Supplemental Online Content

Ashrani AA, Crusan DJ, Petterson T, Bailey K, Heit JA. Age- and sex-specific incidence of cerebral venous sinus thrombosis associated with Ad26.COV2.S COVID-19 vaccination. *JAMA Intern Med.* Published online November 1, 2021. doi:10.1001/jamainternmed.2021.6352

eMethods.

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

1. CVST incidence rate in the general population prior to COVID-19 pandemic:

1.a. *Study setting and population:* Using the resources of the Rochester Epidemiology Project (REP) [Melton LJ, 3rd. *Mayo Clinic Proceedings* 1996;71(3):266-274; St Sauver JL, et al. *Am J Epidemiol.* 2011;173(9):1059-1068; St Sauver JL, et al. *Mayo Clinic Proceedings.* 2012;87(2):151-160], we identified all Olmsted County (2010 census population=144,248), Minnesota, residents older than 18 years with incident or recurrent venous thromboembolism (VTE) over the 50-year period 1966-2015, as previously described [Silverstein MD, et al. *Archives of Internal Medicine* 1998;158(6):585-593; Heit JA, et al. *Thrombosis and Haemostasis.* 2017;117(2):390-400]. For this study, we restricted our cohort to residents with objectively diagnosed incident CVST over the 15-year period, 2001–2015. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

1.b. *Cohort identification and incidence criteria:* A master list of potential Olmsted County residents with VTE (deep vein thrombosis in arm or leg, pulmonary embolism, or thrombosis in other locations like cerebral, renal, hepatic, portal, mesenteric and splenic veins) was constructed as previously described [Silverstein MD, et al. *Archives of Internal Medicine* 1998;158(6):585-5930] and utilizing a validated VTE-phenotype radiology natural language processing (NLP) algorithm. This NLP algorithm “read” every Mayo Clinic and Olmsted Medical Center radiology report and notified the investigators (JAH, AAA) of Olmsted County residents with potential VTE. After investigators’ review and identification of potential cases, trained and experienced nurse

abstractors reviewed all medical records in the community [Kurland LT, et al. *Scientific American.* 1981;245(4):54-63] of these potential VTE cases using explicit criteria and a standardized electronic data collection instrument with appropriate data checks to verify eligibility and record the date and type of incident VTE, baseline characteristics, and vital status at last clinical contact, as previously described [Silverstein MD, et al. *Archives of Internal Medicine* 1998;158(6):585-593; Heit JA, et al. *Thrombosis and Haemostasis.* 2017;117(2):390-400]. For this study, only first lifetime acute CVST cases that were objectively confirmed by CT venography, MR venography, conventional angiography or autopsy were included. Residency in Olmsted County at the time of first diagnosis of VTE was confirmed by the REP.

1.c. *CVST incidence analysis:* The REP census tracks residency status of anyone seen at any medical facility in Olmsted County who has received a medical diagnosis. Each individual ever a resident in Olmsted County from 1966 to present who had a medical diagnosis has a timeline [St Sauver JL, et al. *Am J Epidemiol.* 2011;173(9):1059-1068]. The population living in Olmsted County on July 1st of each year as determined by the REP census was used as the denominator in the incidence calculation. The overall age- and sex-specific incidence rates (per 100,000 person-years) were calculated using incident cases of CVST as the numerator and age-sex-specific determination of the Olmsted County population as the denominator; age- and sex-specific 2010 US population counts were used to determine adjusted rates. Confidence interval (CI) estimates were based on the Poisson distribution for the

numerator, considering the denominator a constant. Stat Pages (https://statpages.info/confint.html) was used for these 95% CI calculations.

2. CVST incidence rate after Ad26.COV2.S vaccination:

2.a. *Cohort identification:* The U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended the administration of a single intramuscular injection of Ad26.COV2.S vaccine for immunization against SARS-CoV-2 (COVID-19) infection after data from phase-3 trial demonstrated the vaccine to be highly effective in reducing the risk of moderate to severe COVID-19 infection [https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/Janssen-covid-19-vaccine; Oliver SE, et al. *MMWR Morbidity Mortality Weekly Report* 2021;70(9):329-332; Sadoff J, et al. *New England Journal of Medicine* 2021;384(23):2187-2201]. Vaccine Adverse Event Reporting System (VAERS; http://vaers.hhs.gov) is a passive reporting system co-managed by the CDC and the FDA for detection of possible adverse events after administration of U.S.-licensed vaccines. Using the CDC Wonder tool (https://wonder.cdc.gov/vaers.html; access date: May 14, 2021), VAERS data were queried using the "Symptoms" search terms "cerebral venous sinus thrombosis" (MedDRA:10083037) and "cerebral venous thrombosis" (MedDRA: 10008138) to identify all potential CVST events that were submitted and processed as of May 7, 2021, and occurred within 92 days after the administration of any U.S.-licensed COVID-19 vaccine. Details of each VAERS CVST event were reviewed and abstracted by a

study investigator (AAA); only “objectively” diagnosed CVST events (i.e., the VAERS report included a detailed event description and/or the radiologic findings that led to the of CVST diagnosis) were included. The VAERS event information and description were also carefully reviewed to exclude potential duplicate reports submitted for the same CVST event by comparing age, sex, date of vaccination, date of onset of symptoms, date of CVST diagnosis (if available), vaccine type/ manufacturer, the U.S. State/ Territory from where the event was submitted, and the overall description of the adverse event.

2.b. *Ad26.COV2.S vaccine associated CVST incidence analysis:* The total number of age-, sex-, and manufacturer-specific COVID-19 vaccinations up to May 7, 2021 was accessed from the CDC’s ACIP conference (https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf; May 12, 2021) and was used as the denominator for the post-Ad26.COV2.S vaccination CVST incidence calculation. Since the period of risk for CVST after Ad26.COV2.S vaccination is unknown, age- and sex-specific incidence rates of Ad26.COV2.S vaccine-associated CVST were calculated assuming three (15-, 30- and 92-day) plausible post-vaccination at-risk periods. CVST events occurring within the specified post-vaccination at-risk period were used as the numerator for incidence rate calculations. The 95% CI intervals were calculated using Stat Pages. Total and age- and sex-specific risk conferred by Ad26.COV2.S vaccination (incidence rate ratio; IRR) was estimated by dividing observed post-vaccination CVST incidence rate by the pre-vaccination expected pre-pandemic incidence rate. To test its

significance, we performed an exact binomial test using the ‘binom.test()’ function in the statistical package R (version 4.0.3) to evaluate whether the proportion of CVST cases post-Ad26.COV2.S vaccination (versus those occurring pre-pandemic in Olmsted County residents) was consistent with their respective proportion of person-years at-risk for CVST. Finally, confidence intervals around IRR for rate of CVST cases occurring post-Ad26.COV2.S vaccination relative to the Olmsted County rate was calculated by using the exact binomial confidence interval utilizing Stat Pages (https://cran.r-project.org/web/packages/rateratio.test/vignettes/rateratio.test.pdf).