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Letter to the Editor

Aspirin and P2Y12 inhibitors in treating COVID-19

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Dear Editor,

Despite the introduction of vaccines, the coronavirus disease of 2019 (COVID-19) is still a major concern due to uncertainty in efficient treatment and managing post-infection complications. Many randomized controlled trials (RCTs) have been conducted to investigate the effects of non-direct anti-viral medications on COVID-19 patients. A group of these trials has investigated the effect of antiplatelets, including aspirin and/or P2Y12 inhibitors (P2Y12i), including three recently published trials in the past two months: ACTCOVID19 (Anti-Coronavirus Therapies to Prevent Progression of COVID-19) [1], COVID-PACT (Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients) [2], and RESIST (Statin and Aspirin in SARS-CoV-2 infection) [3]. We present here the results of a meta-analysis conducted to evaluate the efficacy and safety of antiplatelets in COVID-19 treatment.

Two reviewers (AK and AHB) searched PubMed, SCOPUS, Web of Science, Embase, and Cochrane Library through October 2022 for trials comparing outcomes in COVID-19 patients receiving antiplatelets (aspirin and P2Y12i) and control. Relevant keywords to COVID-19 and antiplatelets (e.g., aspirin, clopidogrel, or ticagrelor) were used in the search. Study characteristics of each study, including location, registration code, design, population, trial arms, and follow-up days, were extracted. We defined primary outcome as all-cause mortality (ACM). Secondary outcomes were in-hospital mortality, need for mechanical ventilation, thrombotic events, major thrombotic events (MTE), major bleeding (MB), and venous thromboembolism (VTE). MTE included pulmonary embolism, acute limb ischemia, stroke, and myocardial infarction, while thrombotic events comprised MTE plus VTE. Meta-analyses were performed by Random-effect analysis by Der-Simonian and Laird method using STATA software (Stata/MP 17.0; StataCorp LLC, College Station, TX, USA). Risk ratios (RRs) with a 95% confidence interval (CI) were reported.

The initial search resulted in 1,244 records, of which 557 were duplicates, 634 were removed after screening with title and abstract, and 46 were excluded after full-text assessment due to being observational, lack of control group, or not including antiplatelets. Finally, seven RCTs consisting of 21,942 COVID-19 patients were included in our analyses. Table 1 summarizes the study characteristics of included RCTs.

Fig. 1 presents the meta-analysis results of antiplatelets compared to usual care. Pooled meta-analysis resulted in no significant difference in terms of ACM (RR 0.93, 95% CI: 0.83-1.04, P=0.19), in-hospital mortality (RR: 0.84, 95% CI: 0.64-1.10, P=0.21), need for mechanical ventilation (RR: 0.95, 95% CI: 0.87-1.04, P=0.29), thrombotic events (RR: 0.89, 95% CI: 0.70-1.13, P=0.32), MTE (RR: 0.99, 95% CI: 0.48-2.06, P=0.98), or VTE (RR: 0.78, 95% CI: 0.59-1.03, P=0.08). However, MB was significantly higher among patients receiving antiplatelet agents (RR: 2.84, 95% CI: 1.11-7.30, P=0.03). The suggestion of antiplatelet agents was based on higher VTE and disseminated intravascular coagulation rates in COVID-19 patients reported in some studies [4]. In addition to their antithrombotic effects, aspirin's anti-inflammatory, antipyretic, and anti-analgesic effects [5] were other influential factors that contributed to their selection as a therapeutic option in hospitalized patients with COVID-19. However, our study did not find obvious overall benefits in administrating these agents.

A recent meta-analysis of observational studies and RCTs by Ma et al. [6] found a lower mortality rate in patients receiving aspirin compared to healthy controls, which was inconsistent with our result, emphasizing the difference between observational studies and RCTs. This study included the RECOVERY trial as the only RCT [7]. Another study by Zong et al. [8] included three RCTs in the systematic review; however, none were included in meta-analyses. In our study, subgroup analyses based on the antiplatelet agent (aspirin or P2Y12i) resulted in nonsignificant differences for all outcomes in patients receiving aspirin compared to controls (Supplementary figures 1-2). However, MB was significantly higher (RR: 2.84, 95% CI: 1.06-7.62, P=0.04) and VTE was also significantly lower (RR: 0.70, 95% CI: 0.50-0.99, P=0.04) in patients receiving P2Y12i (Supplementary figure 1).

