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Age-Stratified Risk of Cerebral Venous Sinus Thrombosis After SARS-CoV-2 Vaccination

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ABSTRACT

Background and Objectives

Cerebral Venous Sinus Thrombosis (CVST) as a part of the thrombosis and thrombocytopenia syndrome is a rare adverse drug reaction of SARS-CoV-2 vaccination. Estimated background rate of CVST with thrombocytopenia is 0.1 per million per month. We assessed the age-stratified risk of CVST with and without thrombocytopenia after SARS-CoV-2 vaccination.

Methods

We estimated the absolute risk of CVST with and without thrombocytopenia within 28 days of first dose of four SARS-CoV-2 vaccinations, using data from the European Medicines Agency's EudraVigilance database (until 13 June 2021). As a denominator, we used data on vaccine delivery from 31 European countries. For 22.8 million adults from 25 countries, we estimated the absolute risk of CVST after the first dose of ChAdOx1 nCov-19 per age category.

Results

The absolute risk of CVST within 28 days of first dose vaccination was 7.5 (95%CI 6.9-8.3), 0.7 (95%CI 0.2-2.4), 0.6 (95%CI 0.5-0.7) and 0.6 (95%CI 0.3-1.1) per million of first doses of ChAdOx1 nCov-19, Ad26.COV2.S, BNT162b2 and mRNA-1273, respectively. The absolute risk of CVST with thrombocytopenia within 28 days of first dose vaccination was 4.4 (95%CI 3.9-4.9), 0.7 (95%CI 0.2-2.4), 0.0 (95%CI 0.0-0.1) and 0.0 (95%CI 0.0-0.2) per million of first doses of ChAdOx1 nCov-19, Ad26.COV2.S, BNT162b2 and mRNA-1273, respectively. In recipients of ChAdOx1 nCov-19, the absolute risk of CVST, both with and without thrombocytopenia, was the highest in the 18-24 years age group (7.3 per million, 95%CI 2.8-18.8 and 3.7 per million, 95%CI 1.0-13.3, respectively). The risk of CVST with thrombocytopenia in ChAdOx1 nCov-19 recipients was the lowest in the age group≥70 years (0.2, 95%CI 0.0-1.3). Age <60 compared to ≥60 was a predictor for CVST with thrombocytopenia (incidence rate ratio 5.79; 95%CI 2.98-11.24, p<0.001).

Discussion

The risk of CVST with thrombocytopenia within 28 days of first dose vaccination with ChAdOx1 nCov-19 was higher in younger age groups. The risk of CVST with thrombocytopenia was slightly increased in patients receiving Ad26.COV2.S, compared with the estimated background risk. The risk of CVST with thrombocytopenia was not increased in recipients of SARS-CoV-2 mRNA vaccines.

INTRODUCTION

Vaccination is the most effective method to combat the COVID-19 pandemic. [1,2] The European Medicines Agency (EMA) has positively evaluated four vaccines against SARS-CoV-2: two adenoviral vector-based vaccines (ChAdOx1 nCov-19, AstraZeneca/Oxford, and Ad26.COV2.S, Janssen/Johnson&Johnson) and two messenger RNA-based vaccines (BNT162b2, Pfizer/BioNTech, and mRNA-1273, Moderna), which were later authorized for use in the European Union. [3]

COVID-19 vaccination campaigns suffered a drawback after cases of cerebral venous sinus thrombosis (CVST), and other thromboses at unusual sites, were reported in individuals who had been recently vaccinated with an adenoviral vector-based vaccine. [4-8] Given concomitant thrombocytopenia, which is otherwise rare in CVST patients [9], an auto-immune-mediated platelet-activating and -consuming pathophysiological mechanism was suggested. [4,5] Indeed, a pivotal role for vaccine-induced auto-immune anti-platelet factor-4 was identified. [4,5] The newly described condition was termed vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis and thrombocytopenia syndrome (TTS). [4,10] Because younger vaccine recipients were thought to be at a higher risk for thrombotic complications, many European countries restricted use of ChAdOx1 nCov-19 and Ad26.COV2.S vaccines by introducing age limits for administration of these vaccines (eTable1). [11,12]

Despite introduction of various strategies for distribution of the adenoviral SARS-CoV-2 vaccines, there is still limited information on the absolute risk of CVST and TTS after SARS-CoV-2 vaccination, especially within specific age groups. This information is crucial for policymakers, so that evidence-based decisions can be made on whether age restrictions on the use of adenoviral vector SARS-CoV-2 vaccines are justified. Therefore, the aim of this study is to provide up-to-date estimates of the rates of CVST and CVST with thrombocytopenia after SARS-CoV-2 vaccination, stratified by age groups, using pharmacovigilance data from countries in the European Economic Area (EEA) and United Kingdom (UK).

