Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase

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To the Editor:

Coronavirus disease 2019 (COVID-19) is associated with a prothrombotic phenotype characterised by coagulopathy and endothelial dysfunction [1–4]. Following some cases of thrombosis after vaccination, the Oxford–AstraZeneca COVID-19 vaccine (AZD1222) was temporarily suspended by some European countries. The European Medicines Agency concluded that the benefits of the vaccine in combating the COVID-19 outbreak continue to outweigh the risk of side-effects. On 19 March, 2021, Germany reported 13 cases of sinus or cerebral vein thrombosis, with more than 1.6 million AstraZeneca COVID-19 vaccine doses administered. Some of these patients also had a heparin-induced thrombocytopenia (HIT)-like syndrome, which suggests an immunological event as one of the potential origins of thrombosis.

Here, we provide a descriptive analysis of the anti-SARS-CoV-2 vaccination thrombotic risk reported to the World Health Organization (WHO) Global Database for Individual Case Safety Reports (VigiBase). VigiBase is a databank developed and maintained by the Uppsala Monitoring Centre, Sweden. It is the world's largest pharmacovigilance database, with submissions from member states since the establishment of the WHO Program for International Drug Monitoring in 1968. Vigibase has been largely used in the past years to detect significant signals for adverse drug reactions [5]. Some adverse drug reactions to vaccines may be identified only after their commercialisation, in particular when the events are very rare or have a delayed time to onset. Therefore, the safety monitoring of vaccines continues in post-marketing surveillance. For example, during the mass vaccination campaign in 2009 for H1N1, several cases of narcolepsy were reported during the post-marketing period [6].

In this context, our study aimed to assess clinical features of arterial and venous thrombosis after injection of three anti-COVID-19 vaccines (Comirnaty® from Pfizer–BioNtech; Moderna COVID-19 vaccine, and AZD1222 from Oxford–AstraZeneca) [7–9] until 16 March, 2021. Between 13 December, 2020 and 16 March, 2021 (94 days), 361 734 967 people received a vaccination according to the international COVID-19 vaccination dataset [10] and 2161 thrombotic events were reported in Vigibase by 16 March, 2021. Spontaneous reports of thrombotic events are shared in 1197 persons for Comirnaty, 325 for the Moderna COVID-19 vaccine and 639 for AZD1222 (table 1). With these data, we were able to evaluate a reporting rate for venous (VTE) and arterial (ATE) thrombotic events cases during the time period (94 days) among the total number of people vaccinated using the following formula: number of thrombotic cases in the given time period divided by the total numbers of vaccinated person-days at risk during the same period. Thus, the rate was 0.21 (95% CI 0.19–0.22) cases of thrombotic events per 1 million vaccinated person-days. For VTE and ATE, rates were 0.075 (95% CI 0.07–0.08) and 0.13 (95% CI 0.12–0.14) cases per 1 million vaccinated person-days, respectively.

First and foremost, we have recorded an imbalance between VTE and arterial thrombotic ATE in mRNA vaccines: 31.8% (381/1197) and 67.9% (813/1197) for Comirnaty, respectively; and 24.6% (80/325) and 77.6% (253/325) for the Moderna vaccine. Conversely, for AZD1222 we have noticed that the proportion of VTE and ATE is more evenly shared: 52.2% (334/639) *versus* 48.2% (308/639), respectively. The time frame between vaccination and ATE is the same for the three vaccines (median of 2 days), whereas we

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This study observed an imbalance between venous and arterial thrombotic events in mRNA vaccines while with AZ1222 they are evenly shared. Our analysis highlights cerebral vein thrombosis with the three vaccines. https://bit.ly/3mZqguE

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TABLE 1 Clinical characteristics of patients described in the World Health Organization database of individual case safety reports, performed at the Uppsala Drug Monitoring Centre until 16 March, 2021 for the three vaccines: Comirnaty from Pfizer–BioNtech, the Moderna COVID-19 vaccine and the Oxford–AstraZeneca vaccine (AZD1222)

