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Cerebral Venous Sinus Thrombosis in the US Population, after Adenovirus-based SARS-CoV-2 Vaccination, and After COVID-19

Brief title: Cerebral Venous Sinus Thrombosis after Vaccination Against SARS-CoV2

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DISCLOSURES

Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. Dr. Monreal has served as an advisor or consultant for Sanofi, Leo Pharma, and Daiichi-Sankyo; and has received a nonrestricted educational grant by Sanofi and Bayer to sponsor the Computerized Registry of Patients with Venous Thromboembolism. Dr. Jimenez has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Leo Pharma, Pfizer, ROVI, and Sanofi; has served as a speaker or a member of a speaker bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Leo Pharma, ROVI, and Sanofi; and has received grants for clinical research from Daiichi-Sankyo, Sanofi, and ROVI. Dr. Krumholz reports personal fees from UnitedHealth, personal fees from IBM Watson Health, personal fees from Element Science, personal fees from Aetna, personal fees from Facebook, personal fees from Siegfried & Jensen Law Firm, personal fees from Arnold & Porter Law Firm, personal fees from Ben C. Martin Law Firm, personal fees from National Center for Cardiovascular Diseases, Beijing, ownership of HugoHealth, ownership of Refactor Health, contracts from the Centers for Medicare & Medicaid Services, grants from Medtronic

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Abbreviations

AZ: AstraZeneca
COVID-19: Coronavirus disease-2019
CVST: Cerebral venous sinus thrombosis
J&J: Johnson & Johnson
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
VITT: Vaccine-Induced Thrombotic Thrombocytopenia

Introduction

Thrombosis has emerged as a major concern in patients with coronavirus disease-2019 (COVID-19).(1, 2) Most recently, thrombotic events, particularly cerebral venous sinus thrombosis (CVST) were reported within days after receiving severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) adenovirus-based vaccines.(3) Initially, cases of CVST were reported in close succession to the use of the ChAdOx1 nCoV-19 vaccine (AstraZeneca), mostly in women of childbearing age, with many cases being associated with thrombocytopenia. Subsequently, 6 cases of CVST were reported from the United States with another adenovirus-based vaccine: Ad26.COV2.S vaccine (Johnson & Johnson), among women of childbearing age. CVST is a rare but potentially devastating disease.(4) Therefore, this issue led to a temporary pause in use of the J&J vaccine in the United States and variable age/sex-based restrictions for the AstraZeneca vaccine in other countries. Herein, we report the rate of CVST associated with these two vaccines based on publicly reported data, versus those occurring after COVID-19, and the estimated incidence rates in the US population.

We used the data from The Medicines and Healthcare products Regulatory Agency (from the United Kingdom),[5] and the US Centers for Disease Control and Prevention[6] to report the number of events per vaccinated people with AstraZeneca and Johnson&Johnson vaccines, respectively. We used the data from a multinational study of cerebrovascular events to report CVST rates in hospitalized patients with COVID-19.([7]) Data from the Nationwide Inpatient Sample database (an all-payer database including an approximate 20% sample of inpatient hospitalizations in the US) from March and April 2018, the latest year with available information, were used to report the weighted mothly incidence of CVST using principal discharge diagnostic codes 437.6 and 325 (with positive predictive value of 92% for CVST)([8]);

divided by the US population as reported by the US census bureau. We estimated 99% confidence intervals around the proportions.

As of April 14, 2021, there were 77 CVST cases out of 21,200,000 AstraZeneca vaccine recipients reported by the Medicines and Healthcare products Regulatory Agency (3.6 per million, 99% CI: 2.7 to 4.8 per million). As of April 13, 2021, the Centers for Disease Control and Prevention reported 6 cases of CVST out of 6.85 million vaccinated people (0.9 per million, 99% CI: 0.2 to 2.3 per million). In the SVIN COVID-19 registry, 3 out of 14,483 patients hospitalized with COVID-19 had CVST (207.1 per million, 99% CI: 23.3 per million to 757.7 per million). In the Nationwide Inpatient Sample, the weighted average rate of CVST in the US population for the months of March and April 2018 was 2.4 per million (99% CI: 2.1 to 2.6 per million) (**Figure**).

Discussion:

The estimated relative frequency and 99% confidence interval estimates for CVST for AstraZeneca and Johnson&Johnson vaccines based on the available reported events are markedly lower than those for patients hospitalized with COVID-19, and not substantially higher than monthly estimates from the US Nationwide Inpatient Sample. The estimates reported herein are in line with recommendations by regulatory authorities and indicative of the low absolute risk of CVST after adenovirus-based vaccination.

