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.

vaccine effectiveness in terms of protection against actual infection; instead, effectiveness was inferred from immunogenicity. Cellular immunity was only studied in 60% of the participants, and aspects of memory B and T cell response are beyond the scope of this study, although staining of intracellular cytokines during preliminary flow cytometry of T cells indicated that heterologous vaccines favoured a T-helper-1 response.

Overall, the paper is dense with data and the results are important and highly relevant to current vaccination programmes. Schedules containing at least one mRNA dose produced the highest neutralising antibody responses, with BNT/m1273 generating a greater humoral immune response than the homologous BNT/BNT schedule, probably reflecting the higher mRNA content in the m1273 vaccine. Mixed vaccines should be recognised for certification during travel, and heterologous vaccination could enhance deployment of vaccines in poorer regions of the world. It also remains to be seen how effective the heterologous vaccines are in preventing disease or reinfection against newer variants, such as the Omicron variant (B.1.1.529).

I declare no competing interests.

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Anticoagulation in COVID-19

Published **Online**
December 15, 2021
https://doi.org/10.1016/S0140-6736(21)02503-4

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Thrombotic complications (arterial and venous) are common in patients admitted to hospital with COVID-19 and are an independent predictor of poor outcome.[1] Microvascular thrombi also contribute to organ dysfunction, including acute respiratory distress syndrome. The pathogenesis of thrombosis in COVID-19 is intimately linked with the inflammatory response to the virus, endothelial infection, activation, and injury as well as hypercoagulability.[2] Recognition that thrombosis is a key contributor to clinical deterioration and death has led to global interest in whether escalated anticoagulation dose or extended duration improves patient outcomes. Early in the COVID-19 pandemic, published guidelines were heterogeneous with some, in the absence of evidence, recommending increased anticoagulation doses (particularly in critical care), stratifying dose by D-dimer results, or extended post-discharge thromboprophylaxis, or both.[3] Since then, randomised controlled trials have focused on all phases of illness—from the community, to hospital admission, when critically ill, and post-hospital discharge—so that high-quality evidence is now informing clinical practice. From these trials, it has become clear that efficacy and safety of antithrombotic treatments depend on timing with respect to illness severity and dose, and that the mechanism of action might also be important.

For non-critically ill patients hospitalised with COVID-19, therapeutic-dose heparin appears beneficial, with a high probability of reducing the need for organ support and the progression to intubation and death, regardless of D-dimer results.[4] Results from two subsequent randomised controlled trials

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have also supported the role of therapeutic-dose heparin in this cohort.[5,6] By contrast, in critically ill patients, therapeutic-dose heparin did not improve outcomes and there was a high probability of harm.[7] The INSPIRATION trial did not demonstrate benefit of intermediate-dose heparin compared with conventional low dose in this critically ill patient group.[8]

An area of ongoing uncertainty is the role of extended duration of anticoagulation post-hospital discharge.[9] For this phase of treatment, if required, an oral anticoagulant is preferable to parenteral anticoagulant to facilitate timely hospital discharge and for patient convenience. In unselected patients hospitalised with COVID-19, reported venous thromboembolism (VTE) rates post-hospital discharge were low,[10,11] which when coupled with bleeding risk,[12] cast doubt as to whether post-discharge thromboprophylaxis was warranted. Additionally, a systemic review and meta-analysis[13] of studies on the thrombotic and bleeding risk associated with COVID-19 showed that thrombotic events occurred earlier after hospital admission than bleeding events (median 7·0 days [IQR 5·9–8·2] *vs* 11·4 days [8·6–14·1] after admission) and the authors suggested avoiding extended duration, therapeutic-dose anticoagulation. In the ACTION trial, therapeutic-dose rivaroxaban (in hospital and post discharge) for 30 days was not superior to prophylactic-dose heparin (mostly in hospital only) and was associated with higher risk of bleeding.[14]

