Does aspirin save lives in patients with COVID-19?

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'An aspirin a day keeps the heart attack away', is this also true in the prevention of thrombotic events associated with COVID-19? The rising COVID-19 pandemic has led to much work in the understanding of the pathophysiology of the disease. COVID-19 infection is thought to be an endothelial disease. Supporting this concept, it has been suggested that infection with SARS-CoV-2, the aetiological agent for COVID-19 infection, leads to a state mimicking Virchow's triad, that is, vascular endothelial injury, blood stasis and clotting in concert with systemic inflammation resulting in systemic thrombosis.

In keeping with this concept, moderately and critically ill patients with COVID-19 have been found to have thrombotic and thromboembolic events during the acute and convalescent state. Accordingly, there has been much interest in treating patients with COVID-19 with anticoagulants. In an analysis of several large series of critically ill patients in multiple studies (534 therapeutic anticoagulation, 564 usual care thromboprophylaxis), therapeutic anticoagulation did not improve survival or the number of days free of cardiovascular or respiratory organ support. On the other hand, among 2244 non-critically ill patients (1190 therapeutic anticoagulation, 1054 thromboembolic prophylaxis), therapeutic anticoagulation improved rates of hospital survival and reduced the use of cardiorespiratory organ support.[1]

Since there is intense platelet activation secondary to endothelial injury and inflammation, there is also interest in the use of antiplatelet drugs in patients with COVID-19. Currently, recommendations for antiplatelet agents to treat or prevent COVID-19-related thrombotic events are lacking due to absence of data from prospective clinical trials. With multiple mechanisms of tissue protection besides inhibition of platelet aggregation, aspirin may have unexplored potential to treat/prevent COVID-19 complications.

To evaluate the benefit of antiplatelet therapy, Santoro *et al*[2] selected 7824 patients from the HOPE-COVID-19 registry; 730 (9.3%) received at least one antiplatelet agent (645 aspirin, 33 clopidogrel, 1 ticlopidine and 1 ticagrelor; 35 aspirin and clopidogrel, 10 aspirin and ticagrelor, 5 aspirin and prasugrel). Among 730 patients, 68% were males, 80% had a history of hypertension, 16% had cancer and 68% had an elevation of D-dimer, and in-hospital concomitant anticoagulation was administered in 66% of patients. The multivariate analysis revealed a lower mortality risk (relative risk 0.39, 95% CI 0.32 to 0.48, p<0.01) in patients receiving antiplatelet agents—principally aspirin. No difference was identified for in-hospital mortality or the use of invasive ventilation or bleeding whether patients were given antiplatelet drugs or not.

Several other investigators have evaluated the role of antiplatelet agents in patients with COVID-19 (table 1). Viecca *et al*[3] and Liu *et al*[4] demonstrated potential benefits in terms of patient mortality and severity of ventilation abnormality. The clinical outcomes measured in each of these studies varied considerably. Viecca *et al* measured A-a O_2 gradient and Liu *et al* measured concentrations of D-dimer and blood cell counts, hospital discharge rate and mechanical ventilation use to conclude that patients who received aspirin had improved outcomes. Extreme caution should be maintained while extrapolating these results to improved mortality. Russo *et al*[5] observed an insignificant decrease in mortality or risk of developing acute respiratory distress syndrome in patients given antiplatelet drugs. Sivaloganathan *et al*[6] identified no benefit in terms of mortality in patients with COVID-19, and Pan *et al*[7] observed no benefit in terms of disease severity of antiplatelet drug therapy based on the Modified Ordinal Scale (MOS). It is of note that the value of these studies is limited by small sample size, retrospective cohorts and lack of homogeneity in the outcomes measured and antiplatelet agent/s used. Furthermore, a study (preprint) by the RECOVERY collaborative group (Horby *et al*) randomised 14 892 patients with COVID-19 (7351 aspirin and 7541 usual care).[8] This is the only randomised controlled study on aspirin use in patients with COVID-19, which observed that aspirin did not reduce 28-day mortality or the risk of progressing to invasive mechanical ventilation or death. There was a small increase in the rate of being discharged alive within 28 days, bleeding risk and slight reduction in the thrombotic events and duration of hospitalisation among the aspirin group.

The findings of Santoro *et al* reported in this issue of the journal is the largest retrospective study on aspirin use among patients with COVID-19. However, there are some limitations of the study. Whether or not to give antiplatelet agent and the choice of antiplatelet agent (aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor, either with single or dual antiplatelet therapy) was at the discretion of the treating physician, and the mention of major bleeding episode relied on the diagnosis codes. All this brings in the issue of bias. The patients who are admitted are usually elderly with significant comorbidities. Administering aspirin to these patients is subjected to bias, that is, 'confounding by indication', where the real benefits or risks of aspirin may not be truly representative of the whole population.

