Thromboembolism and the Oxford–AstraZeneca COVID-19 vaccine: side-effect or coincidence?

By mid March, 2021, vaccination against COVID-19 using the ChAdOx1 nCoV-19 (AZD1222) vaccine from Oxford–AstraZeneca[1,2] was paused in a number of European countries due to reports of thromboembolic events in vaccinated individuals.[3] According to the European Medicines Agency (EMA), 30 cases of thromboembolic events (predominantly venous) had been reported by March 10, 2021, among the approximately 5 million recipients of the Oxford–AstraZeneca COVID-19 vaccine in the European Economic Area.[3] The EMA subsequently stated that "The number of thromboembolic events in vaccinated people is no higher than the number seen in the general population".[4] To inform the ongoing discussion on the safety of the Oxford–AstraZeneca COVID-19 vaccine, we analysed nationwide population-based data from Denmark to estimate the natural incidence of venous thromboembolism.[5]

Denmark has a tax-supported universal health-care system,[6] in which all hospital contacts are registered in the Danish National Patient Registry.[7] We first used the Danish Civil Registration System[6] to identify all Danes who were at least 18 years old between Jan 1, 2010, and Nov 30, 2018. Using data from the Danish National Patient Registry, we then identified all first-time cases of venous thromboembolism in the general adult population in this period (corresponding to the available data period). We focused on venous thromboembolism because the thromboembolic events reported in relation to the Oxford–AstraZeneca COVID-19 vaccine by March 10, 2021, were predominantly venous, according to publicly available data on EudraVigilance.[3] We followed all individuals from Jan 1, 2010, or their 18th birthday (whichever came first), until their first incident venous thromboembolism (see definition below), death, emigration, or Nov 30, 2018. Individuals with a diagnosis of venous thromboembolism before Jan 1, 2010, or their 18th birthday were not included in the analyses. Incident venous thromboembolism was defined as the first primary or secondary inpatient hospital diagnosis or outpatient clinic diagnosis of venous thromboembolism. Specifically, the following diagnoses were included in the outcome definition: deep vein thrombosis (International Classification of Diseases version 10 [ICD-10]: I80.1–3), pulmonary embolism (ICD-10: I26), portal vein thrombosis (ICD-10: I81), hepatic vein thrombosis (ICD-10: I82.0), thrombophlebitis migrans (ICD-10: I82.1), embolism or thrombosis of vena cava (ICD-10: I82.2), embolism or thrombosis of renal vein (ICD-10: I82.3), mesenteric thrombosis (ICD-10: K55.0H), cerebral infarction due to non-pyogenic cerebral venous thrombosis (ICD-10: I63.6), and non-pyogenic thrombosis of intracranial venous system (ICD-10: I67.6).[5,8] The diagnoses of venous thromboembolism in the Danish National Patient Registry have a documented high positive predictive value.[9]

We then calculated incidence rates for venous thromboembolism (any of the diagnoses listed above) for all Danish adults (aged 18 years or older censored at the 100th birthday) as well as for Danes aged 18–64 years. The 18–64-year age group represents the age group in which the Oxford–AstraZeneca COVID-19 vaccine, due to initial perceptions of limited evidence on its efficacy among those aged 65 years and older, has predominantly been used in most European countries—with the exception of the UK, where the vaccine has also been administered among those aged 65 years and older from the outset.[10,11] We repeated the analysis restricting outcomes to deep vein thrombosis or pulmonary embolism, as they account for more than 95% of all diagnoses, and stratified by sex. All incidence rates were calculated by dividing the number of incident venous thromboembolisms during follow-up by the sum of person-years during follow-up and reported per 1000 person-years. Subsequently, using these incidence rates for venous thromboembolism, we estimated the number of cases that would be expected over the course of 1 week and 1 month, respectively, in a population with the same size as that having received the Oxford–AstraZeneca COVID-19 vaccine in Europe by March 10, 2021. This was done by rescaling the incidence rates to the weekly (7 days) and monthly level (30·5 days) per individual, and multiplying them by 5 million. An example of the calculation carried out for this estimation is provided in the appendix.

The study population aged 18–99 years included 4 915 426 individuals, with a total follow-up time of 38 449 703 person-years. The study population aged 18–64 years included 3 963 153 individuals, with a total follow-up time of 29 537 310 person-years. Equivalent sex-stratified numbers are provided in the appendix.

