What is the association of COVID-19 with heart attacks and strokes?

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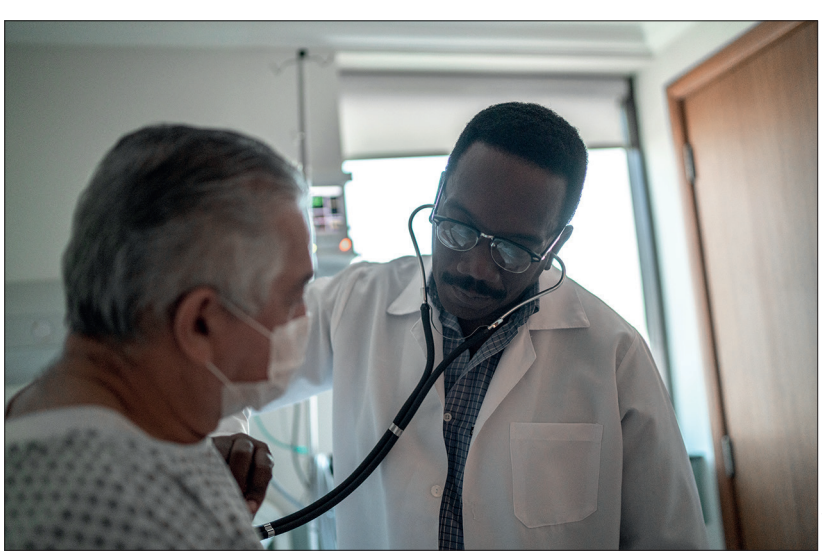
It has been known for several decades that there is a transient increase in the risk of myocardial infarction and stroke in association with influenza, pneumonia, acute bronchitis, and other chest infections.[1–4] It is against this background that Ioannis Katsoularis and colleagues[5] studied a possible association of these conditions with COVID-19 during the first wave of the pandemic in Sweden, between February and September, 2020, which they report in *The Lancet*. The study linked data from the national registers for outpatient and inpatient clinics and the cause of death register for all 86 742 people (median age 48 years [IQR 31–62]; 37 235 [43%] male, 49 507 [57%] female) with COVID-19 who were reported to SmiNet (Swedish Public Health Agency) and 348 481 matched controls. Two analysis methods were used to assess the association of COVID-19 with the risk of acute myocardial infarction and of ischaemic stroke. First, the investigators used the self-controlled case series (SCCS) method to compare incidence rate ratios (IRRs) for first acute myocardial infarction and ischaemic stroke before and after patients were determined to have COVID-19. Second, they used a matched cohort study to compare the odds of an acute myocardial infarction or ischaemic stroke in the 14 days following onset of COVID-19 with control individuals who did not have a diagnosis of COVID-19 and who were similar in age, sex, and region, with additional adjustment for comorbid disease, income, education, and country of birth.[5]

Because the actual date of infection was unknown, the researchers defined the closest available surrogate (the date of COVID-19 symptom onset, SARS-CoV-2 sample date, or the date of the relevant clinic visit or hospital admission), and denoted it as day 0. There was a large peak of both acute myocardial infarctions and ischaemic strokes recorded on day 0. If day 0 was excluded, the risks of acute myocardial infarction were about three times higher in the first few weeks after COVID-19, irrespective of the study method (IRR 2·89 [95% CI 1·51–5·55] in the first week and 2·53 [1·29–4·94] in the second week after day 0 in the SCCS study, and odds ratio [OR] 3·41 [95% CI 1·58–7·36] in the first 2 weeks in the matched cohort study). If day 0 was included, the risks of acute myocardial infarction were much higher (IRR 8·44 [95% CI 5·45–13·08] in the first week and 2·56 [1·31–5·01] in the second week after day 0 in the SCCS study, and OR 6·61 [95% CI 3·56–12·20] in the first 2 weeks in the matched cohort study). Similarly, COVID-19 was associated with a three times higher risk of ischaemic stroke when day 0 was excluded (IRR 2·97 [95% CI 1·71–5·15] in the first week and 2·80 [1·60–4·88] in the second week after day 0 in the SCCS study, and OR 3·63 [95% CI 1·69–7·80] in the first 2 weeks in the matched cohort study). Again, the risks were much higher when day 0 was included (IRR 6·18 [95% CI 4·06–9·42] in the first week and 2·85 [1·64–4·97] in the second week after day 0 in the SCCS study, and OR 6·74 [95% CI 3·71–12·20] in the first 2 weeks in the matched cohort study).

How should these results be interpreted, and what are their implications for the management of patients with COVID-19? The most important consideration is the potential for bias. Why is there such a striking peak of myocardial infarction and stroke on day 0? Such a peak could occur if COVID-19 is a potent cause of myocardial infarction and stroke, events that in turn lead patients to seek medical help, but it could also occur if patients presenting with such a condition were more likely to be tested for SARS-CoV-2 than those without symptoms suggestive of such a diagnosis (ie, a test bias). Excluding



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day 0 removes the potential for test bias, but might lead to an underestimate of the true risks of myocardial infarction and stroke secondary to COVID-19.

If there is indeed a moderately increased risk of myocardial infarction and stroke secondary to COVID-19, then why was there a 30–40% fall in admissions for both acute coronary syndromes[6,7] and stroke[8,9] during the first wave of the pandemic? The answer is that any possible attributable excess due to COVID-19 was far smaller than the numbers of people who did not seek medical attention for symptoms of acute coronary syndrome or stroke during this period. For myocardial infarction, for example, during the period from February to mid-September, 2020, there were 381 000 confirmed cases of COVID-19 in the UK.[10] The estimated excess attributable risk due to COVID-19 in the present study was 0·02%,[5] which, if it had been observed in the UK, would have caused about 76 additional myocardial infarctions, as compared with approximately 5000 people who might not have presented to hospital with myocardial infarction during the first wave of the pandemic.[6]

It seems reasonable to infer that the persistence of risk for several weeks after SARS-CoV-2 infection is consistent with COVID-19 causing an increased risk of thrombo-occlusive disease, as has been reported for other respiratory infections.[1-4] The absolute risks are small, but further studies are needed to evaluate the time course of increased cardiovascular risk in patients with COVID-19 and to investigate possible mechanisms. However, it is important to keep in mind that the excess risks of myocardial infarction and stroke in a person with COVID-19 are substantially smaller than those resulting from respiratory failure.

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