Antiplatelet Therapy in Patients With COVID-19—More Is Less?
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Because venous and arterial thromboembolism are common among patients hospitalized with COVID-19,1,2 anticoagulant therapies were among the first to be evaluated in clinical trials to improve outcomes in moderately ill patients hospitalized with COVID-19. These studies have yielded thus far somewhat mixed results, varying from beneficial effects of therapeutic doses of low-molecular-weight heparin in the ATTACC, ACTIV-4a, and REMAP-CAP trials3 to no difference between therapeutic and prophylactic doses of low-molecular-weight heparin in the INSPIRATION, ACTION, and RAPID trials.4-6 Therefore, it remains to be determined whether the addition of antiplatelet therapy will yield different results.

Although platelets are thought to play a pivotal role in COVID-19-related hypercoagulability,7 the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed no obvious benefit of aspirin added to standard thromboprophylaxis or anticoagulant therapy in hospitalized patients with COVID-19.8 Nevertheless, other antiplatelet drugs, such as P2Y12 inhibitors, may have more potent platelet inhibiting properties and have been linked to certain anti-inflammatory effects.9

In this issue of JAMA, Berger and colleagues10 report the results of the ACTIV-4a clinical trial. In this open-label, international, multicenter, randomized clinical trial, patients were randomly assigned in a 1:1 ratio to receive a therapeutic dose of heparin plus a P2Y12 inhibitor or a therapeutic dose of heparin only (usual care) and were stratified by hospital site and severity of illness. Ticagrelor was the preferred P2Y12 inhibitor, but clopidogrel and prasugrel were allowed. Duration of P2Y12 inhibitor therapy was 14 days or until hospital discharge. The current study described the analyses for the non–critically ill participants after the data safety and monitoring board stopped the trial early for this patient category based on futility. The enrollment of critically ill patients is still ongoing.

Non–critically ill patients were enrolled if they were hospitalized for COVID-19 and met 1 of the following criteria: elevated D-dimer level (≥2-fold the upper limit of normal) or aged 60 to 84 years. Patients younger than 60 years could be enrolled if they met at least 1 of the following criteria: had a need for oxygen greater than 2 L per minute or had hypertension, diabetes, chronic kidney disease, cardiovascular disease, or a body mass index of 35 or greater. Altogether, 562 patients from 60 hospital sites (mean age, 52.7 years; 41.5% women; and 87% received a therapeutic dose of heparin) were randomized and they all completed the trial. The investigators found no significant differences in the primary outcome (a composite of organ support–free days evaluated on an ordinal scale combined with in-hospital death; for survivors, the number of days free of respiratory or cardiovascular organ support), in the secondary outcome (a composite of major thrombotic events or death by 28 days), or in the primary safety outcome (major bleeding as defined by International Society on Thrombosis and Hemostasis). The median number of organ support–free days was 21 days in both the P2Y12 inhibitor group (IQR, 20-21 days) and in the usual care group (IQR, 21-21 days). The odds ratio (OR) for the effect of a P2Y12 inhibitor on organ support–free days was 0.83 (95% credible interval, 0.55-1.25), yielding a posterior probability of futility of 96%. Major bleeding occurred in 6 participants (2.0%) in the P2Y12 inhibitor group vs 2 participants (0.7%) in the usual care group (adjusted OR, 3.31 [95% CI, 0.64-17.2]).

During the first 28 days, death or need for organ support occurred in 75 participants (26%) in the P2Y12 inhibitor group vs 58 participants (22%) in the usual care group (adjusted hazard ratio, 1.19 [95% CI, 0.84-1.68]; P = .34). The key secondary outcome of major thrombotic events or death occurred in 18 participants (6.1%) in the P2Y12 inhibitor group vs 12 participants (4.5%) in the usual care group (adjusted OR, 1.42 [95% CI, 0.64-3.13]).