METHODS

EudraVigilance database

EudraVigilance is a European passive surveillance system hosted and maintained by the European Medicines Agency, in which all reported suspected adverse drug reactions (ADRs) are collected. [13,14] The medicines regulatory authorities (national competent authorities) in all EEA countries, and the marketing authorization holders with products in those countries have a legal obligation to report all ADRs to EudraVigilance within 15 days for serious ADRs and 90 days for non-serious ADRs. All serious ADRs associated with products licensed on the European market occurring in the non-EEA countries (including the UK) are also reported to EudraVigilance. [15]

EudraVigilance data were obtained as described in a previous study. [16] Following formal requests by the authors (submitted 1 April 2021 and 10 June 2021), EMA authorities provided the authors with Level 2A access to EudraVigilance data for medicinal products for human use for each of the four approved SARS-CoV-2 vaccines (ChAdOx1 nCov-19, BNT162b2, mRNA-1273, and Ad26.COV2.S). The dataset contains Individual Case Safety Report (ICSR) data included in the Medical Dictionary for Regulatory Activities High Level Group Term (MedDRA HLGT, version 24.0) "Central nervous system vascular disorders". The extracted data include the suspected ADRs reported to the EudraVigilance post-marketing module until 13 June 2021.

Standard Protocol Approvals, Registrations, and Patient Consents

This analysis is based on data collected for pharmacovigilance purposes. Retrieved data included non-identifiable patient information only. No patients were directly recruited or actively involved. Since no human participants were involved, ethical approval or patient informed consent was not required.

Identification of CVST cases

Cases with reactions coded with MedDRA Preferred Terms (PTs) specific to CVST were considered to have CVST (eTable 2). In addition, we screened cases with other PTs that could potentially indicate CVST. Clinical data of these cases were independently screened by two investigators (KK, AM), using information from the reported Data Elements available (eTable 3). Cases marked as "potential CVST" by at least one of the investigators were adjudicated by a senior vascular neurologist (JMC), who made the final decision on whether to classify the case as CVST. After identification of the CVST cases, duplicate cases and cases with symptom onset before vaccination or longer than 28 days after the vaccination were excluded (Figure 1). We excluded cases associated with the second dose of SARS-

CoV-2 vaccines because the available data suggests that the risk of VITT after the second dose is much lower than after the first dose. [17]

Identification of CVST with and without thrombocytopenia

In order to identify cases and promote research aimed at confirming whether or not this condition is indeed linked to vaccination, the Brighton Collaboration has proposed a definition of TTS, which relies on evidence of thrombosis and new onset thrombocytopenia. [10] Therefore, we used reported thrombocytopenia as a close correlate of this condition.

Cases were considered to have thrombocytopenia if platelet counts <150 $x10^9$/L were reported in the "Result Unstructured Data" (F.r.3.4) (eTable 3) or if there was a concomitant "thrombocytopenia" PT reported (eTable 2). We assumed normal platelet counts in patients with no information on thrombocytopenia in the pharmacovigilance report.

Data collection on vaccine use

Aggregated data from 30 EEA countries on number of SARS-CoV-2 vaccine doses administered, per week and by age group, were collected through European Surveillance System (TESSy), a meta-data driven system from the European Centre for Disease Prevention and Control (ECDC) to which all EEA countries report data on communicable diseases. [18] In order to account for the reporting delay and the vaccine-to-symptom onset delay, the data on the vaccinated population was considered up to and including 30 May 2021 (week 21). Data on vaccine delivery from the UK was extracted from the safety update report from the Medicines & Healthcare products Regulatory Agency (MHRA), namely the analysis including data up to 2 June 2021. [19] Out of the 31 European countries that were assessed, age-stratified data on vaccine delivery per week was not available for France, Germany, Liechtenstein, the Netherlands, Norway and the United Kingdom.

