Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Anticoagulation in COVID-19: reaction to the ACTION trial

See Articles page 2253

Early in the COVID-19 pandemic, it became clear that coagulopathy leading to macrovascular and microvascular thrombotic events was a considerable potential complication for patients with COVID-19.[1] Increased inflammation and coagulopathy were independently associated with critical illness and all-cause mortality and had a synergistic role in the pathogenesis of COVID-19.[2] Early observations of a benefit from heparin[3] in a selected cohort of severely ill patients with COVID-19 in China, followed by reports of increased thromboembolic events in patients with COVID-19 (both in and outside of intensive care units [ICUs]) despite the use of standard-dose venous thromboembolism prophylaxis,[4,5] led many physicians to use increased anticoagulant doses, even without robust data available.[6] Autopsy findings, showing widespread pulmonary microvascular thrombosis, suggested that the hypoxaemia and respiratory failure in COVID-19 resulted from microvascular thrombosis.[7,8] A need to further understand these findings and the potential role of anticoagulation in this context prompted new research.

Among these studies, three platforms—ACTIV-4a, ATTACC, and REMAP-CAP—joined forces to evaluate therapeutic-dose versus prophylactic-dose heparin in hospitalised patients with COVID-19. In December, 2020, this multiplatform randomised clinical trial paused enrolment into the severe COVID-19 stratum (ie, patients receiving ICU level of care) because of futility,[9] and a month later terminated enrolment into the moderate COVID-19 stratum (ie, hospitalised patients not receiving ICU level of care) for superiority. In patients with moderate disease, regardless of D-dimer concentration, therapeutic anticoagulation decreased the number of days on organ support.[10] These seemingly discrepant results suggested that therapeutic heparin worked best when started early in the disease course, before patients became critically ill.

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In *The Lancet*, Renato Lopes and colleagues[11] report the results of the ACTION trial of therapeutic versus prophylactic anticoagulation for patients hospitalised with COVID-19. 615 patients (mean age 56·6 years [SD 14·3]; 368 [60%] men and 247 [40%] women) admitted to hospitals in Brazil with confirmed COVID-19 and elevated D-dimer concentration were randomly assigned to either a therapeutic or a prophylactic anticoagulation strategy. The therapeutic strategy (311 patients) was either therapeutic-dose rivaroxaban (20 mg or 15 mg daily) with extended post-discharge rivaroxaban (20 mg daily) up to 30 days, if clinically stable; or enoxaparin (1 mg/kg twice per day) or unfractionated heparin in hospital, if clinically unstable. 280 (90%) patients in the therapeutic group were given rivaroxaban. The prophylactic anticoagulation strategy (304 patients) consisted of standard-of-care inpatient enoxaparin or unfractionated heparin at a prophylactic dose, and 38 (13%) also received heparin for 30 days post discharge at the treating physician's discretion. The median time from symptom onset to hospital admission was 8·0 days (IQR 6·0–10·0) and from hospital admission to randomisation was 2·0 days (1·0–3·0). 460 (75%) patients required oxygen support and 510 (83%) were receiving systemic corticosteroids at baseline.

The primary outcome was a hierarchical analysis of time to death, duration of hospitalisation, or duration of supplemental oxygen use through 30 days, conducted with the win ratio method. This method, a novel approach to the analysis of composite endpoints in clinical trials based on clinical priorities,[12] compares treatment assignment between every patient in both groups to identify a "winner" on the basis of prespecified criteria. This method accounts for relative

priorities of the composite endpoint by prioritising fatal outcomes, allowing for enhanced statistical power. The therapeutic anticoagulation group had 34·8% wins, versus 41·3% wins in the prophylactic group (win ratio 0·86 [95% CI 0·59–1·22], p=0·40). Risk of a secondary composite outcome of thromboembolic events was not significantly different in the therapeutic group versus the prophylactic group (relative risk 0·75 [95% CI 0·45–1·26], p=0·32), nor was all-cause death (1·49 [0·90–2·46], p=0·13). However, risk of the primary safety outcome, major or clinically relevant non-major bleeding, was significantly higher (3·64 [1·61–8·27], p=0·0010) in the therapeutic group (26 [8%] of 310 patients) than in the prophylactic group (seven [2%] of 304).

The Brazilian investigators from the ACTION trial deserve recognition for conducting this important trial that contributes new information for the management of patients with COVID-19. A strategy of inpatient and post-discharge therapeutic rivaroxaban is not superior to inpatient-only use of prophylactic heparin, highlighting that the choice of drug, dose, and timing of anticoagulant are important. Whether improvements in care, with systemic corticosteroids and antivirals, have mitigated thromboinflammation is also unclear. Similarly, criteria for admission to the hospital might vary from region to region and during different stages of the pandemic, affecting risk of both thrombotic and fatal outcomes. Although the previous multiplatform trial used therapeutic heparin, ACTION used rivaroxaban in 92% of patients in the therapeutic group. Heparin, unlike other anticoagulants, has anti-inflammatory and possibly direct antiviral effects.[13] It is also possible that the 20 mg dose of rivaroxaban is suboptimal in patients hospitalised with the highly coagulopathic thromboinflammation of SARS-CoV-2 infection driving microvascular thrombosis, as 15 mg twice per day is used for acute treatment of venous thromboembolism; however, bleeding was already markedly increased. The additional 30 days of anticoagulation post discharge might be of no benefit and only cause harm in patients with COVID-19 who have cleared the virus and survived to hospital discharge. A dedicated randomised trial is ongoing in the post-discharge population (NCT04650087).

