Antithrombotic Therapy for Outpatients With COVID-19
Implications for Clinical Practice and Future Research

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**COVID-19**, the infectious disease caused by the SARS-CoV-2 virus, has been associated with an inflammatory and hypercoagulable state characterized by increases in levels of D-dimers, fibrin, fibrin degradation products, and fibrinogen.\(^1\) Observational studies suggest that elevations in levels of these markers translate into increased rates of mortality and thromboembolic events.\(^2,3\) These findings motivated the design and conduct of several randomized clinical trials aimed at evaluating the efficacy and safety of antithrombotic regimens in patients with COVID-19.\(^4\)

Compared randomized clinical trials of antithrombotic therapies have focused on both critically ill and noncritically ill patients with COVID-19. In critically ill patients, therapeutic-dose anticoagulation with heparin did not improve clinical outcomes and was associated with an excess risk of major bleeding events when compared with routine prophylactic heparin.\(^5\) Trials in moderately ill patients with COVID-19 have reached mixed results. In the international, adaptive, multiplatfor randomized clinical trial that combined data from the ACTIV-4a, REMAP-CAP, and ATTACC studies,\(^6\) therapeutic-dose heparin or low-molecular-weight heparin increased the probability of survival until hospital discharge with a reduced need for organ support when compared with usual-care thromboprophylaxis. Conversely, the ACTION,\(^7\) INPIRATION,\(^8\) and RAPID\(^9\) trials found no difference between the therapeutic-dose and prophylactic-dose groups in the primary outcome.

In all trials, intermediate or therapeutic doses of antithrombotic drugs were also associated with increased risk of bleeding events when compared with prophylactic doses. Therefore, the optimal anticoagulation regimen for noncritically ill patients with COVID-19 remains to be determined. Preliminary findings from the RECOVERY trial\(^10\) indicate that aspirin does not improve survival in patients hospitalized with COVID-19. The role of other antiplatelet agents for patients with COVID-19 is unclear.

In outpatients with COVID-19, the risks and benefits of anticoagulants and antiplatelet agents have not been established. This represents an important clinical question, because outpatients comprise the largest population of individuals infected with SARS-CoV-2. Moreover, considering the uneven global vaccination rates, a large part of this population remains at risk for COVID-19. Few effective therapies are available to prevent disease progression among patients with COVID-19 who are not hospitalized.

In this issue of *JAMA*, Connors and colleagues\(^11\) report the results of the ACTIV-4B Outpatient Thrombosis Prevention Trial. This randomized, adaptive, double-blind, placebo-controlled trial involved minimal face-to-face interactions with the participants. The study was conducted as part of the National Heart, Lung, and Blood Institute (NHLBI) ACTIV platform of trials at 52 sites in the US. Participants were randomly assigned in a 1:1:1:1 ratio to receive aspirin (81 mg orally once daily), prophylactic-dose apixaban (2.5 mg orally twice daily), therapeutic-dose apixaban (5 mg orally twice daily), or matching placebo for 45 days. The trial originally planned to include a total of 7000 symptomatic, clinically stable outpatients with COVID-19. Nevertheless, because of lower than anticipated primary event rates, the trial was stopped early by the independent data monitoring committee (DMC) after only 657 participants were enrolled. The median age of included participants was 54 years (IQR, 46-59), 59.1% were women, and 12.7% self-identified as Black and 28.1% as Hispanic. Therefore, the trial included a relatively young population, the majority of which did not have cardiovascular risk factors (35.3% had a history of hypertension and 18.3% had diabetes). The median time from diagnosis to randomization was 7 days, and the median time from randomization to initiation of study medications was 3 days.

The primary adjudicated outcome was a composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary causes. The primary efficacy and safety analyses were restricted to participants who received at least 1 dose of trial medication (558 patients). The authors found that the absolute risk reductions compared with placebo for the primary outcome were 0.0% (95% CI not calculable) in the aspirin group, 0.7% (95% CI, −2.1% to 4.1%) in the prophylactic-dose apixaban group, and 1.4% (95% CI, −1.5% to 5.0%) in the therapeutic-dose apixaban group. There were no major bleeding events reported during the trial. The absolute risk differences compared with placebo for clinically relevant nonmajor bleeding events were 2.0% (95% CI, −2.7% to 6.8%) in the aspirin group, 4.5% (95% CI, −0.7% to 10.2%) in the prophylactic-dose apixaban group, and 6.9% (95% CI, 1.4% to 12.9%) in the therapeutic-dose apixaban group. Findings were similar for the efficacy and safety analyses that included all randomized patients.

The ACTIV-4B Outpatient Thrombosis Prevention Trial is the first study to provide reliable information about the effects of antithrombotic therapy in outpatients with COVID-19. Strengths of the trial were the low risk of bias (concealed randomization and blinding of patients, investigators, caregivers, and outcome assessors), surveillance for the
identification of potential efficacy and safety events, and careful adjudication of outcomes. A limitation that merits consideration is related to the low number of events and the consequent limited statistical power. Only 5 suspected primary efficacy outcomes and no deaths occurred during the trial treatment period. In addition, the trial included few participants who were vaccinated or infected with the delta variant or other recent COVID-19 variants. These factors limit the generalizability of the trial findings.

What are the main implications of the ACTIV-4B Outpatient Thrombosis Prevention Trial? First, the trial results may help to inform treatment decisions in clinical practice. Given the null results for major cardiovascular and pulmonary events, currently, the use of aspirin or apixaban for symptomatic but stable ambulatory patients with COVID-19 does not seem justifiable. Second, findings from ACTIV-4B Outpatient Thrombosis Prevention Trial provide useful insights for the conduct of trials of antithrombotic therapy in outpatients with COVID-19. A recent review found that at least 10 randomized clinical trials are underway in this setting. These studies are testing interventions such as antplatelet agents, direct oral anticoagulants, and standard prophylactic doses of low-molecular-weight heparins. Most studies are open-label, and the sample sizes are variable. The most typical primary outcomes are either need for hospitalization or a composite of major cardiopulmonary outcomes. The lower than anticipated event rates observed in the ACTIV-4B Outpatient Thrombosis Prevention Trial should prompt steering committees and independent data monitoring committees of ongoing trials to review issues like statistical power, outcome choices, recruitment feasibility, and even futility.

Early observations from clinical practice and promising results from nonrandomized studies led many physicians to use therapeutic-dose anticoagulants and antplatelet agents for a variety of patients with COVID-19, including stable outpatients. Nevertheless, even during a pandemic, well-designed and adequately powered randomized clinical trials are needed to establish the benefits and risk of therapies. Research efforts like the National Heart, Lung, and Blood Institute ACTIV platform of randomized trials constitute evidence that such collaborative studies are feasible despite the multiple challenges associated with a pandemic such as COVID-19. A key element for the success of these initiatives is related to their innovative, pragmatic, and decentralized trial design. In this sense, features like minimal in-person contacts, electronic informed consent, direct shipment of study drug to participants’ homes, and patient-reported outcomes enable a more efficient trial conduct. In addition, decentralization broadens trial access to reach a larger and more diverse population. Lessons learned from the successful implementation of these innovative trial models represent an important legacy for research not only in COVID-19 or future pandemics but also for studies in cardiovascular disorders, cancer, and other common conditions.

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REFERENCES