Data imputation

We used multiple imputation with predictive mean matching for imputing missing age and days between vaccination and symptom onset for the CVST cases in the EudraVigilance database. Missing data on age category, first or second dose, and vaccine brand in the ECDC database were imputed using a weighted average, based on the assumption that distribution of missing data followed the observed distribution of dose, age and vaccine brand in complete cases.

Absolute risk and age-stratified analysis

We calculated the proportion and 95% confidence intervals (95%CI) of CVST with and without thrombocytopenia per one million individuals vaccinated with a first dose of a SARS-CoV-2 vaccine using the Wilson score method. For the age-stratified analysis we excluded

BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines given the low numbers of CVST cases after each of these three vaccines. We extracted data on vaccine delivery for all age categories provided by the ECDC, including individuals aged <18 years old. Pediatric cases were excluded from the age-stratified analysis because of limited numbers of vaccines administered (12617 in total for all four vaccines of which 360 (3%) were ChAdOx1 nCov-19 vaccinations). Absolute risk analyses were stratified according to the following age groups used by the ECDC for vaccine delivery: 18-24, 25-49, 50-59, 60-69 and ≥70 years. To calculate the overall absolute risk of CVST, data from both EEA countries and the United Kingdom were used. In the age-stratified analysis, we excluded countries for which age-stratified data were not available (eTable 4 in the Supplement).

Additionally, we fitted a Poisson regression model to investigate the incidence rate ratio of CVST with thrombocytopenia conditional on age (<60 versus ≥60) with a logarithm of total number of vaccines delivered as an offset variable. No interaction terms were included. We performed a sensitivity analysis restricted to cases for which we had no missing data on any of the variables of interest (baseline features of CVST cases and vaccine delivery).

Risk before and after the implementation of age restrictions in vaccine delivery

We performed a sensitivity analysis comparing age-stratified absolute risks before and after 28 March 2021 (week 12). This cut-off date was chosen because most European countries had implemented age restrictions for ChAdOx1 nCov-19 vaccine use by then (eTable 1). [20] The aim was to confirm a decrease in the absolute risk, without changes in the estimated age-stratified risk, based on the hypothesis of increased risk in younger recipients. Moreover, the pre-print of the first article about VITT was published on 28 March 2021, [4,21] which could have resulted in increased reporting of CVST cases, particularly with thrombocytopenia, after SARS-CoV-2 vaccination.

Vaccination dates in cases with missing date of first vaccination were calculated using the date of the symptom onset and the imputed number of days between vaccination and symptom onset. Cases with both unknown date of vaccination and date of symptom onset were excluded from this analysis (n=5). Data from Romania were additionally excluded from the age-stratified data in this temporal analysis since cumulative age-stratified data were provided for Romania after week 13 only.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0.0.1 (IBM Corp., Armonk, N.Y., USA), RStudio version 1.3.1093 (RStudio, PBC, Boston, USA) and R version 4.0.3 (2020, R Core Team, Vienna, Austria) using the “Hmisc” and “ISwR” and packages.

Data Availability

De-identified participant data from the EudraVigilance database are not publicly available, but may be obtained from the European Medicines Agency upon official request. [22] Data on vaccine delivery from the ECDC are publicly available.

RESULTS

By 30 May 2021, and considering first doses only, 61.7 million doses of ChAdOx1 nCov-19, 128.2 million doses of BNT162b2, 15.6 million mRNA-1273 and 3.0 million doses of Ad26.COV2.S had been administered in the 31 European countries that were assessed (eTable 4). Between 4 December 2020 and 13 June 2021, among 8,537 individual cases with at least one reaction in the MedDRA HLGT 'Central nervous system vascular disorders' , we identified 550 CVST cases in the EEA and the UK, 276 (50%) of whom had concomitant thrombocytopenia reported.

Of the 276 CVST cases with thrombocytopenia that originated from the EEA or UK, 269 (97%) occurred after ChAdOx1 nCov-19 vaccination, 2 (1%) after Ad26.COV2.S, and 5 (2%) after BNT162b2. Of the CVST cases without thrombocytopenia, 197 (72%) occurred after ChAdOx1 nCov-19 vaccination, 68 (25%) after BNT162b2 and 9 after (3%) mRNA-1273. The baseline characteristics of patients with CVST after ChAdOx1 nCov-19 vaccination are described in eTable 5. Mortality was higher in patients with CVST with thrombocytopenia (31% [95%CI 26-37]), compared to CVST without thrombocytopenia (7% [95%CI 4-12]) after ChAdOx1 nCov-19 vaccination.

