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Research letter

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

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To the Editor:

COVID-19 is associated with a prothrombotic phenotype characterized by coagulopathy and endothelial dysfunction (1-4). Following some cases of thrombosis after vaccination, Oxford-AstraZeneca vaccine (AZD1222) was temporarily suspended by some European countries. The European medicines agency (EMA) concluded that the benefits of the vaccine in combating COVID-19 outbreak continue to outweigh the risk of side effects. On March 19, 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 does suggest an immunological event as one of the potential origin 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 (UMC), Sweden. It is the world's largest pharmacovigilance database with submission 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 drugs reaction (ADRs) (5). Some ADRs may be identified only after vaccine commercialization, in particular when they 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 narcolepsia have been reported during post marketing period (6).

In this context, our study aims at assessing clinical features of arterial and venous thrombosis after injection of three anti-COVID-19 vaccines (Comirnaty® from Pfizer-BioNtech; COVID-19 vaccine Moderna and AZD1222 from Astra Zeneca) (7-9) until March 16th, 2021. Between December 13th, 2020 to March 16th, 2021 (94 days), 361734967 people received vaccination in international COVID-19 vaccination dataset (10) and 2161 thrombotic events (795 venous and 1374 arterial thrombotic event) were reported in Vigibase on March 16th 2021. Spontaneous reports of thrombotic events are shared in 1197 for Comirnaty, 325 for COVID-19 vaccine Moderna and 639 for AZD1222 vaccine (**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 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 person vaccinated-days. For VTE and ATE, rates were respectively 0,075 [95% CI: 0.07-0.08] and 0,13 [95% CI: 0.12-0.14] cases per 1 million person vaccinated-days.

First and foremost, we have been recording an imbalance between VTE and arterial thrombotic ATE in mRNA vaccines, respectively 31.8% (381/1197) and 67.9% (813/1197) for Comirnaty; 24.6% (80/325) and 77.6% (253/325) for Moderna vaccine. Conversely, for AZD1222 we have been noticing a proportion of VTE and ATE evenly shared (52.2% (334/639) vs 48.2%) (308/639) respectively). The timeframe between vaccination and ATE is the same for three vaccines (median of 2 days), whereas we 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 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) for COVID-19 vaccine Moderna (0.9% (3/325) of events reported; time to event: 2 to 39 days; range: 30-37 years-old; 3 women), for AZD1222 (1.1% (7/639) of events reported; time to event: 2 to 16 days; range: 19-59 years-old; 3 women and 4 men) and with Comirnaty (0.4% (4/1197) of events reported; time to event: 1-10 days;range:30-84 years-old; 4 women). Three patients out of four with Comirnaty, all 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 to thrombocytopenia. Moreover, we noticed thrombocytopenia associated to 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 extraction of the WHO database, several other cases of HIT has been described by two groups after AZ1222 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 purpose, the appropriate term is reporting rate. Incidence or prevalence are not appropriate since we have no information about 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 ADRs is well known (13). In a published

study, the median underreporting rate across 37 studies included was 94% (interquartile range 82-98%) even for serious/severe ADRs.

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, ADRs reported in VigiBase do not allow us to have this kind of paired data. Third, we could have an unusual reporting because of the novelty of the vaccine. Indeed, studies design may modify reporting of ADRs (15). Open-label studies have been described to overestimate the risk of vascular adverse events by at least 50% in contrast to double blind randomized trials (15). Pharmacovigilance spontaneous reporting is different from clinical trials but probably close to open-label studies for potential unusual estimation of thrombotic events that could be influenced by novelty of the drug, media interest and/or conflicting results in 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 investigations including extensive clinical and biological studies. Benefits of the vaccine 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 better characterize VIPIT and other thrombocytopenia associated or not with thrombotic events after the three vaccines.

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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 March 16th for the three vaccine Comirnaty® from Pfizer-BioNtech, COVID-19 vaccine Moderna and Oxford-AstraZeneca vaccine

Comirnaty® from Pfizer-BioNtech, n=1197 cases, median age 76 yo (18-102)			**COVID-19 vaccine Moderna, n=325 cases, median age: 72 yo (19-102)**			**Oxford-AstraZeneca vaccine (AZD1222), n=639, median age: 67 yo (19-99)**		
Patient sex	**Count**	**Percentage**	**Patient sex**	**Count**	**Percentage**	**Patient sex**	**Count**	**Percentage**
Female	708	59,1	Female	173	53,2	Female	332	52
Male	483	40,4	Male	152	46,8	Male	291	45,5
Unknown	6	0,5				Unknown	16	2,5
Death	**Count**	**Percentage**	**Death**	**Count**	**Percentage**	**Death**	**Count**	**Percentage**
	223	18,6		53	16,3		82	12,8
Global Time to thrombotic event: median (range): 3 days (0-52)			**Global Time to thrombotic event: median (range): 2days (0-63)**			**Global Time to thrombotic event: median (range): 5days (0-55)**		
Venous thrombotic events n=381/1197 (31,8%)			**Venous thrombotic events n=80/325 (24,6%)**			**Venous thrombotic events n=334/639 (52,3%)**		
Age median (range): 62 (21-98) Time to thrombotic event: median (range): 4 days (0-50)	**Count**	**Percentage in cases reported (n=1197)**	**Age median (range): 58,5 (19-96) Time to thrombotic event: median (range): 4 days (0-39)**	**Count**	**Percentage in cases reported (n=325)**	**Age median (range): 63 (18-99) Time to thrombotic event: median (range): 6 days (0-55)**	**Count**	**Percentage in cases reported (n=639)**
Pulmonary Embolism	211	17,6	Pulmonary Embolism	53	16,3	Pulmonary Embolism	115	18

