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NEWS ANALYSIS

Covid-19 and thrombosis: what do we know about the risks and treatment?

Doctors are seeing high rates of blood clots in patients who are seriously ill with covid-19, but questions remain over best practice, reports **Jacqui Wise**

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How common is thrombosis in critically ill patients with covid-19?

A recent Dutch study of 184 patients with covid-19 pneumonia admitted to an intensive care unit (ICU) found a 49% cumulative incidence of thrombotic complications—mainly changes seen on computed tomography (CT) pulmonary angiograms.¹

The authors said that this level was “remarkably high,” given that all patients received at least standard doses of thromboprophylaxis. Other studies from France and the Netherlands have also suggested that thrombosis occurs in 20-30% of critically ill covid-19 patients, even with prophylaxis.^{2,3}

“The extent of thrombosis we are seeing with covid is extraordinary,” Roopen Arya, clinical director for haematology at King’s College Hospital, told *The BMJ*. “I would say that one third of those severely affected with covid in critical care is a conservative estimate.”

Why are covid-19 patients at particular risk of thrombosis?

Covid-19 causes massive inflammation boosting cytokines, which increase the liver’s production of clotting factors, explains Beverley Hunt, medical director of Thrombosis UK and a practising clinician. For example, fibrinogen levels in a severely ill covid-19 patient are 10-14 g/L, compared with 2-4 g/L normally and 5-6 g/L in a pregnant woman. “A covid patient’s blood is enormously sticky,” she told *The BMJ*.

Is the rate of thrombosis in covid patients higher than in non-covid patients in critical care?

“All patients in critical care are at increased risk from clots because they are immobile, and when you are sick you have sticky blood,” says Hunt. Studies of venous thromboembolism rates among non-covid patients in critical care show that rates of thrombosis can be as high as 28% if patients are not given

any prophylaxis. Among patients given prophylaxis the rates are halved. So, we seem to be seeing significantly higher rates of thrombosis in covid patients.

Is thrombosis contributing to the covid death rate?

“Thrombosis is definitely contributing to the high mortality rate from covid,” says Hunt. “Not only can it lead to a pulmonary embolism, which can be fatal, but there are also higher rates of strokes and heart attacks.”

Are the clots in covid patients different from those seen in other critically ill patients?

Postmortem studies are finding clots in the capillaries of the lungs in covid-19 patients, restricting the oxygenated blood from moving through the lungs. Hunt says, “We are not only seeing high rates of deep vein thrombosis and pulmonary embolisms in covid patients but we are also seeing immunothrombosis with lung destruction because of inflammation.”

How should covid-19 patients be treated to prevent thrombosis?

In the NHS, anyone coming into hospital is routinely assessed for risk of hospital associated venous thromboembolism and given appropriate prophylaxis with blood thinners. “However, we are still seeing these high rates of deep vein thrombosis, pulmonary embolism, and immunothrombosis in covid patients, and some people are arguing that we should be giving bigger doses,” says Hunt. Without evidence from randomised controlled trials, however, it is not clear what the correct dose should be.

Some UK hospitals are going ahead and using a higher treatment dose of heparin, rather than a prophylactic dose, for seriously ill patients with covid. “It’s like the Wild West out there with lots of different protocols,” says Arya. “But giving a higher dose could increase the risk of bleeding. Our hospital is taking

a pragmatic approach. Instead of giving the standard prophylactic dose of heparin we are giving half the treatment dose.”

You should definitely use a treatment dose in patients who have had a pulmonary embolism, Hunt advises. But she also favours intermediate doses for other patients because of the as yet unknown risk of bleeding with higher doses. However, she says that clotting is right down the chain of events with covid. “If you have less viral load, you would have less inflammation, less sticky blood, and less VTE [venous thromboembolism] and immunothrombosis,” she says.

What has happened to the NHS England guidance?

NHS England commissioned a group of experts to write clinical guidance on thrombosis and critical care for patients with covid, which was submitted for dissemination on 28 April. Hunt, who was one of the experts consulted, says that she feels frustrated that this guidance is not yet out there to help clinicians.

Lyn Brown, chair of the all party parliamentary thrombosis group, has submitted a written question to the health secretary, asking when the guidance will be published. “We’ve known for many years that preventable thrombosis tragically kills large numbers every year in the UK. The pandemic is putting far, far more people at risk, and clinicians need specialist guidance as soon as possible,” she told *The BMJ*. “Despite this, the guidance that NHS England has commissioned, and which was delivered more than two weeks ago, still hasn’t been published. We need to move much more quickly to save lives.”

What research is needed?

Even when the guidance comes out it will be limited, as so little research is currently available. A randomised controlled trial is desperately needed to compare the standard prophylactic dose of heparin with a standard dose in severely ill patients with covid-19.

Hunt says that she and others in the thrombosis community are “hugely frustrated” that they submitted a research proposal to answer this question and it was turned down by Public Health England as a “low priority.” After pressure from researchers the question is eventually going to be included as part of the RMAP-CAP platform trial. However, Hunt believes that researchers have “missed the boat somewhat” and should have been gathering data during the peak of infections.

Another question that urgently needs answering, says Hunt, is whether blood thinners should be given to covid patients when they leave hospital and for how long. She told *The BMJ*, “Covid patients are still going to have sticky blood when they go home, and we know that 60% of patients will have clots in the 90 days after discharge.”

- 1 Klok F, Kruij M, van der Meer N, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;S0049-3848(20)30157-2.
- 2 Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020;(May). 10.1111/jth.14888. 32369666
- 3 Poissy J, Goutay J, Caplan M, et al. Lille ICU Haemostasis COVID-19 group. Pulmonary embolism in covid-19 patients: awareness of an increased prevalence. *Circulation* 2020. 10.1161/CIRCULATIONAHA.120.047430. 32330083

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