Overall absolute risk of CVST after vaccination for SARS-CoV-2

The overall absolute risk of CVST after ChAdOx1 nCov-19 and Ad26.COV2.S vaccinations was 7.5 (95%CI 6.9-8.3) and 0.7 (95%CI 0.2-2.4) per million of first doses administered, respectively (Figure 2, Table 1). The overall absolute risk of CVST after mRNA vaccines – i.e. BNT162b2 and mRNA-1273,was 0.6 (95%CI 0.5-0.7) and 0.6 (95%CI 0.3-1.1) per million first doses, respectively.

The absolute risk of CVST with thrombocytopenia after ChAdOx1 nCov-19 vaccination was 4.4 (95%CI 3.9-4.9) per million. The risk of CVST with thrombocytopenia after Ad26.COV2.S was lower, at 0.7 (95%CI 0.2-2.4) per million first doses. The risk of CVST with thrombocytopenia after mRNA vaccines was negligible at 0.0 (95%CI 0.0-0.1) per million first doses for BNT162b2 and 0.0 (95%CI 0.0-0.2) per million first doses for mRNA-1273 (Figure 2, Table 1).

Similar to CVST with thrombocytopenia, the overall absolute risk of CVST without thrombocytopenia for ChAdOx1 nCov-19 vaccination – 3.2 (95%CI 2.8-3.7) per million – was the highest of all vaccines. The remaining three vaccines showed absolute risks of 0.6 (95%CI 0.3-1.1), 0.5 (95%CI 0.4-0.7) and 0.0 (95%CI 0.0-1.3) for mRNA-1273, BNT162b2 and Ad26.COV2.S, respectively (Figure 2, Table 1).

Age-stratified risk of CVST after vaccination with ChAdOx1 nCov-19

In the age-stratified analysis (Figure 3 and eTable 6), the absolute risk of CVST after ChAdOx1 nCov-19 was the highest in the 18-24 years age group (total CVST 11.0 [95%CI 5.0-23.9]). In the age groups 60-69 years and ≥70 years the risk of CVST in general was the lowest – 2.2 (95%CI 1.4-3.3) and 1.3 (95%CI 0.6-2.9), respectively (Figure 3 and eTable 6). No pediatric CVST cases were reported.

The risk of CVST with thrombocytopenia was also the highest in the age category between 18-24 years (7.3 [95%CI 2.8-18.8] per million first doses administered), and the lowest in the ≥70 years age category (0.2 [95%CI 0.0-1.3]) per million first doses administered). The risk of CVST with thrombocytopenia in the category between 60 and 69 years old, was at 1.1 (95%CI 0.6-2.0) per million first doses administered (Figure 3 and eTable 6).

The aggregated absolute risk of CVST with thrombocytopenia for people aged below 60 was 7.8 (95%CI 6.2-9.9) per million first doses, whereas for the group aged 60 and above it was 1.9 (95%CI 1.3-2.8). The incidence rate ratio for CVST with thrombocytopenia after ChAdOx1 nCov-19 vaccination for people under 60 was 5.79 (95%CI 2.98-11.24), compared to the people aged 60 and above ($p<0.001$).

The age-stratified risk of CVST without thrombocytopenia after ChAdOx1 nCov-19 vaccination was, similarly to the total CVST and CVST with thrombocytopenia, the highest in the 18-24 years age group (3.7 [95%CI 1.0-13.3]) and the lowest in the 60-69 and ≥70 years age groups (1.1 [95%CI 0.6-2.0] and 1.1 [95%CI 0.5-2.6]).

Sensitivity analysis comparing CVST risk before and after 28 March 2021

The absolute risk of CVST with thrombocytopenia after ChAdOx1 nCov-19 vaccination was higher before 28 March 2021 when compared to the absolute risk after 28 March 2021 (5.6 per million first doses [95%CI 4.5-7.0] versus 2.2 per million (95%CI 1.7-2.9), respectively) (eTable 7). The same trend was observed in absolute risk of CVST without thrombocytopenia before and after 28 March 2021 (5.5 per million first doses [95%CI 4.4-6.9] compared to 1.8 per million first doses [95%CI 1.3-2.4], respectively) (eTable 7). The age-stratified risk of CVST with thrombocytopenia before and after 28 March 2021 was comparable (eTable 8).

