 6.60)	16707 (2 RCTs)	⊕⊕⊕◯ Moderate[b,c]	
Serious adverse events	REMAP-CAP: Serious adverse events were reported in 5 of 565 (0.9%), 4 of 455 (0.9%), and 3 of 529 (0.6%) participants in the aspirin, P2Y12 inhibitor, and control groups, respectively (critically ill) RECOVERY: There were 18 events of SAEs of bleeding related to aspirin, 13 non-fatal and 5 fatal.			16707 (2 RCTs)	⊕⊕◯◯ Low[d]	
Adverse reactions	35 per 1,000	**32 per 1,000** (27 to 38)	**RR 0.89** (0.75 to 1.06)	14892 (1 RCT)	⊕⊕⊕⊕ High[e]	

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

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

Outpatients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care/placebo	Risk with Antiplatelet therapy (Aspirin and P2Y12 inhibitors)				
Mortality	6 per 1,000	**2 per 1,000** (0 to 50)	**RR 0.33** (0.01 to 8.12)	328 (1 RCT)	⨁⨁◯◯ Low[a]	
Thromboembolic events	6 per 1,000	**6 per 1,000** (0 to 97)	**RR 1.00** (0.06 to 15.85)	328 (1 RCT)	⨁⨁◯◯ Low[b,c]	
Bleeding events	18 per 1,000	**43 per 1,000** (11 to 162)	**RR 2.33** (0.61 to 8.87)	328 (1 RCT)	⨁⨁◯◯ Low[d,e]	
Major bleeding	There no major bleeding events in either arm			(1 RCT)	⨁⨁◯◯ Low[f,g]	

Undesirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large **X Moderate (*In patient population)*** ○ Small ○ Trivial ○ Varies **X Don't know (*Out-patient population*)**	Undesirable effects: Bleeding, adverse events, adverse reactions	

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low **X Low (*Out-patient population*)** **X Moderate (*In-patient population)*** ○ High ○ No included studies		Different agents in different settings

Values: Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability (*In- and out-patient populations*)** ○ No important uncertainty or variability		

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison **X Does not favor either the intervention or the comparison (*In- and out-patient populations)*** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required: How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs **X Negligible costs and savings (*In- and out-patient populations*)** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Price of medicines/treatment course:** **Medicine** / **Price (ZAR)** Aspirin, PO 75mg daily for 30 days — ***30 days: R0.62*** *Ref: MHPL** Clopidogrel, PO, 300mg loading dose followed by 75mg daily for 29 days — ***30 days: Approximately R120.98*** *Ref: SEP*** Prasugrel, PO, 60mg loading dose followed by 10mg daily — ***30 days: R1198,32*** *Ref: SEP*** Ticagrelor, PO, 60mg twice daily (Only 90mg available in South Africa, this dose was used for costing) — ***30 days: Approximately R672.24*** *Ref: SEP*** **MHPL – Master Health Products List, available from Affordable Medicines Directorate (through SAEDP@health.gov.za)* ***SEP – Single Exit Price available from https://medicineprices.org.za/ [accessed 30 June 2022]*	Costs vary as per agent. Not applicable.

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Not Applicable (NA)	**NA**

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	NA	NA
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes o Yes o Varies o Don't know	NA	NA
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes o Yes o Varies o Don't know	NA	NA

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	4 July 2022	HD, TK, NB, SE.	The use of antiplatelets is not recommended. The addition of antiplatelets to standard of care in hospitalised patients did not improve outcomes, and the balance of benefit and harms does not support their inclusion, particularly for in-patient populations. Use in ambulatory patients are less clear. Patients who are on regular antiplatelet agents for other indications should continue their use.