	Comirnaty	Moderna	AZD1222
Total cases	1197	325	639
Age years	76 (18–102)	72 (19–102)	67 (19–99)
Patient sex			
Female	708 (59.1%)	173 (53.2%)	332 (52%)
Male	483 (40.4%)	152 (46.8%)	291 (45.5%)
Unknown	6 (0.5%)		16 (2.5%)
Death	223 (18.6%)	53 (16.3%)	82 (12.8%)
Global time in days to thrombotic event	3 (0–52)	2 (0–63)	5 (0–55)
Venous thrombotic events	381 (31.8%)	80 (24.6%)	334 (52.3%)
Age years	62 (21–98)	58.5 (19–96)	63 (18–99)
Time in days to thrombotic event	4 (0–50)	4 (0–39)	6 (0–55)
Pulmonary embolism	211 (17.6%)	53 (16.3%)	115 (18%)
Lower limb thrombosis	111 (9.3%)	13 (4%)	113 (17.7%)
Cerebral venous sinus thrombosis	3 (0.3%)	3 (0.9%)	6 (0.9%)
Cerebral venous thrombosis	1 (0.1%)		1 (0.2%)
Undetermined venous thrombotic event	42 (3.5.%)	10 (3.1%)	92 (14.4%)
Others	13 (1.1%)	1 (0.3%)	7 (1.1%)
Arterial thrombotic events	813 (67.9%)	253 (77.6%)	308 (48.2%)
Age years	80 (18–102)	75 (21–102)	70 (21–99)
Time in days to thrombotic event	2 (0–52)	2 (0–63)	2 (0–38)
Stroke	561 (46.9%)	173 (53.1%)	219 (34.3%)
Acute myocardial infarction	238 (19.9%)	67 (20.6%)	81 (12.7%)
Stroke and myocardial infarction	2 (0.2%)	3 (0.9%)	
Others	12 (1%)[#]	10 (3.1%)	8 (1.3%)[¶]
Concomitant arterial and venous thrombotic events	10 (0.8%)	8 (2.4%)	4 (0.6%)
Age years	70.5 (25–86)	56 (37–94)	57.5 (31–71)
Time in days to thrombotic event	3.5 (0–11)	2 (0–22)	3 (1–12)
Acute myocardial infarction and pulmonary embolism	4 (0.3%)		1 (0.15%)
Stroke and pulmonary embolism	3 (0.3%)	6 (1.85%)	1 (0.15%)
Stroke and lower limb ischaemia	1 (0.1%)		
Arterio-venous fistula thrombosis	1 (0.1%)		
Arterial limb ischaemia and lower limb thrombosis	1 (0.1%)		
Stroke and lower limb thrombosis		1 (0.31%)	
Arterial and venous thrombosis		1 (0.31%)	
Pulmonary embolism and multiple thrombosis			1 (0.15%)
Acute myocardial infarction and venous thrombosis			1 (0.15%)
Associated thrombocytopenia and/or immunothrombosis disorders	32 (2.6%)	8 (2.4%)	14 (2.2%)
Age years	56 (19–92)	64 (51–77)	46.5 (19–73)
Time in days to event	4.5 (0–25)	4 (0–10)	8 (2–14)
Thrombocytopenia associated with pulmonary embolism	2 (0.2%)	1 (0.3%)	3 (0.5%)
Thrombocytopenia associated with acute myocardial infarction	3 (0.3%)		
Thrombocytopenia associated with stroke	13 (1.1%)		1 (0.2%)
Thrombocytopenia linked to purpura thrombotic thrombocytopenia	7 (0.6%)		
DIC	2 (0.2%)		
DIC positive lupus anticoagulant associated with visceral venous thrombosis	1 (0.1%)		
Positive lupus anticoagulant without thrombosis	2 (0.2%)		
Positive lupus anticoagulant associated with pulmonary embolism	2 (0.2%)	1 (0.3%)	
Positive lupus anticoagulant associated with stroke		4 (1.2%)	
Positive lupus anticoagulant associated with myocardial infarction		2 (0.6%)	
Thrombocytopenia associated with splenic venous thrombosis			1 (0.2%)
Thrombocytopenia with HIT-like mAb positive and multiple thrombosis			1 (0.2%)
Thrombocytopenia associated with cerebral venous sinus thrombosis			4 (0.6%)
Thrombocytopenia associated with cerebral venous thrombosis			1 (0.2%)
DIC and pulmonary embolism			1 (0.2%)
DIC and stroke			2 (0.3%)