Sensitivity analysis on data imputation

The sensitivity analysis removing the imputed data on both vaccine delivery and baseline features of reported CVST cases yielded similar absolute risks of CVST with and without thrombocytopenia in comparison with the absolute risks when including the imputed data (eTable 9).

DISCUSSION

In this study we used post-authorization safety reports and official data on vaccine delivery from 30 EEA countries and the UK, from December 2020 to June 2021, to calculate the absolute risk of CVST within 28 days after SARS-CoV-2 vaccination.

The overall risk of CVST with thrombocytopenia was the highest after vaccination with ChAdOx1 nCov-19. This finding is in accordance with previous studies, specifically a cohort study from Norway and Denmark and a study based on a web-questionnaire that covered nine German States. [23,24] The Scandinavian study showed an excess of 25 (95%CI 9-52) CVST cases per million individuals vaccinated with ChAdOx1 nCov-19 vaccine. [23] Although this number is higher than 7.5 (95%CI 6.9-8.3) per million absolute risk estimated in our study, this could be explained by differences in the reporting rates between countries, as well as variability in true incidence, possibly related to differences in the vaccinated population. Of note is the fact that in these countries ChAdOx1 nCov-19 has been primarily given to healthcare and social workers, resulting in a large part of the vaccinated population being relatively young, and therefore carrying a higher background risk of CVST. Moreover, since the individuals were followed up from the moment of vaccination, they were more likely to be readily diagnosed, including the mild cases, which might have been missed in our study. Nevertheless, we believe that the numbers we provide are more generalizable because of the wider study time interval and data from 31 countries. Importantly, the rate of CVST with thrombocytopenia was not specifically assessed in these studies and the estimated rates were rather imprecise..

The incidence of thrombocytopenia among CVST cases not related to vaccination is only 8%[9]. Therefore, assuming an annual CVST risk of 13 cases per million[25] and a time window of 4 weeks, the expected background risk of CVST with thrombocytopenia would be approximately 0.1 persons per million. Compared to this expected background risk, the calculated risk of CVST with thrombocytopenia in the current study is clearly higher for the ChAdOx1 nCov-19 vaccine (4.4 per million [95%CI 3.9-4.9]) and – to a lesser extent – for the Ad26.COV2.S vaccine (0.7 per million [95%CI 0.2-2.4]). In contrast, the calculated risks of CVST with thrombocytopenia after both mRNA vaccines (BNT162b2 and mRNA-1273 - 0.0 [95%CI 0.0-0.1 and 0.0-0.2, respectively]) are in line with the background risk [9,25], which suggests that there is no causal link between these vaccines and CVST with thrombocytopenia.[16]

The absolute risk of CVST with thrombocytopenia was lower after Ad26.COV2.S than after ChAdOx1 nCov-19. This observation, however, should be interpreted with caution, since the number of people vaccinated with Ad26.COV2.S vaccine was much smaller than with ChAdOx1 nCov-19. These findings are in accordance with the data from the Center for Disease Control and Prevention (CDC) in the United States, which has estimated the risk of

CVST with thrombocytopenia after Ad26.COV2.S as 0.87 per million doses administered. [26] Nevertheless, possible differences in age and sex distribution of vaccine recipients between the United States and Europe should be acknowledged when making this comparison.

The age-stratified analysis confirms that the risk of developing CVST with thrombocytopenia after ChAdOx1 nCov-19 vaccination varies with age and provides a quantification per age group. People between 18 to 24 years had the highest risk, although with a wide confidence interval (7.3 per million, [95%CI 2.8-18.8]). This group was followed by the age category from 25 to 49 years (4.1 per million first doses [95%CI 2.7-6.3]) and 50 to 59 years (5.0 per million first doses [95%CI 3.1-8.1]). Although the risk in people aged from 60 to 69 years was substantially lower, we still found 1.1 (95%CI 0.6-2.0) events per million first doses. At the age of 70 and above, the risk of developing CVST with thrombocytopenia was extremely low, i.e. around one per five million vaccine recipients.