The results of ACTION add important information on how best to treat patients with COVID-19. In these primarily stable hospitalised patients, therapeutic dose rivaroxaban in hospital with post-discharge treatment up to 30 days conferred no additional benefit when compared with in-hospital prophylactic-dose heparin. Although COVID-19 outcomes have improved over time, 15% of patients in ACTION still had either a thrombotic event or died. Continued investigation with randomised controlled trials assessing the use of anticoagulants and antiplatelets and the timing of administration during the course of COVID-19 are much needed.

JSB is a principal investigator for the ACTIV4a randomised controlled trial investigating antithrombotic therapy in adults with COVID-19 requiring hospitalisation, and has received research funding to his institution from AstraZeneca for investigating ticagrelor in rheumatoid arthritis and peripheral artery disease. JSB has received personal fees for consulting from Amgen and from Janssen, outside the area of work commented on here, and payments for expert testimony from Saxton on the work-up of ischaemic stroke. JMC is the principal investigator for the ACTIV4b randomised controlled trial investigating antithrombotic therapy in adults with COVID-19 not requiring hospitalisation; has received personal fees from Bristol-Myers Squibb (for scientific advisory board membership), Abbott (for scientific advisory board membership and consulting), Alnylam (for consulting), Five Prime Therapeutics (for consulting), Portola (for scientific advisory board membership), and Pfizer (for scientific advisory board membership), and Data Safety and Monitoring Board membership for Abbott, Bristol-Myers Squibb, Pfizer, Portola, and Takeda, all outside the area of work commented on here; and has received research funding to the institution from CSL Behring, outside the area of work commented on here.

*Jeffrey S Berger, Jean Marie Connors
jeffrey.berger@nyulangone.org

Center for the Prevention of Cardiovascular Disease, New York University School of Medicine, New York, NY 10016, USA (JSB); New York University Langone Health, New York, NY, USA (JSB); Brigham and Women's Hospital, Boston, MA, USA (JMC)

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Widespread diabetes screening for cardiovascular disease risk estimation

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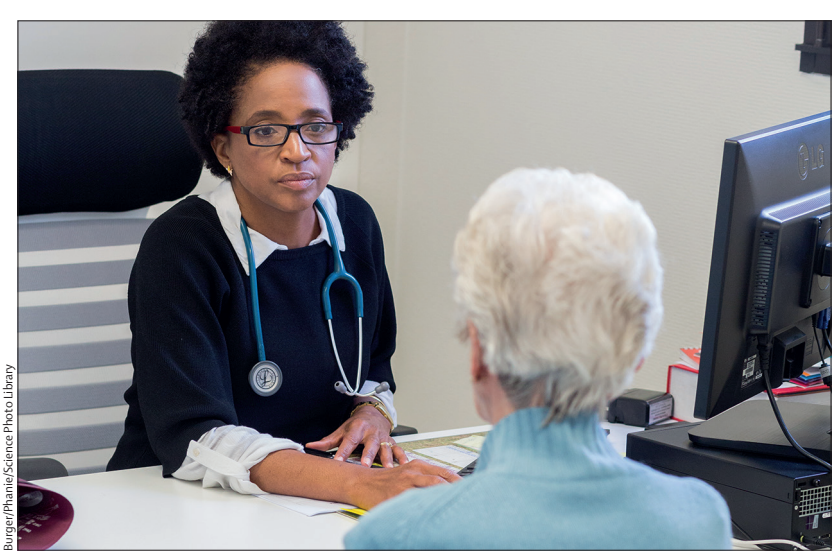
See **Articles** page 2264

Estimating an individual's future absolute cardiovascular disease risk helps balance the anticipated benefit with the potential harm from overtreatment for cardiovascular disease risk factors.[1] However, current cardiovascular disease risk estimation tools can overestimate[2] or underestimate[3] risk due to multiple factors (eg, treatment recommendations change over time, newer treatments might be more effective, and risk factors trend toward higher [obesity] or lower [smoking] cardiovascular disease risk). Nonetheless, a characteristic of these flawed risk estimates is that the relationship between a score's risk factors and cardiovascular disease differs between the observed population and the score's derivation cohort.

Estimation of cardiovascular disease risk is being widely used throughout the world, and as the calculation requires determination of the diabetes status, increasingly more adults are being screened for diabetes. However, nearly half of people who have diabetes remain undiagnosed, particularly in Africa, southeast Asia, and the western Pacific,[4] making calculation of accurate risk scores challenging in these populations. By contrast, in parts of the world that have adopted enhanced diabetes screening for cardiovascular disease risk calculation, risk estimation among people with diabetes is shifting towards those who are considered to be healthier (with respect to younger age, less hypertension, and less hypercholesterolaemia), as more people are being diagnosed with diabetes before they become symptomatic, and thus before the stage associated with increased cardiovascular disease risk.[5] Thus, cardiovascular disease risk scores derived in populations that relied on clinically diagnosed diabetes rather than screening diagnosed diabetes might overestimate cardiovascular disease risk. In fact, in the Multi-Ethnic Study of Atherosclerosis, diabetes was among the risk factors that were associated with risk overestimation in a single-variable analysis.[2]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Since the early 2000s, the New Zealand Ministry of Health has recommended the use of cardiovascular disease risk prediction to inform preventive treatment decisions, and that recommendation resulted in an increase in screening for diabetes status. However, in 2012, only 50% of eligible adults had been screened for diabetes. Therefore, New Zealand created a new national initiative to increase screening for diabetes in the eligible population, which replaced fasting blood glucose with non-fasting glycated haemoglobin (HbA_{1c}) as the recommended screening test. By September, 2016, the programme met its goal of diabetes screening in 90% of the eligible population.

In *The Lancet*, Romana Pylypchuk and colleagues evaluated the impact of widespread diabetes