As the apparent efficacy of these agents in cohort studies could not be confirmed with RCTs, there may be a reduced need for focusing on these medications in clinical practice and future research.

Although this study demonstrated no beneficiary effect for antiplatelet drugs in COVID-19 patients, some limitations should be addressed. First, as the primary outcome, ACM was the most reported outcome in the studies, which does not differentiate the cause of death,

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Table 1
Study characteristics of randomized controlled trials.

Trial Name	ACTCOVID19 2022	ACTIV-4A 2022	ACTIV-4B 2022	RECOVERY 2021	REMAP-CAP 2022	RESIST 2022	COVID-PACT 2022
Design	Open label	Open label	Double blind	Open label	Open label	Open label	Open label
Registration	NCT04324463	NCT04505774	NCT04498273	NCT04381936	NCT02735707	CTRI/2020/07/026791	NCT04409834
Location (s)	11 countries	Brazil, Italy, Spain and the United States	United States	United Kingdom, Indonesia, and Nepal	8 countries	India	United States
Population	Adults aged >30 with symptomatic laboratory-confirmed COVID-19 not requiring hospitalization	Patients with laboratory-confirmed SARS-CoV-2 infection who were hospitalized for COVID-19	Ambulatory patients aged 40 to 80 with newly diagnosed symptomatic SARS-CoV-2 infection with positive PCR or antigen test results	Adults clinically suspected or microbiologically confirmed COVID-19 who were admitted to hospital	Adults clinically suspected or microbiologically confirmed CVID-19 who were admitted to hospital	PCR-positive COVID-19 patients aged 40 to 75 who were hospitalized due to symptoms	Adults with acute SARS-CoV-2 infection who required ICU admission
Antiplatelet arm (s)	Aspirin (100 mg daily)	P2Y12i (different dosage based on the drug used) + heparin*	Aspirin (81 mg daily)	Aspirin (150 mg daily)	Group 1) Aspirin (75 to 100 mg daily) Group 2) P2Y12i (clopidogrel 75 mg daily; ticagrelor 60 mg loading dose followed by 5 or 10 mg daily)	Aspirin (75 mg daily)	P2Y12i: Clopidogrel (300 mg loading dose followed by 75 mg daily)
Antiplatelet duration (days)	28	14 or until discharge	45	Until discharge	14 or until discharge	10 or until discharge	Median= 8.6
Control arm	Usual care	Usual care + heparin*	Placebo	Usual care	Usual care	Usual care	Usual care
Follow-up (days)	45	90	75	28 or until discharge	90	10 or until discharge	28 or until discharge
Primary outcome of the trial	A composite of major thrombosis, hospitalization, or death	Major bleeding and composite of organ support-free days, in-hospital death, alive and free of organ support, and alive with organ support	A composite of thrombotic events, or hospitalization for cardiovascular or pulmonary cause	28-day mortality	Organ support–free days	Clinical deterioration to WHO Ordinal Scale for Clinical Improvement ≥6	A composite of thrombotic events

* Heparin was administered at its therapeutic dose.

COVID-19: coronavirus disease of 2019, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, PCR: polymerase chain reaction, ICU: intensive care unit, P2Y12i: P2Y12 inhibitors, WHO: world health organization.