The association between lower age and increased risk of CVST with thrombocytopenia in people vaccinated with ChAdOx1 nCov-19 is further supported by the observed decline in the overall rate of CVST with thrombocytopenia after the implementation of age restrictions in Europe, with comparable age-stratified rates of CVST and thrombocytopenia over time.

Finally, we also found an increased rate of CVST without thrombocytopenia in recipients of ChAdOx1 nCov-19, compared to the other vaccines. CVST is a rare disease, with an overall incidence among adults of around one person per million per month. [25] Even so, we cannot exclude that this high overall risk of CVST without thrombocytopenia after ChAdOx1 nCov-19 vaccination compared to the risk of CVST without thrombocytopenia after the mRNA vaccines is related with underreporting of thrombocytopenia in some of these cases, causing incorrect classification to this group. The slightly higher mortality rate in these patients, comparing with historical data (7% vs 4%), may support this hypothesis. [27]

The main strength of our study is its multinational population-based approach, implemented in the European setting of pharmacovigilance, which includes centralized and updated registries both of vaccine delivery and of adverse reactions, with national coverage across most European countries and mandatory reporting to the European Medical Agency.

The findings in this report are subject to several limitations. First, EudraVigilance data are based on a well-established but passive surveillance system and, therefore, reported cases of CVST with thrombocytopenia are likely to be an underestimation of the true number of cases of CVST with thrombocytopenia. Nevertheless, the large difference found in the mortality rates among patients with CVST with and without thrombocytopenia, in line with the rates described in previous cohort studies, suggests that this strategy is accurate in

identifying patients with TTS. [4,27,28] Moreover, underreporting of thrombocytopenia among earlier CVST cases is plausible, particularly before March 2021 when details of this new condition were not yet known. [4,29] Also, reporting bias associated to increased surveillance of vaccine recipients, and particularly younger people, cannot be excluded. Moreover, reporting practices likely differed over time, per country, and per vaccine. As awareness of TTS increased, reporting of CVST likely improved. However, we performed a sensitivity analysis comparing these two time periods, in which we could confirm similar rates of events per age group over time. In addition, early reports of TTS after the ChAdOx1 nCov-19 and Ad26.COV2.S vaccines might have led to more complete reporting for the adenoviral vector vaccines compared to the mRNA vaccines. Second, age-stratified data on vaccine delivery was only available for 25 European countries, leading to the exclusion of a substantial number of reports that originated from other European countries. The overall risk analysis was based on 61.7 million first doses of ChAdOx1 nCov-19 vaccine administered, whereas the age-stratified analysis was based on 22.8 million administered first doses of the ChAdOx1 nCov-19 vaccine (37%). Also, because of the lower numbers of Ad26.COV2.S vaccines distributed and the rarity of the reported events of CVST with thrombocytopenia associated to this vaccine in Europe, we could not provide age-stratified estimates of risk for this adenoviral-based vaccine. Furthermore, this analysis could not include stratification according to sex, which could be an important modifier when identifying the populations at risk. Third, because TTS is not reported as a diagnosis in EudraVigilance, instead we relied on the reporting of thrombocytopenia as a correlate of this condition, whereas further diagnostics, such as anti-Platelet Factor 4 tests, were hardly reported. Although we cannot exclude alternative causes of thrombocytopenia, it is unlikely that previous thrombocytopenia would be reported as an adverse event. Fourth, we restricted our analysis to the risk associated with the first dose of vaccine. Still, the number of suspected TTS cases associated to the second dose of a SARS-CoV-2 vaccine is, thus far, very low. [30] Fifth, the CVST diagnoses were not centrally validated, and therefore the accuracy of the diagnosis cannot be ascertained. Since CVST can be a challenging diagnosis, a risk of selective reporting and underreporting is present. Furthermore, as the background rate estimate is low and imprecise, we also do not provide excess risk calculation. Lastly, the data collected refers only to European countries (EEA countries and UK), and therefore the risk estimates might not be generalizable to the entire population of persons who have received SARS-CoV-2 vaccines.