After being reassured by the design and adequate statistical analysis plan, in which monthly adaptive analyses of the data were performed to determine superiority or futility, what conclusions can be drawn from these null results? First, and as suggested by the investigators, it is possible that P2Y12 inhibition in moderately ill patients with COVID-19 is of no additional benefit to therapeutically dosed heparin. Moreover, it seems quite ambitious to expect improvement on a composite outcome of in-hospital death and organ support–free days, which has a multifactorial origin that is not expected to be substantially driven by platelet reactivity; however, there is also no signal of benefit for thrombotic outcomes, suggesting little added antithrombotic effect with antiplatelet therapy.

In this study, the median duration of use with a P2Y12 inhibitor was 6 days (IQR, 4-8 days), which may not be sufficient to observe beneficial effects. Given the short lifespan of platelets (7-9 days) and the fact that COVID-19–associated platelet activation may have already reached a maximum level by the time of hospital admission, it might be plausible that the timing of administration of the antiplatelet therapy was too late. This would explain why observational studies in patients using antiplatelet therapy prior to hospitalization showed an association with lower mortality in hospitalized patients with COVID-19.11

Platelet activation not only drives thrombosis, but also can mediate inflammation.12 Hence, antiplatelet therapy may be beneficial by attenuating 2 aspects of the thromboinflammatory phenotype in COVID-19.13 However, it is unclear whether
current antplatelet agents could achieve anti-inflammatory actions by reducing platelet activation, or through other, distinct mechanisms directly interfering with inflammatory pathways.12 This is of particular interest because neither aspirin nor P2Y12 inhibitors, both mainly inhibiting autocrine activation of platelets, appear to be effective in COVID-19.8,10 This instigates the question whether any antplatelet agent, in doses commonly used and with large variation in metabolite concentrations in case of clopidogrel (used in 37% of patients in the ACTIV-4a trial) due to genetic variation in metabolism, as well as potential interactions with agents like remdesivir, would be able to attenuate any of the pathogenic inflammatory pathways in COVID-19.

The coagulopathy in COVID-19 is characterized by high blood fibrinogen levels.14 Conceptually, glycoprotein IIb/IIIa inhibitors (such as abciximab, eptifibatide, or tirofiban) could be more effective because they directly interfere with platelet aggregation via the fibrinogen bridge. Other novel inhibitors, such as the P-selectin inhibitor crizanlizumab, part of the ACTIV-4a and Crizanlizumab for Treating COVID-19 Vasculopathy (CRITICAL; NCT04435184) study protocol, and the Glenozocimab in SARS-CoV-2 Acute Respiratory Distress Syndrome Related to COVID-19 (GARDEN; NCT04659109) trial are currently tested in clinical trials of which the results are awaited. P-selectin inhibition is of interest because it targets both the activated platelet and endothelium, thereby potentially providing more effective protection against microvascular thrombosis.7 Glycoprotein VI inhibition may be promising because of its postulated antithrombotic potency, while leaving hemostasis largely unaffected.15 This specific drug property makes it worthwhile to further investigate glycoprotein VI inhibitors as add-on antplatelet therapy because it may have a more favorable risk-benefit ratio in terms of bleeding risk compared with other antplatelet therapies. This is of particular interest given the 3-fold increased risk of major bleeding without any reduction in thrombotic events in the current P2Y12 trial.10 Moreover, all clinical trials thus far have consistently reported an increased bleeding risk, regardless of whether additional therapies or dose escalation over standard thromboprophylaxis were investigated.2-6,8

In conclusion, although excitement had surrounded the signals of benefit of anticoagulant therapy, there is a clear unmet need for additional therapies that further improve clinical outcome in patients with COVID-19. Based on pathophysiological insights, platelets may still represent a promising therapeutic target in COVID-19. Nevertheless, the results reported by Berger et al16 in this issue of JAMA demonstrate that in moderately ill hospitalized patients with COVID-19, additional P2Y12 inhibition did not improve outcome. Therefore, while awaiting the current trials, further studies should explore the role of other antplatelet agents, which may potentially also target some of the pathogenic inflammatory pathways, and also may have a favorable risk-benefit ratio that provides protection without further compromising the individual patient’s bleeding risk.

**REFERENCES**


**ARTICLE INFORMATION**

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