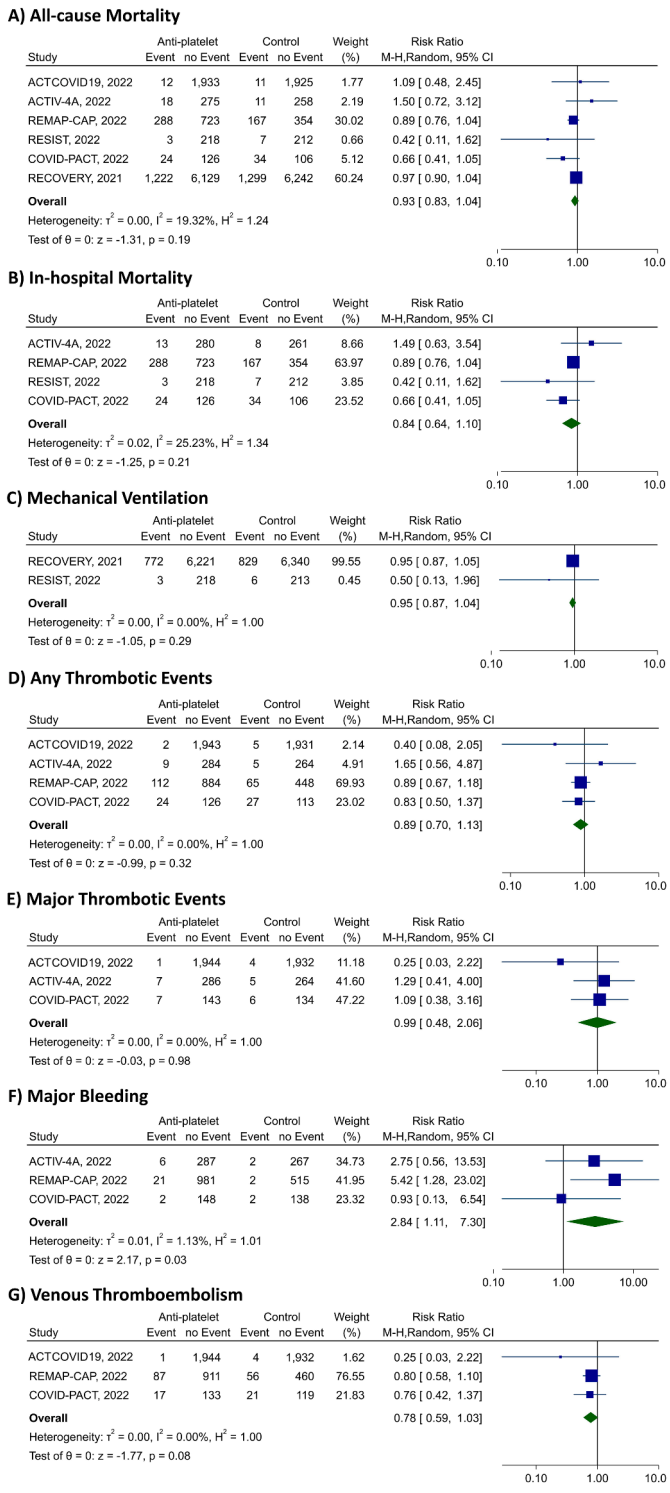

Fig. 1. Meta-analysis results for comparison of antiplatelet treatment vs. usual care in terms of A) All-cause mortality; B) In-hospital mortality; C) Mechanical ventilation; D) Any thrombotic events; E) Major thrombotic events; F) Major bleeding; and G) Venous thromboembolism.

such as cardiovascular, thromboembolic, or other reasons. Second, the limited number of trials for some outcomes could affect their generalizability, even when the overall pooled results were insignificant. Third, there was no subgroup analysis for age, gender, or other comorbidities; hence, we could not determine any result for these populations. Finally, the different dosages of aspirin and the difference in P2Y12i agents could have impacted our results.

To the best of our knowledge, this is the most comprehensive meta-analysis, consisting of seven RCTs to compare the antiplatelet medications with controls in COVID-19 patients. In conclusion, in treating COVID-19 patients, our study did not find significant benefit from adding antiplatelets in terms of mortality and other efficacy outcomes, while using P2Y12i was associated with a higher risk of MB.

Authors' contribution

AK and AHB: Study conception, design, analysis, and writing; SP: Study conception, writing, and critical revision.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.11.027.

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