In conclusion, using health surveillance data from 31 European countries, we have observed an increased risk of CVST with and without thrombocytopenia in patients receiving a first dose of ChAdOx1 nCov-19, variable according to the age group. People aged 18-24 had the highest risk of CVST after ChAdOx1 nCov-19. The risk of CVST with thrombocytopenia was increased after Ad26.COV2.S compared to the expected background risk, albeit to a much

lesser extent than after ChAdOx1 nCov-19. The risk of CVST with thrombocytopenia after mRNA vaccines was negligible. This study provides age-stratified estimates for the risk of CVST with and without thrombocytopenia in patients receiving the first dose of the SARS-CoV-2 vaccination ChAdOx1 nCov-19. Although the finding of increased risk of CVST with thrombocytopenia in younger patients receiving ChAdOx1 nCov-19 has important public health implications, it should be noted that even the highest absolute risk for CVST calculated in our study - 11.0 (95%CI 5.0-23.9) cases per million (in population between 18 and 24 years old vaccinated with ChAdOx1 nCov-19) is low compared to the rate of 42.8 (95%CI 28.5-64.2) CVST cases per million recently reported in a study assessing COVID-19-infected individuals.[31,32] Therefore, several factors have to be considered at a national and regional level, such as the risk of COVID-19 infection, the efficacy of each vaccine against the circulating viral variants, the availability of other vaccines and the capacity of the local healthcare systems.

Supplement --- http://links.lww.com/WNL/B686

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TABLES

Table 1. Absolute risk of CVST after ChAdOx1 nCov-19, BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines in the European Economic Area and United Kingdom.

Vaccine	Total number of vaccines delivered (first/single dose)[1]	Total CVST		CVST with thrombocytopenia		CVST without thrombocytopenia[2]	
		Number of reported cases	Absolute risk per million doses (95%CI)	Number of reported cases	Absolute risk per million doses (95%CI)	Number of reported cases	Absolute risk per million doses (95%CI)
ChAdOx1 nCov-19	61,738,630	466	7.5 (6.9-8.3)	269	4.4 (3.9-4.9)	197	3.2 (2.8-3.7)
BNT162b2	128,192,215	73	0.6 (0.5-0.7)	5	0.0 (0.0-0.1)	68	0.5 (0.4-0.7)
mRNA-1273	15,569,573	9	0.6 (0.3-1.1)	0	0.0 (0.0-0.2)	9	0.6 (0.3-1.1)
Ad26.COV 2.S	3,023,204	2	0.7 (0.2-2.4)	2	0.7 (0.2-2.4)	0	0.0 (0.0-1.3)

CVST: cerebral venous sinus thrombosis.
[1] missing data on the dose (n = 9,114) and vaccine type (n = 611,459) was imputed
[2] defined as all CVST with exclusion of CVST with reported thrombocytopenia