Lower limb thrombosis	111	9,3	Lower limb thrombosis	13	4	Lower limb thrombosis	113	17,7
Cerebral venous sinus thrombosis	3	0,3	Cerebral venous sinus thrombosis	3	0,9	Cerebral venous sinus thrombosis	6	0,9
Cerebral venous thrombosis	1	0,1	Undetermined venous thrombotic event	10	3,1	Cerebral venous thrombosis	1	0,2
Undetermined venous thrombotic event	42	3,5	Others	1	0,3	Undetermined venous thrombotic event	92	14,4
Others	13	1,1				Others	7	1,1
Arterial thrombotic events n=813/1197 (67,9%)			**Arterial thrombotic events n=253 (77,6%)**			**Arterial thrombotic events n=308 (48,2%)**		
Age median (range): 80 (18-102) Time to thrombotic event: median (range): 2days (0-52)	**Count**	**Percentage in cases reported (n=1197)**	**Age median (range): 75 (21-102) Time to thrombotic event: median (range): 2 days (0-63)**	**Count**	**Percentage in cases reported (n=325)**	**Age median (range): 70 (21-99) Time to thrombotic event: median (range): 2 days (0-38)**	**Count**	**Percentage in cases reported (n=639)**
Stroke	561	46,9	Stroke	173	53,1	Stroke	219	34,3
Acute myocardial infarction	238	19,9	Acute myocardial infarction	67	20,6	Acute myocardial infarction	81	12,7
Stroke and MI	2	0,2	Stroke and MI	3	0,9	Others (retinal, intestinal)	8	1,3
Others (limb, intestinal)	12	1	Others	10	3,1			

Concomitant Arterial and Venous thrombotic events n=10/1197 (0,8%)			**Concomitant Arterial and Venous thrombotic events n=8/325 (2,4%)**			**Concomitant Arterial and Venous thrombotic events n=4/639 (0,6%)**		
Age median (range): 70,5 (25-86) - Time to thrombotic event: median (range): 3,5 days (0-11)	**Count**	**Percentage in cases reported (n=1197)**	**Age median (range): 56 (37-94) - Time to thrombotic event: median (range): 2days (0-22)**	**Count**	**Percentage in cases reported (n=325)**	**Age median (range): 57,5 (31-71) - Time to thrombotic event: median (range): 3day (1-12)**	**Count**	**Percentage in cases reported (n=639)**
Acute myocardial infarction and Pulmonary Embolism	4	0,3	Stroke and Pulmonary Embolism	6	1,85	Stroke and Pulmonary Embolism	1	0,15
Stroke and Pulmonary Embolism	3	0,3	Stroke and lower limb thrombosis	1	0,31	Acute myocardial infarction and Pulmonary Embolism	1	0,15
Stroke and lower limb ischemia	1	0,1	Arterial and venous thrombosis	1	0,31	Pulmonary Embolism and multiple thrombosis	1	0,15
arterio-venous fistula thrombosis	1	0,1				Acute myocardial infarction and venous thrombosis	1	0,15
Arterial limb ischemia and lower limb thrombosis	1	0,1						
Associated thrombocytopenia and/or immunothrombosis disorders n=32/1197 (2,6%)			**Associated thrombocytopenia and/or immunothrombosis disorders n=8/325 (2,4%)**			**Associated thrombocytopenia and/or immunothrombosis disorders n=14/639 (2,2%)**		

Age median (range): 56 (19-92)- Time to event: median (range): 4,5 days (0-25)	**Count**	**Percentage in cases reported (n=1197)**	**Age median (range): 64 (51-77)-Time to event: median (range): 4days (0-10)**	**Count**	**Percentage in cases reported (n=325)**	**Age median (range): 46,5 (19-73)-Time to event: median (range): 8days (2-14)**	**Count**	**Percentage in cases reported (n=639)**
Thrombocytopenia associated to Pulmonary Embolism	2	0,2	Thrombocytopenia associated to Pulmonary Embolism	1	0,3	Thrombocytopenia associated to Pulmonary Embolism	3	0,5
Thrombocytopenia associated to Acute myocardial infarction	3	0,3	positive lupus anticoagulant associated to Pulmonary Embolism	1	0,3	Thrombocytopenia associated to splenic venous thrombosis	1	0,2
Thrombocytopenia associated to stroke	13	1,1	positive lupus anticoagulant associated to stroke	4	1,2	Thrombocytopenia associated to stroke	1	0,2
Thrombocytopenia linked to purpura thrombotic thrombocytopenia	7	0,6	positive lupus anticoagulant associated to myocardial infarction	2	0,6	Thrombocytopenia with HIT-like mAb positive and multiple thrombosis	1	0,2
DIC	2	0,2				Thrombocytopenia associated to cerebral venous sinus thrombosis	4	0,6

DIC positive lupus anticoagulant associated to visceral venous thrombosis	1	0,1				Thrombocytopenia associated to cerebral venous thrombosis	1	0,2
positive lupus anticoagulant without thrombosis	2	0,2				DIC and Pulmonary Embolism	1	0,2
positive lupus anticoagulant associated to Pulmonary Embolism	2	0,2				DIC and stroke	2	0,3

Yo: years old; MI: myocardial infarction; DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia; mAb: antibody