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Thromboembolism and bleeding after covid-19

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It is now clear, from meta-analyses of case series (1, 2), cohort studies (3), and self-controlled case series (4, 5), that the risk of venous thromboembolism is elevated following SARS-CoV-2 infection. However, several important questions remain: for how long post-infection is the risk elevated, and does mild infection also confer increased risk? In this edition, Katsoularis and colleagues (doi:) (6) address these questions by applying two complementary study designs to several Swedish registries.

Katsoularis and colleagues identified over one million individuals with laboratory-confirmed SARS-CoV-2 infection from the start of the pandemic to mid-2021 and over 4 million age-, sex- and country-matched individuals who had not had a positive test. Following adjustment for a wide range of potential confounders they reported a five-fold risk of deep vein thrombosis (relative incidence 4.98, 95% confidence interval 4.96-5.01), 33-fold risk of pulmonary embolism (relative incidence 33.05, 95% confidence interval 32.8-33.3), and almost 2-fold risk of bleeding (relative incidence 1.88, 95% confidence interval 1.71-2.07) in the 30 days following infection. The results were largely consistent when they applied a self-controlled case series approach; comparing the risk 30 days after infection with 30 days before. The benefit of this approach is that comparing two time periods in the same individual eliminates confounders that are stable over time, e.g. genetics (7).

The large study population enabled novel, granular analysis. Previous studies have already demonstrated that the association between SARS-CoV-2 and thromboembolic events is much stronger for pulmonary embolism than deep vein thrombosis (8). Katsoularis and colleagues were able to show that the increased risk of thromboembolism also lasts longer for pulmonary embolism than deep vein thrombosis; 3 months for the latter compared with 6 months for the former. Consistent with previous studies, Katsoularis and colleagues demonstrated an increased risk of bleeding following SARS-CoV-2 infection. Use of thromboprophylaxis following SARS-CoV-2 infection clearly carries a risk of bleeding. However, COVID-19 has also been associated with coagulopathy and disseminated intravascular coagulation (9). Whilst not able to elucidate the underlying mechanism, they demonstrated that the association with bleeding was independent of anti-coagulation prior to SARS-CoV-2 infection and lasted for 2 months following it.

As this study showed that infection severity was associated with subsequent risk of thromboembolism and bleeding, COVID-19 vaccination could reduce the overall risk of thromboembolism both by preventing infection and reducing its severity when it does occur. Moreover, the findings of Katsoularis and colleagues help contextualise the risks and benefits of COVID-19 vaccination. Whilst there is a risk of thromboembolic events following vaccination (5, 10), the magnitude of risk is modest and persists for a shorter duration than that associated with infection. Are the study findings still relevant now that nearly 65% of the world's population has received at least one vaccine dose (11)? Yes. Whilst current vaccines are highly effective against severe COVID-19, they produce only moderate reduction in the

risk of infection with the Omicron variant (12, 13). Even with a booster, breakthrough infections are common (14) and the effectiveness against symptomatic disease has been estimated to fall to less than 50% ten weeks after vaccination (13). While most infections with Omicron are mild owing to the vaccination coverage, the results of this study, consistent with those of a previous self-controlled case series study (4), demonstrated increased risk of venous thromboembolism even among individuals with milder infection not requiring hospitalisation. Whilst their association was much weaker (relative incidence 5.87, 95% confidence interval 4.88-7.05 for pulmonary embolism) than that of hospitalised patients (relative incidence 64.49, 95% confidence interval 53.91-77.15) and those admitted to intensive care (relative incidence 196.98, 95% confidence interval 128.71-301.46), they account for a much larger proportion of SARS-CoV-2 infections (94.5% in this study). Therefore, they may nonetheless produce a significant number of thromboembolic events. An English study (15) reported a doubling in the incidence and mortality of thromboembolism since the start of pandemic in 2020 compared with the same periods in 2018 and 2019. Furthermore, it highlighted a similar magnitude of increase among individuals without positive test results. Whilst some of these people will have been infected prior to testing being available, others will have had mild or asymptomatic infection (16).

Notwithstanding the potential for new variants of concern, most governments around the world are removing restrictions and shifting focus to how we should 'live with covid' (17). Whilst this is an encouraging development, this study reminds us of the need to remain vigilant to the complications associated with even mild SARS-CoV-2 infection, such as thromboembolism.

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References

1. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine*. 2020;29:100639.
2. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AW, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thrombosis research*. 2020;196:67-74.
3. Dalager-Pedersen M, Lund LC, Mariager T, Winther R, Hellfritsch M, Larsen TB, et al. Venous thromboembolism and major bleeding in patients with coronavirus disease 2019 (COVID-19): a nationwide, population-based cohort study. *Clinical Infectious Diseases*. 2021;73(12):2283-93.
4. Ho FK, Man KK, Toshner M, Church C, Celis-Morales C, Wong IC, et al. Thromboembolic risk in hospitalized and nonhospitalized COVID-19 patients: a self-controlled case series analysis of a nationwide cohort. *Mayo Clinic Proceedings*. 2021;96(10):2587-97.
5. Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. *bmj*. 2021;374.

6. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Jerndal H, Lundevaller EH, Sund M, et al. Risk of pulmonary embolism, deep vein thrombosis and bleeding after COVID-19: nationwide self-controlled cases series and matched cohort study. *BMJ*. 2022.
7. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *bmj*. 2016;354.
8. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136(4):489-500.
9. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *International journal of hematology*. 2021;113(1):45-57.
10. Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nature medicine*. 2021;27(7):1290-7.
11. Our World in Data. Coronavirus (COVID-19) Vaccinations Oxford: Global Change Data Lab; 2022 [Available from: <https://ourworldindata.org/covid-vaccinations>].
12. Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *New England Journal of Medicine*. 2022;386(5):494-6.
13. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B. 1.1. 529) variant. *New England Journal of Medicine*. 2022.
14. Kuhlmann C, Mayer CK, Claassen M, Maponga T, Burgers WA, Keeton R, et al. Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *The Lancet*. 2022.
15. Aktaa S, Wu J, Nadarajah R, Rashid M, de Belder M, Deanfield J, et al. Incidence and mortality due to thromboembolic events during the COVID-19 pandemic: Multi-sourced population-based health records cohort study. *Thrombosis research*. 2021;202:17-23.
16. Wise J. Covid-19: What's going wrong with testing in the UK? *bmj*. 2020;370.
17. Johnson B. PM statement on living with COVID: 21 February 2022. Oral statement to Parliament London: UK Government; 2022 [Available from: <https://www.gov.uk/government/speeches/pm-statement-on-living-with-covid-21-february-2022>].