FIGURE LEGENDS

Figure 1. Selection of cases from the EudraVigilance database

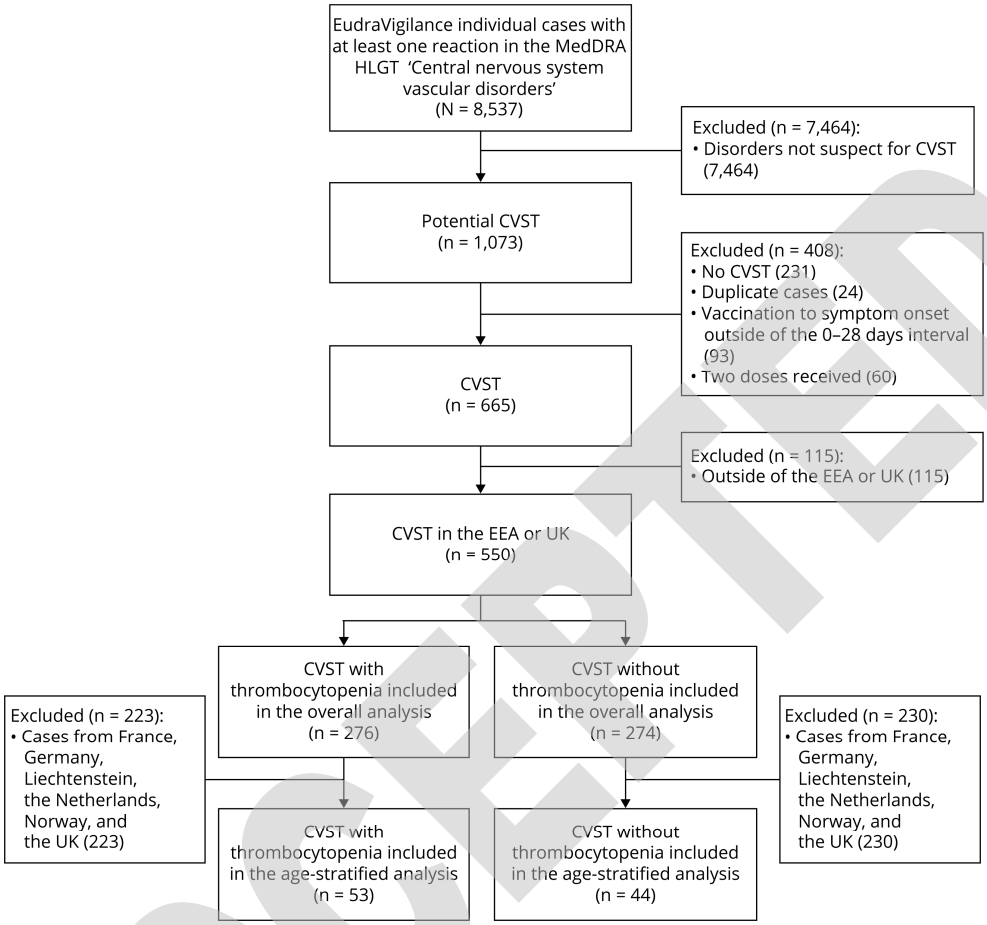


Figure 2. Overall absolute risk of CVST with and without thrombocytopenia for all licensed vaccines in the European Economic Area and the United Kingdom

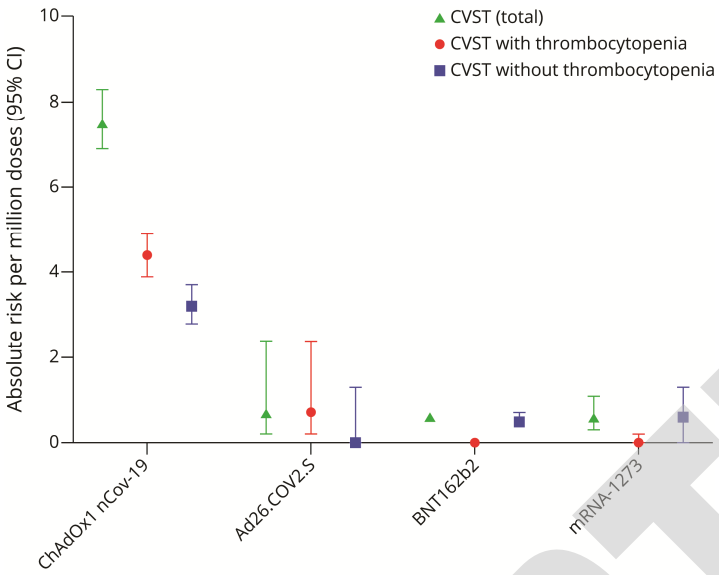
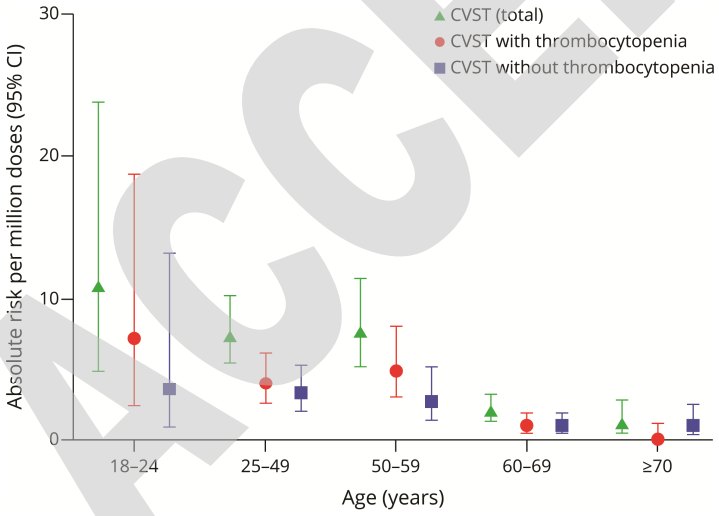


Figure 3. Age-stratified absolute risk of CVST with and without thrombocytopenia after ChAdOx1 nCov-19 vaccination



Age-Stratified Risk of Cerebral Venous Sinus Thrombosis After SARS-CoV-2 Vaccination

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