A unique feature of CVST after vaccination for SARS-CoV2 is the phenomenon of vaccine-induced thrombotic thrombocytopenia. This condition has features resembling heparin-induced thrombocytopenia, despite the absence of heparin exposure. The general consensus is to avoid heparin in these patients.(3) Some experts recommend the administration of intravenous

immunoglobulin or corticosteroids in patients with CVST associated with thrombocytopenia and antibodities against platelet factor-4.([9])

This study has several limitations. First, we attempted to provide relatively similar follow-up intervals. Nevertheless, the data sources have inherent differences. The AstraZeneca vaccine has not been authorized or used in the United States. Therefore, we report the events based on the data from the MHRA in the United Kingdom. Although some regional variability due to biological, social, or healthcare associated reasons are plausible, within the limits of some variation, the event rates may be relevant to a broad audience. Second, the data from the Nationwide Inpatient Sample indicates the hospitalization rates, rather than incidence. However, most patients with CVST will require hospitalization for the initial stay. Third, the events are subject to underreporting, especially for cases for CVST after vaccination against SARS-CoV-2. The current analyses included updated estimate of these events. As additional events accrue over time, the estimated event rates will be affected. Fourth, we were unable to report event rates per specific age groups, since the numerators and denominators for such analyses are not publicly available from all the four data sources used in this manuscript. Fifth, the surveillance reports from the Centers for Disease Control and Prevention and the Medicines and Healthcare products Regulatory Agency do not provide sufficient details to understand the event rates for CVST associated with thrombocytopenia (so called Vaccine-Induced Thrombotic Thrombocytopenia [VITT]). Sixth, the used to estiimte the CVST event rates in hospitalized patients with COVID-19 may be limited by voluntary inclusion of some hospitals in the registry. ([7]) However, the study was multicenter and conducted from several countries. Even if some variation is expected across centers, the magnitude of risk for CVST appears to be several folds higher in hospitalized

patients with COVID-19, than in other groups. Finally, we were not able to report CVST with mRNA-based vaccines.

In conclusion, CVST is rare in the general population and after adenovirus-based SARS-CoV-2 vaccination, but appears to be several-fold more common in hospitalized patients with COVID-19. Additional research is required to fully elucidate the event rates, to understand the risk factors for vaccine-associated CVST and to identify strategies to prevent it. In the meantime, transparent realistic communication of the risk estimates will be helpful for shared-decision-making between patients and clinicians.

REFERENCES

1. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:2950-2973.

2. Talasaz AH, Sadeghipour P, Kakavand H, et al. Recent Randomized Trials of Antithrombotic Therapy for Patients With COVID-19: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021;77:1903-1921.

3. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021. doi: 10.1056/NEJMoa2104882.

4. Piazza G. Cerebral venous thrombosis. Circulation. 2012;125:1704-9.

5. Siegler JE, Cardona P, Arenillas JF, et al. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry. Int J Stroke. 2020:1747493020959216.

6. Center for Disease Control and Prevention: https://emergency.cdc.gov/han/2021/han00442.asp, Date last accessed: April 25, 2021.

7. Siegler JE, Cardona P, Arenillas JF, et al. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry. Int J Stroke. 2020:1747493020959216.

8. Siddiqui FM, Weber MW, Dandapat S, et al. Endovascular Thrombolysis or Thrombectomy for Cerebral Venous Thrombosis: Study of Nationwide Inpatient Sample 2004-2014. J Stroke Cerebrovasc Dis. 2019; 28: 1440-1447.

9. American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and Management of Cerebral Venous Sinus Thrombosis with Vaccine-Induced Thrombotic Thrombocytopenia. Stroke. 2021. doi: 10.1161/STROKEAHA.121.035564.

Figure 1. Estimated Rate of CVST Per 1,000,000 People. Note the difference in event rates for CVST after AstraZeneca and Johnson&Johnson vaccination, compared with event rates in hospitalized patinets with COVID-19. Note that the upper bound of the 99% confidence interval for patients hospitalized with COVID-19 was 757.7. Blue rectangles indicate the point estimates per 1,000,000 and the black lines indicate the estimated 99% confidence intervals. COVID-19: Coronavirus disease 2019, CVST: cerebral vein sinus thrombosis.