Now in *The Lancet*, Eduardo Ramacciotti and colleagues report the results of the MICHELLE trial,[15] which addresses the role of extended duration rivaroxaban post discharge. In the MICHELLE trial, the mean age of patients was 57·1 years (SD 15·2), 127 (40%) were women, 191 (60%) were men, and the mean body-mass index was 29·7 kg/m² (SD 5·6). Unlike the ACTION trial, patients received standard heparin thromboprophylaxis in hospital and were then randomly assigned (1:1) to receive low-dose rivaroxaban (10 mg once per day for 35 days) post discharge or no anticoagulation. The eligibility criteria meant only patients at high VTE risk were included (inpatient ≥3 days, IMPROVE VTE score of ≥4 or 2–3 with D-dimer >500 ng/mL). More than half (165 [52%]) of the 318 randomly assigned patients were in the intensive care unit or cardiac care unit during hospitalisation (associated with VTE risk). Patients with risk factors for bleeding, such as thrombocytopenia and severe renal failure, were excluded. The primary efficacy outcome was a composite of symptomatic or fatal VTE, asymptomatic VTE (assessed by screening bilateral lower-limb venous ultrasound and CT pulmonary angiogram), symptomatic arterial thromboembolism, and cardiovascular death at day 35. The primary endpoint occurred in five (3%) of 159 patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk [RR] 0·33; 95% CI 0·12–0·90; p=0·0293). There were no major bleeding events in either group and rates of clinically relevant non-major bleeding were similar.

The MICHELLE trial specifically evaluates the efficacy and safety of extended thromboprophylaxis after hospitalisation for COVID-19 (at prophylactic rather than therapeutic dose). The trial has a number of strengths, including the randomised design and enrolment across 14 sites, increasing the generalisability of the findings and the use of low-dose rivaroxaban appropriate for this phase of treatment. The eligibility criteria selected patients at low bleeding risk and high VTE risk, with symptomatic and fatal VTE reported in eight (5%) of 159 patients in the control group—a rate higher than that reported in observational studies of unselected COVID-19 patients post discharge (0·5–1·6%).[10–12] The limitations of this trial include that it was an open-label study, although reporting bias was reduced by routine scanning at follow-up and blinded independent adjudication of events. More scans were done in the rivaroxaban group, which might have increased the number of VTE diagnoses in this group. Another limitation was that the primary outcome included asymptomatic VTE, subsegmental pulmonary

embolism, and distal deep vein thrombosis of less clear clinical significance. However, there was also a reduction in the secondary efficacy endpoint of symptomatic and fatal VTE (RR 0·13, 95% CI 0·02–0·99; p=0·0487). Finally, the sample size was relatively small, with only a total of 20 patients reaching the primary outcome (five patients were asymptomatic).

Before this trial, evidence to inform the use of thromboprophylaxis post-hospital discharge was mostly limited to observational studies. The MICHELLE trial has reported that in patients estimated to be at high VTE risk and low bleeding risk, post-discharge low-dose rivaroxaban is effective at reducing thrombotic events and thrombotic-related death with a low risk of major bleeding. These results are encouraging, but in view of the small size of this trial, clinicians are likely to wait for results from other ongoing trials (HEAL-COVID NCT04801940; ACTIV-4c NCT04650087; XACT NCT04640181; and NCT 04508439) evaluating post-discharge thromboprophylaxis before changing standard practice and guideline recommendations.

ZM declares no competing interests. Related to the topic, CAB has received speaker's fees from Bayer for non-promotional education and conference funding from Bayer to present research data unrelated to rivaroxaban. Unrelated to the topic, CAB has received speaker's fees from Amgen, Bristol Myers Squibb/Pfizer Alliance, Janssen, Eli Lilly, and Novartis; support to attend conferences from Amgen and Novartis; and advisory fees from Ablynx, Bristol Myers Squibb/Pfizer Alliance, Lilly, Novartis, and Portola.

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An urgent challenge for Europe: from tackling liver diseases to protecting liver health

The liver is an amazing organ. It is the largest solid internal organ and has more than 500 vital functions, such as breaking down toxic substances and waste products, storing energy and vitamins, and producing and regulating hormones. The liver can also regenerate itself if at least 25% of healthy liver remains. Yet, the liver is neglected by individuals, health professionals, governments, policy makers, and international agencies. The *Lancet* Commission on liver disease in the UK, published in 2014 with annual progress reports, drew attention to the poor provision of services for liver diseases in the UK and made recommendations for improvement.[1–5] In its final report, this Commission highlighted the

Published **Online** December 2, 2021 https://doi.org/10.1016/S0140-6736(21)02726-4

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