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.

FDG-PET-CT with the ever-increasing array of infectious biomarkers, and favourable economic effects.

I declare no competing interests.

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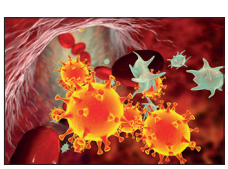
Antithrombotic prophylaxis for symptomatic outpatients with COVID-19: less is consistently more

COVID-19 is associated with an inflammatory vascular and hypercoagulable response leading to increased risk of venous and arterial thromboembolism. Microvascular pulmonary thrombosis also contributes to clinical deterioration, hospitalisation, respiratory failure, and death. Early in the pandemic, observational studies in outpatients who had never been hospitalised reported rates from 18% to 23% of pulmonary embolus on CT imaging in emergency departments, and autopsy reports found pulmonary embolus as the probable cause of death in patients never hospitalised who died at home from COVID-19.[1–4] Yet, whether starting antithrombotic therapy in newly diagnosed patients with COVID-19 not requiring hospitalisation would prevent thrombosis and mitigate progression of COVID-19 was unknown.

To address this question, a series of antithrombotic trials in symptomatic outpatients with COVID-19 were done globally, of which one, the North American ACTIV-4B trial has previously been reported.[5] In that placebo-controlled trial which evaluated aspirin, prophylactic dose apixaban, and therapeutic dose apixaban among 657 participants, rates of thrombotic events and hospitalisations for cardiopulmonary indications were low with no difference between treatment groups other than a small bleeding hazard among those allocated to therapeutic dose apixaban. On the basis of those data, the trial Data and Safety Monitoring Board (DSMB) recommended early termination of ACTIV-4B because the neutral findings were considered clinically actionable.

In *The Lancet Haematology*, two further trials are reported with remarkably similar results. In the first, Stefano Barco and colleagues for the OVID investigators present data comparing enoxaparin 40 mg daily for 14 days with open control among 472 symptomatic outpatients with COVID-19 in Switzerland and Germany.[6] In a manner almost identical to ACTIV-4B, the OVID DSMB elected to terminate the trial early on the basis of lower than anticipated event rates and a low probability of showing efficacy associated with active intervention; overall, the trial primary endpoint of any hospitalisation or death occurred in eight individuals in the group allocated to enoxaparin and eight in those allocated to open control (hazard ratio [HR] 0·98 95% CI 0·37–2·56; p=0·96). All hospitalisations were due to respiratory insufficiency or COVID-19 pneumonia with no deaths recorded. In secondary analyses limited to documented arterial or venous events, there were two in the enoxaparin group and four in the open control group.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See **Articles** pages e585 and e594

In the second trial, Frank Cools and colleagues for the ETHIC investigators present data comparing enoxaparin 40 mg once or twice daily on the basis of bodyweight for 21 days with open control among 219 symptomatic unvaccinated outpatients with COVID-19 in six countries: Belgium, Brazil, India, South Africa, Spain, and the UK.[7] In a manner yet again almost identical to both ACTIV-4B and OVID, the DSMB of ETHIC elected to terminate the trial early on the basis of lower than anticipated event rates and a lack of efficacy associated with active intervention; overall, the trial primary endpoint of any hospitalisation or death at 21 days occurred in 12 individuals in the group allocated to enoxaparin and in 12 allocated to open control (HR 1·09 95% CI 0·49–2·43; p=·83). In ETHIC, which randomly assigned trial participants soon after diagnosis, there was a single death of unknown cause in the enoxaparin group, one venous thrombosis in each allocation group, and three bleeding events in each allocation group.

When the ACTIV-4B, OVID, and ETHIC trials were designed, the true risk of thrombosis and progression to severe COVID-19 in acutely infected outpatients was unknown and no data were available to inform the use of antithrombotic agents in an outpatient setting. These three trials, done during difficult pandemic conditions when newly diagnosed patients and often investigators were required to quarantine or work from home, address the important question of the role of antithrombotic agents in this population. All three trials overestimated the baseline event rate in these primarily unvaccinated outpatient populations. In retrospect, the high rates of thrombosis reported in early observational studies of outpatients with COVID-19 were biased in part because of underestimates of the background prevalence of COVID-19, a consequence of low testing capacity early in the pandemic.

