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## Thromboembolism and bleeding after covid-19

### Risks are increased even after mild infections

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It is now clear from meta-analyses of case series,<sup>1,2</sup> cohort studies,<sup>3</sup> and self-controlled case series<sup>4,5</sup> that the risk of venous thromboembolism is increased after SARS-CoV-2 infection. However, two important questions remain: for how long post-infection is the risk increased, and does mild infection also increase risk? In a linked paper, Katsoularis and colleagues (doi:10.1136/bmj-2021-069590) address these questions by applying two complementary study designs to data from several Swedish registries.<sup>6</sup>

The authors identified more than one million people with laboratory confirmed SARS-CoV-2 infection from the start of the pandemic to mid-2021, matched on age, sex, and county of residence to more than four million people who had not had a positive SARS-CoV-2 test result. After adjustment for a wide range of potential confounders, the authors reported a fivefold increase in risk of deep vein thrombosis (relative incidence 4.98, 95% confidence interval 4.96 to 5.01), 33-fold increase in risk of pulmonary embolism (33.05, 32.8 to 33.3), and an almost twofold increase in risk of bleeding (1.88, 1.71 to 2.07) in the 30 days after infection.

The results were largely consistent in alternative analyses using a self-controlled case series approach comparing risk 1-30 days after the infection with a control period. The advantage of this approach is that comparing two periods in the same individual eliminates confounding by factors that are stable over time, such as genetics.<sup>7</sup>

The large study population enabled novel, granular analyses. Previous studies have already shown that the association between SARS-CoV-2 and thromboembolic events is much stronger for pulmonary embolism than for deep vein thrombosis.<sup>8</sup> Katsoularis and colleagues were able to show that the increased risk of thromboembolism also lasts longer for pulmonary embolism than for deep vein thrombosis; six and three months, respectively.

These authors also report an increased risk of bleeding after SARS-CoV-2 infection that is consistent with previous studies. Use of thromboprophylaxis after SARS-CoV-2 infection clearly carries a risk of bleeding. However, covid-19 has also been associated with coagulopathy and disseminated intravascular coagulation.<sup>9</sup> Although unable to identify the underlying mechanism, the authors show that the association with bleeding is independent of anticoagulation before SARS-CoV-2 infection and lasts for two months after infection.

Since risks of thromboembolism and bleeding were highest among participants with more severe covid-19, vaccination could reduce the overall risk both by preventing infection and by reducing its

severity when it does occur. While risk of thromboembolic events is increased after vaccination,<sup>5,10</sup> the magnitude of risk remains smaller and persists for a shorter period than that associated with infection.

Are the new study findings still relevant now that nearly 65% of the world's population has received at least one vaccine dose<sup>11</sup>? Yes—current vaccines are highly effective against severe covid-19 but confer only moderate protection against infection with the omicron variant.<sup>12,13</sup> Breakthrough infections are common, even after a third dose,<sup>14</sup> and effectiveness against symptomatic disease appears to decrease to less than 50% 10 weeks after vaccination.<sup>13</sup>

Although many infections with the omicron variant are mild, the new study confirms an increased risk of venous thromboembolism even among those with milder infections who do not require admission to hospital.<sup>4</sup> The association was much weaker (relative incidence 5.87, 95% confidence interval 4.88 to 7.05 for pulmonary embolism) than that among patients admitted to hospital (64.49, 53.91 to 77.15) and those admitted to intensive care (196.98, 128.71 to 301.46), but mild disease accounts for a much larger proportion of infections (94.5% in this study). This patient group may therefore contribute a substantial number of thromboembolic events.

A study from England<sup>15</sup> reported a doubling in the incidence of, and mortality from, thromboembolism since the start of the pandemic in 2020 compared with the same periods in 2018 and 2019. The same study reported comparable increases among individuals without positive SARS-CoV-2 test results. Some of those without a positive test result will have been infected before widespread testing was available, but others will have had mild or asymptomatic infections.<sup>16</sup>

Despite the potential for new variants of concern, most governments are removing restrictions and shifting their focus to determining how best to “live with covid.”<sup>17</sup> Katsoularis and colleagues' study reminds us of the need to remain vigilant to the complications associated with even mild SARS-CoV-2 infection, including thromboembolism.

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