The number of venous thromboembolic events, as well as the incidence rates in the Danish population in the period from 2010 to November, 2018 are also provided in the appendix. The incidence rate per 1000 person-years was 1·76 (95% CI 1·75–1·78) for venous thromboembolism among Danes aged 18–99 years, and 0·95 (0·94–0·96) among Danes aged 18–64 years. When restricting to deep vein thrombosis or pulmonary embolism, the incidence rate per 1000 person-years was 1·70 (95% CI 1·68–1·71) among Danes aged 18–99 years and 0·91 (0·89–0·92) for those aged 18–64 years. The results were consistent for women and men (appendix).

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See **Online** for appendix

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In a population of 5 million people (ie, size matching the approximate number of people having received the Oxford–AstraZeneca COVID-19 vaccine in Europe by March 10, 2021[4]), this incidence would correspond to approximately 169 expected cases of venous thromboembolism per week, or 736 expected cases per month (if based on the incidence rate among the 18–99-year-old Danes). Similarly, if estimated based on the incidence rate among 18–64-year-old Danes, one would expect 91 cases of venous thromboembolism per week, or 398 cases per month.

The Danish data provided here cannot rule out the possibility that some venous thromboembolic events reported in relation to the use of the Oxford–AstraZeneca COVID-19 vaccine are caused by the vaccine. However, although affected by several limitations, these data suggest that the reported number of thromboembolic events among Europeans who have received the Oxford–AstraZeneca COVID-19 vaccine (at least those reported as deriving from the venous system) does not seem to be increased relative to the expected number estimated from incidence rates from the entire Danish population before the introduction of the vaccination programme.

Our findings should be interpreted in the context of their limitations. The number of cases of thromboembolism reported in relation to the Oxford–AstraZeneca COVID-19 vaccine cannot be directly compared to the numbers estimated based on the incidence rates from the Danish population for several reasons. First, data on the sex and age distribution from those who received the Oxford–AstraZeneca COVID-19 vaccine are not yet publicly available. In Denmark, about 99% of those having receiving the Oxford–AstraZeneca COVID-19 vaccine are health-care workers (Valentiner-Branth P, Statens Serum Institut, Denmark, personal communication). The median age of all COVID-19 vaccinated health-care workers in Denmark is 47 years (IQR 36–57), and 82·2% of health-care workers are women.[12] Second, data on the duration of the period during which the Oxford–AstraZeneca COVID-19 vaccinated population developed the reported thromboembolic events are also not publicly available, making it impossible to estimate incidence rates for this population. Third, detailed clinical descriptions of the thromboembolic events reported in relation to Oxford–AstraZeneca COVID-19 vaccinations are still lacking.[4] We are, however, aware that although a substantial fraction of the thromboembolisms seem to be venous, reports are emerging of rare types of multiple thrombosis, bleeding, and thrombocytopenia, apparently similar to disseminated intravascular coagulation, occurring in otherwise healthy individuals shortly after receiving the Oxford–AstraZeneca COVID-19 vaccine.[13] These outcomes are not included in the present analysis. Fourth, as even the most efficient spontaneous reporting of adverse events is unlikely to capture all cases, the true incidence rate of thromboembolic events in relation to the Oxford–AstraZeneca COVID-19 vaccine is unknown, and the 30 reported cases by March 10, 2021, is probably an underestimate. Finally, our estimated weekly and monthly venous thromboembolism case numbers in the population of 5 million individuals are based entirely on incidence rates from Denmark and might not be representative of the other countries where the Oxford–AstraZeneca COVID-19 vaccine has been used. However, previous studies of the incidence rate of venous thromboembolism in other countries have found numbers within range of the Danish rates.[14–16]

When making decisions on the use of drugs based on pharmacovigilance, it is important to take into account the natural incidence of illnesses, such as venous thromboembolisms, that might be interpreted as serious adverse events. Here, based on pre-pandemic incidence rates from the entire Danish population, we report that the number of venous thromboembolisms reported in relation to the Oxford–AstraZeneca COVID-19 vaccine does not seem to be increased beyond the expected incidence rate. Nevertheless, recent reports of thrombocytopenia-associated cerebral venous sinus thrombosis, multiple thrombosis, and bleeding within a short timeframe after receipt of the vaccine are concerning and are receiving due attention from health authorities. On March 18, 2021, with reference to the Oxford–AstraZeneca COVID-19 vaccine, the EMA concluded that "benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets".[17]

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*Søren Dinesen Østergaard, Morten Schmidt, Erzsébet Horváth-Puhó, Reimar Wernich Thomsen, Henrik Toft Sørensen
soeoes@rm.dk

Department of Affective Disorders (SDØ) and Department of Cardiology (MS), Aarhus University Hospital, 8200 Aarhus, Denmark; Department of Clinical Medicine (SDØ, MS, EH-P, RWT, HTS) and Department of Clinical Epidemiology (MS, EH-P, RWT, HTS), Aarhus University Hospital, Aarhus, Denmark

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