Data are presented as n (percentage of cases reported) or median (range). [#]: others (limb, intestinal); [¶]: others (retinal, intestinal). DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia; mAb: antibody.

identified a significant difference between AZD1222 (median of 6 days) and both mRNA vaccines (median of 4 days, with p=0.007 and 0.02, respectively, for Comirnaty and the Moderna vaccine) for VTE. Concerning ATE, the patients' profile for the three vaccines appear to be similar.

Moreover, we observed unexpected cerebral venous thrombosis (CVT) with the Moderna vaccine (0.9% (3/325) of events reported; time to event: 2–39 days; age range: 30–37 years old; three women), with AZD1222 (1.1% (7/639) of events reported; time to event: 2–16 days; age range: 19–59 years old; three women and four men) and with Comirnaty (0.4% (4/1197) of events reported; time to event: 1–10 days; age range: 30–84 years-old; four women). Three patients out of four with Comirnaty, all with Moderna vaccine and six out of seven with AZ1222 had a particular form of CVT, called cerebral sinus vein thrombosis (CVST). Five out of seven CVT cases observed after AZD1222 were associated with thrombocytopenia. Moreover, we noticed thrombocytopenia associated with thrombotic events and/or disseminated intravascular coagulation and/or antiphospholipids antibodies for all three vaccines, and one thrombocytopenia associated with HIT-positive tests after AZD1222. Since we performed the data extraction from the WHO database, several other cases of HIT have been described by two groups after AZD1222 vaccination [11, 12]. They proposed to name this phenomenon vaccine-induced immune thrombotic thrombocytopenia (VITT).

There are several limitations in our data presented here. First, for pharmacovigilance purposes, the appropriate term is reporting rate. Incidence or prevalence are not appropriate since we have no information about the precise denominator for each separate vaccine and about the extent of underreporting. Indeed, these pharmacovigilance spontaneous reports are part of the post-marketing surveillance for drugs and underreporting of adverse drug reactions is well known [13]. In a published study, the median underreporting rate across the 37 studies included was 94% (interquartile range 82–98%) even for serious/severe adverse drug reactions.

Second, the best way to evaluate thrombotic events in the vaccinated population should be to match to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics [14]. However, using adverse drug reactions reported *via* VigiBase does not allow us to utilise this kind of paired data. Third, unusual reporting may have occurred because of the novelty of the vaccines. Indeed, study design may modify the reporting of adverse drug reactions [15]. Open-label studies have been described to overestimate the risk of vascular adverse events by at least 50% in comparison to double blind randomised trials [15]. Pharmacovigilance spontaneous reporting is different from clinical trials, but probably close to that of open-label studies for potential unusual estimation of thrombotic events that could be influenced by the novelty of the drug, media interest and/or conflicting results in the literature.

All in all, our data represents a hypothesis-generating study suggesting that thrombotic events, including CVT, might occur in association with all three vaccines, but this hypothesis requires further investigation, including extensive clinical and biological studies. The benefit of the vaccines is a non-discussion point in COVID-19 outbreak epidemiology. However, there is an urgent need for a prospective evaluation of coagulopathy and thrombotic events to fathom rare but serious side-effects after COVID-19 vaccination, and to better characterise VITT and other thrombocytopenia associated or not with thrombotic events after the three vaccines.

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