Although the results of these trials indicate that the overwhelming majority of acutely infected outpatients do not require antithrombotic therapy, some patient groups nonetheless require close follow-up. In ACTIV-4B, 3·3% of randomly assigned participants required hospitalisation for COVID-19 pneumonia, similar to findings in both OVID and ETHIC. Although elevated D-dimer did not predict progression of COVID-19, patient characteristics of elevated C-reactive protein, male sex, Black race, and Hispanic ethnicity were predictive in ACTIV-4B; these are known characteristics associated with more severe COVID-19.[8] Notably, some high-risk groups were under-represented in all three trials including those with advanced age, diagnosis of cancer, and history of venous thromboembolism; further study of antithrombotics in these populations might be warranted.

Based on data from 1348 participants enrolled in three randomised trials done in diverse settings, there is no evidence to support routine use of aspirin, factor Xa inhibitors, or LMWH for the prevention of adverse arterial or venous thrombosis, or progression of COVID-19 among symptomatic outpatients with COVID-19. ACTIV-4B, OVID, and ETHIC share not only high degrees of adherence, compliance, and follow-up, but also very low absolute event rates despite being done at times of low or absent vaccination and before the availability of oral agents designed for outpatient use such as nirmatrelvir–ritonavir, which markedly further reduce hospitalisation rates.[9] Investigations of the utility of antithrombotic treatments to prevent respiratory failure and mortality in any patient population with SARS-CoV-2 infection have generally shown little if any role for antithrombotics. Thus, in the absence of new data, the bottom line for a global clinical community that continues to deal with a frustrating ongoing pandemic, less consistently appears to be more with regard to antithrombotic therapy for outpatients with COVID-19.

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COVID-19 vaccination antibody responses in patients with aplastic anaemia and paroxysmal nocturnal haemoglobinuria

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Paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia are part of a spectrum of rare and potentially life-threatening bone marrow failure disorders that are thought to result from an autoimmune attack targeting normal bone marrow haematopoietic stem cells. There is a concern that patients with these disorders might be less able to mount an effective immune response due to their underlying disease or treatment-related immunosuppression, and might be at risk of more severe SARS-CoV-2 infections. In the Leeds PNH service, we have seen suboptimal meningococcal vaccine responses in up to 42% of patients on anti-complement therapy (unpublished data).

In a post-implementation, real-world, prospective, observational study, we aimed to investigate antibody responses to SARS-CoV-2 vaccination in adult patients with aplastic anaemia and PNH. All patients under the care of the UK PNH National Service in Leeds were eligible for inclusion, except those with previous allogeneic bone marrow transplantation (detailed methods are in the appendix [p 1]). Healthy volunteers were recruited from among UK National Health Service and University of Leeds staff. Blood samples were obtained before vaccination and 4–6 weeks after the first and second vaccinations. Vaccinations were administered by local health-care providers as per the UK prioritisation schedule and there was no limitation on the type of SARS-CoV-2 vaccine received for inclusion in the study. Serum spike-specific composite IgA, IgG, and IgM antibodies were tested at the Leeds University (Leeds, UK) laboratory using an ELISA (The Binding Site Group, Birmingham, UK). Responses from all patients and healthy controls were compared. Post hoc, we also did subgroup analyses according to the variables: diagnosis (classic PNH, aplastic anaemia–PNH overlap, and aplastic anaemia), age, calcineurin inhibitor therapy, vaccine type, and, in patients with PNH on complement inhibitory treatment, history of a suboptimal meningococcal vaccination response. The study was approved by the independent Yorkshire and The Humber Leeds East Research Ethics Committee (16/YH/0290; Independent Research Application System identification number 105641) and conducted in agreement with Good Clinical Practice guidelines and according to the Declaration of Helsinki.

Between Jan 1 and Dec 1, 2021, 175 patients and 45 healthy volunteers were enrolled and their SARS-CoV-2 antibody responses were measured. Four patients were excluded from final analysis due to concurrent immunosuppression for other indications. In the analysable population, the median age was 52 years (IQR 40–67) and 118 (55%) of 216 were female and 98 (45%) were male; data on race and ethnicity were not collected (appendix p 5). After one vaccination, patients had a substantially reduced seroconversion rate of 63% (83 of 131 patients with data) compared with 95% (39 of 41) of healthy volunteers, which was similar across patient subgroups (63% [43 of 68] in those with classic PNH, 68% [28 of 41] in those with aplastic anaemia–PNH, and 55% [12 of 22] in those with aplastic anaemia; appendix p 6). Overall, patients showed a 2·4-fold lower antibody response than healthy volunteers (median optical density [OD] ratio 1·2 [IQR 0·8–2·0] *vs* 2·9 [1·8–4·1]; p<0·0001; figure). The absolute antibody levels were significantly lower in all patient subgroups

See **Online** for appendix