Thromboinflammation and Antithrombotics in COVID-19
Accumulating Evidence and Current Status
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Thrombotic complications of SARS-CoV-2 infection were recognized early in the pandemic, when infected patients often presented with abnormal coagulation findings and acute macrovascular obstruction, and evidence of pulmonary microvascular thrombosis was identified on autopsy.\(^1\)\(^3\) The inflammatory response to SARS-CoV-2 infection commonly results in marked activation of coagulation— the process of thromboinflammation—with evidence of systemic endothelial damage and a resultant loss of normal anticoagulant properties.\(^3\)\(^4\) In this milieu of acute endothelial dysfunction and coagulopathy, platelets are hyperreactive with increased responsiveness to activation stimuli, have altered gene expression profiles, and present phenotypic changes indicative of abnormal platelet-leukocyte interactions.\(^5\)\(^6\) Given this situation, multiple randomized trials were initiated early in the pandemic to address the platelet-mediated consequences of COVID-19. Yet, while the rationale for adding antithrombotic therapy to anticoagulation was compelling, 3 recent clinical trials that addressed the potential utility of aspirin or P2Y12 inhibitors among COVID-19 inpatients as well as 1 trial of COVID-19 outpatients do not support this approach.

First, in the RECOVERY open-label platform trial\(^7\) conducted in the United Kingdom, Indonesia, and Nepal, 14,892 hospitalized patients with COVID-19 were randomly allocated to receive aspirin plus usual care or usual care alone. Most hospitalized participants in RECOVERY were not critically ill, and virtually all were receiving anticoagulation therapy at the time of randomization (34% high-dose low-molecular-weight heparin and 60% standard-dose low-molecular-weight heparin). At 28 days, mortality was 17% in both the aspirin and usual care groups (rate ratio, 0.96; 95% CI, 0.89-1.04; \(P = .38\)), with an increased risk of hemorrhage among those randomized to adjunctive antithrombotic therapy (1.6% vs 1.0%).

Second, in the ACTIV-4a trial\(^8\) conducted in the United States, Brazil, Italy, and Spain, 562 non–critically ill patients hospitalized for COVID-19 were randomly allocated to receive therapeutic heparin alone or therapeutic heparin plus a P2Y12 inhibitor (63% ticagrelor and 37% clopidogrel). Using a bayesian analysis structure, the trial was terminated for futility because the prespecified primary end point of organ support–free days was 21 in both treatment groups (96% posterior probability of futility, defined as an odds ratio <1.2). Major bleeding occurred among 6 participants taking a P2Y12 inhibitor plus heparin compared with 2 participants taking heparin alone.

Third, as reported in this issue of JAMA,\(^9\) the REMAP-CAP Investigators undertook a complex bayesian platform adaptive design trial in which critically ill patients with COVID-19 who were receiving anticoagulation therapy were randomly allocated to receive aspirin (at doses between 75 mg and 100 mg; \(n = 565\)), to receive 1 of 3 P2Y12 inhibitors (clopidogrel, 75 mg; ticagrelor, 60 mg; or prasugrel, 60 mg; \(n = 455\)), or to open control (\(n = 529\)). The primary end point was organ support–free days through day 21, and decisions regarding antithrombotic therapy after 14 days were at the discretion of treating clinicians.

Following the observation of equivalence between the aspirin and P2Y12 inhibitor groups of the trial (odds ratio, 1.00; 95% credible interval, 0.86-1.23; >90% posterior probability of equivalence), the 2 antithrombotic treatment groups were pooled for comparison with open control. In this subsequent adaptive pooled analysis, the median number of organ support–free days was 7 in both the antithrombotic and control groups (adjusted odds ratio for the effect of antithrombotic therapy compared with control, 1.02; 95% credible interval, 0.86-1.23; 95.7% posterior probability of futility). While the authors report a modest benefit on the secondary end point of in-hospital mortality, the median organ support–free days were again equal (14 days) among survivors in both trial groups. Yet, consistent with data among less critically ill patients in RECOVERY, antithrombotic therapy in critically ill REMAP-CAP participants resulted in a small but certain increase in risk of major bleeding (2.1% vs 0.4%; adjusted odds ratio, 2.97; 95% credible interval, 1.23-8.28; with a posterior probability of harm exceeding 99%).

Fourth, the US ACTIV-4B trial\(^10\) of 657 symptomatic outpatients with COVID-19 was stopped early because of unanticipated low event rates and no evidence of efficacy when comparing 81 mg of aspirin with placebo. ACTIV-4B also found no evidence of efficacy in comparisons of placebo with either prophylactic-dose or therapeutic-dose apixaban, although apixaban was associated with increased hemorrhage.

What are clinicians to make of these 4 well-conducted trials, each of which demonstrated a net hazard when antithrombotic treatments were added to anticoagulation alone? First and foremost, the accumulated data should provide physicians with the rare confidence to do less rather than more, a finding that also has become apparent with anticoagulation therapy.

For example, several trials among critically ill patients with COVID-19 have reported no net benefit of therapeutic-dose or intermediate-dose anticoagulation compared with standard prophylactic heparin alone using end points that assessed progression of COVID-19.\(^11\)\(^-\)\(^13\) In moderately ill patients, therapeutic-dose compared with prophylactic-dose anticoagulation resulted in a net clinical benefit of 3% with no difference in mortality in 1 trial of 2219 patients,\(^14\) while
in another trial of 465 patients,\textsuperscript{15} there was no benefit of therapeutic-dose anticoagulation compared with standard-dose anticoagulation for the primary composite end point of death, mechanical ventilation, or admission to the intensive care unit by 28 days. Identifying the characteristics of moderately ill patients who might benefit from therapeutic-dose heparin is currently being investigated.

In contrast, when evaluated for the end point of venous thromboembolism prevention rather than for COVID-19 progression, 1 trial of 253 patients has shown benefit for therapeutic-dose compared with standard-dose anticoagulation among selected hospitalized patients\textsuperscript{16} and a second trial of 318 patients has demonstrated higher efficacy of prophylactic anticoagulation compared with no therapy among selected patients following hospital discharge.\textsuperscript{17} Another ongoing trial of anticoagulants with and without the addition of antiplatelet agents is being conducted among hospitalized patients (with a goal of 750 patients) and is focused on thrombotic events and all-cause mortality rather than on COVID-19 progression (COVID-PACT; NCT04409834).

As Bernard Lown\textsuperscript{18} stated, “Do as much as possible for the patient, and as little as possible to the patient.” At this juncture in the global pandemic, all hospitalized patients with COVID-19 and low risk of bleeding should receive at least prophylactic-dose anticoagulation with a heparin anti-coagulant, with consideration of therapeutic-dose heparin in some cases, but there is no proven efficacy supporting the addition of traditional antiplatelet therapies to prevent progressive thromboinflammatory complications of COVID-19. Nontraditional targeting of alternative platelet function pathways with agents like crizanlizumab, a P-selectin inhibitor (NCT04435184), or gENCZomib, a platelet glycoprotein VI inhibitor (NCT04659109), is under investigation. The clinical goal, however, should be to avoid thromboinflammation and hospitalization in the first place, an objective largely achievable through aggressive vaccination.

ARTICLE INFORMATION

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