EDITORIAL

COVID-19 Exposures, Vaccines, and Acute Ischemic Stroke Risk

On Balance and in Balance

Alexis N. Simpkins, MD, PhD, MSCR, and Susan Cheng, MD, MMSc, MPH

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Correspondence
Dr. Simpkins
alexis.simpkins@cshs.org

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Most stroke prevention strategies involve optimizing medication regimens, diet, activity, lifestyle, and behavioral changes to promote cerebrovascular and cardiovascular health.[1] However, soon after the World Health Organization declared the SARS-CoV-2 infection COVID-19 a global pandemic, it became more apparent that SARS-CoV-2 infection would become an unignorable risk factor for stroke.[2] Patients with COVID-19, particularly severe respiratory manifestations of the disease, were found early on to have evidence of a prothrombotic and proinflammatory state along with a propensity for cardiac dysfunction and stroke.[3] Stroke incidence in patients with COVID-19 was particularly higher in those with cardiovascular risk factors but could also occur in younger patients and those without preexisting traditional cardiovascular risk factors.[2] After the advent of COVID-19 vaccines, there emerged similarly concerning case reports of thrombotic events such as acute ischemic stroke (AIS) and cerebral venous thrombosis post–COVID-19 vaccine exposure, potentially resulting from thrombotic thrombocytopenia syndrome (TTS), cardiac dysfunction, or an excess of the vaccine-induced immune response.[4-7] As the pandemic evolves to endemic and repeated "booster" doses of vaccine are inevitably needed to stave off severe COVID-19 illness, these events obligate us to weigh the stroke risks from COVID-19 infection against the stroke risks from COVID-19 vaccination.

Given the global scale of vaccine delivery, even a low-frequency rate of events related to vaccination could affect a substantial number of individuals across the population at large.

Recognizing this critical issue, Stefano et al.[8] conducted a meta-analysis to evaluate the risk of AIS post-COVID vaccination, and in turn, the occurrence rates of TTS in those with post-vaccine AIS. The authors analyzed 782,989,363 COVID-19 vaccine exposures by pooling data from 11 registries, 3 cohort studies, 2 randomized controlled clinical trials, and 40 case reports.[8] Overall, 17,481 (0.002%) of COVID vaccine exposures were associated with an AIS event.[8] Notably, TTS was exceedingly rare, occurring in only 3% of the AIS events and not dependent on vaccine type.[8] Interestingly, there was also no difference in AIS risks by age, sex, or between mRNA and adenovirus-based vaccine type in sensitivity analyses accounting for the time between the vaccine exposure and the event.[8] To contextualize their findings, the authors reported that the postvaccine AIS events occurring at a rate of 4.7 per 100,000 vaccinations were ~20 times less frequent than strokes occurring in the general population (95–98 per 100,000) and ~200 times less frequent than strokes occurring in patients hospitalized with COVID-19 (1,000 per 100,000).[8] In effect, the results of this meta-analysis by Stefano et al. could be interpreted to suggest that COVID-19 vaccination actually offers some benefit when compared with stroke risk in the general population. Accordingly, extrapolation of the estimates provided in the study suggests that the number needed to vaccinate is comparable with the number needed to treat to prevent stroke with antiplatelet agents such as aspirin.

Notwithstanding several strengths of the study, including the sizable, diverse pool of patients and the analysis of different COVID-19 vaccine types, there are caveats to consider. Fully adjusted analyses accounting for key potential confounders could not be conducted because

From the Department of Neurology (A.N.S.), Cedars-Sinai Medical Center; and Department of Cardiology (S.C.), Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA.
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data reporting and collection methods varied between data sources. The confounders of particular relevance include the traditional factors associated with stroke risk and outcomes, including preexisting conditions and treatments, but also those characteristics associated with COVID-19 exposures, including prior infections and vaccine dosing as well as the timing. With respect to interpreting these results in context, it is also important to consider issues of temporality. Estimates of stroke risk in the general population, in the absence of COVID-19 exposures, are intrinsically difficult to compare with contemporaneous general stroke risks in the era of the pandemic–even unvaccinated, never-infected individuals are likely to have experienced endogenous or environmental stressors during the pandemic that may exacerbate stroke risk. In addition, the available estimates of post-COVID stroke risks and the available estimates of postvaccine stroke risks are not generally matched in timing, with the former having originated from predominantly first-wave pandemic outcomes data and the latter from data collected during the first phase of the vaccine era. Consequently, stroke risk estimates are not so easily matched on differences in the temporality of exposure effects, for instance, with earlier SARS-CoV-2 variant surges conferring greater risks for greater COVID-19 illness severity than later variants–and vaccine regimens appearing later on and still changing with respect to the timing and effects of each dose. It is quite possible that results similar to those of the main analysis would have been achieved with continuous assessment and evaluation of outcomes–perhaps facilitated by real-time big data curation and artificial intelligence analytics. Given the dynamic and still evolving nature of COVID-19 exposures and their effects at the individual and public health level, ongoing efforts are needed to facilitate continuous monitoring of events.

One reliable constant is the knowledge that patients at the highest risk of COVID-19–related adverse outcomes, and stroke, in particular, are those with preexisting cardiovascular risk factors. What we do know is that patients at the highest risk of severe COVID-19 and stroke are those who already have cardiovascular risk factors. Therefore, despite the many challenges of managing primary and secondary stroke prevention during the pandemic,[3] the imperative to prioritize stroke prevention for those at risk has never been greater.[9,10] Fortunately, the meta-analysis results reported by Stefano et al. offer reassurance that the frequency of postvaccine AIS is generally lower than the frequency of post-COVID AIS. Thus, while always prioritizing a personalized approach to risk assessment for any outcome, these data confirm that–on balance–the benefits of vaccination outweigh the risks.

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Disclosure

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