The study by Santoro *et al* is a step in the right direction to improve the outcomes of patients with COVID-19. The use of an antiplatelet agent, mainly aspirin, might improve clinical outcomes without increasing the risk of side effects such as bleeding. Aspirin is a safe, cheap, universally available and well-tolerated medication. Using this drug in patients with COVID-19 should be encouraged unless contraindicated. Further, while the most common antiplatelet drug used in these studies was aspirin, a significant number of patients received other antiplatelet agents alone or with aspirin. Thus, it is difficult to state with certainty whether the beneficial effects were related to the use of aspirin with its multiple mechanisms of action and/or the other antiplatelet

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Table 1 Previous studies with antiplatelet drugs and outcome in patients with COVID-19

Study	Aim of the study	Population/methods	Antiplatelet agent	Results
Viecca *et al*[3]	Assess the effect of administration of antiplatelet therapy on arterial oxygenation and clinical outcomes in patients with severe COVID-19	5 patients received antiplatelet drugs/5 controls. Case–control study	25 µg/kg/body weight tirofiban as bolus infusion, followed by a continuous infusion of 0.15 µg/kg/body weight per minute for 48 hours. Before tirofiban, patients received aspirin 250 mg infusion and oral clopidogrel 300 mg; both were continued at a dose of 75 mg daily for 30 days.	Reduction in A-a O_2 gradient of −32.6 mm Hg (61.9, p=0.154), −52.4 mm Hg (59.4, p=0.016) and −151.1 mm Hg (56.6, p=0.011; p=0.047 vs controls) at 24 hours, 48 hours and 7 days after treatment, respectively. PaO_2/FiO_2 ratio increased by 52 mm Hg (50, p=0.172), 64 mm Hg (47, p=0.040) and 112 mm Hg (51, p=0.036) after 24 hours, 48 hours and 7 days, respectively.
Liu *et al*[4]	Assess the effect of dipyridamole effects in patients with COVID-19 to study concentrations of D-dimers, lymphocyte and platelet recovery in the circulation, and clinical outcomes	14 patients received antiplatelet drugs/17 controls. Case–control group.	Dipyridamole 50 mg oral three times per day for 14 consecutive days	Decreased concentrations of D-dimer (p=0.041), increased but statistically not significant lymphocyte (p=0.112) and platelet recovery (p=0.128) in the circulation, and markedly improved clinical outcomes (mechanical ventilation 14.3% vs 11.8%: discharge rate 78.6% vs 41.2%). P value not reported.
Russo *et al*[5]	Investigate the association between preadmission antiplatelet therapy and occurrence of death and ARDS in patients with COVID-19.	55 patients received antiplatelet drugs/137 controls. Case–control group.	44 (22.9 %) aspirin 5 (2.6 %) P2Y12 inhibitor, 6 (3.1 %) dual antiplatelet therapy. Dose not available.	No benefit in the risk of death. Unadjusted risk ratio=1.00 (95% CI 0.48 to 1.80), p=0.991. Adjusted risk ratio=0.51 (95% CI 0.21 to 1.15), p=0.110. No benefit for the risk of ARDS. Unadjusted risk ratio=0.81 (95% CI 0.54 to 1.28), p=0.530. Adjusted risk ratio=0.58 (95% CI 0.38 to 1.14), p=0.165.
Sivaloganathan *et al*[6]	Assess the association between preadmission antiplatelet/ anticoagulant use and COVID-19 mortality.	29 patients received antiplatelet drugs/58 controls. Case–control study.	18 (62%) aspirin, 8 (28%) clopidogrel, 3 (10%) aspirin+clopidogrel. Dose not available.	No benefit in mortality with antiplatelet drugs (p=0.516). No benefit in mortality with aspirin (p 0.62).
Pan *et al*[7]	Assess the association between pre-hospitalisation antiplatelet medication use and COVID-19 disease severity.	239 patients received antiplatelet drugs/534 controls	199 (83.3%) aspirin, 9 (3.8%) clopidogrel, 1 (0.4%) ticagrelor. (12.6%) DAPT, of which 24 (80.0%) aspirin and clopidogrel, 5 (16.7%) aspirin and ticagrelor, 1 (3.3%) aspirin and prasugrel. Dose not available.	No benefit in disease severity based on MOS. Peak MOS / OR / 95% CI 6 vs 5–2 / 1.13 / 0.70 to 1.82 6–5 vs 4–2 / 1.02 / 0.66 to 1.57 6–4 vs 3–2 / 0.98 / 0.65 to 1.46 6–3 vs 2 / 0.88 / 0.55 to 1.41
RECOVERY collaborative group[8]	Evaluate the outcomes in a randomised controlled study with aspirin and usual care among patients with COVID-19. 1:1 randomisation.	7351 usual standard of care plus 150 mg aspirin once daily until discharge. 7541 usual standard of care alone.	7351 patients 150 mg aspirin once daily.	17% in aspirin group and 17% in usual care died within 28 days (rate ratio 0.96; 95% CI 0.89 to 1.04; p=0.35). Aspirin group have shorter duration of hospitalisation (median 8 vs 9 days) and a higher proportion were discharged from hospital alive within 28 days (75% vs 74%; rate ratio 1.06; 95% CI 1.02 to 1.10; p=0.0062). Aspirin group: absolute reduction in thrombotic events of 0.6% (SE 0.4%) and an absolute increase in major bleeding events of 0.6% (SE 0.2%).

ARDS, acute respiratory distress syndrome; DAPT, dual antiplatelet therapy; MOS, Modified Ordinal Scale.

agents with selective antiplatelet effects.

Correction notice The following sentence has been corrected since it was first published: "The multivariate analysis revealed a lower mortality risk (relative risk 0.39, 95% CI CI 0.32 to 0.48, p<0.01)".

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