Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after Oxford-AstraZeneca COVID-19 vaccination: A Danish-Norwegian cohort study

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Risk : Benefit

Objectives. To assess rates of cardiovascular and haemostatic events during the first 28 days following administration of Oxford-AstraZeneca COVID-19 vaccine.

Methods

Observed vs. Expected

Methods

Observed number of prespecified outcomes among
Danish and Norwegian vaccine recipients
age 18-65 years (n=281,264)
within 28 days of first vaccination

compared to

Expected number of outcomes, based on incidence rates
among the general population 2016-2018 (Denmark)
and 2018-2019 (Norway), standardized on age, sex,
and country to the vaccine cohort.

	Denmark (n=148,792)	**Norway** (n=132,472)
Female sex	119,119 (80)	102,848 (78)
Age, median (IQR)	45 (33-55)	44 (32-55)

Almost exclusively health care professionals
or social service workers!

Arterial events

SMR 0.97 (95% CI 0.77 to 1.20)

Venous thromboembolism

SMR 1.97 (95% CI 1.50 to 2.54)

Thrombocytopenias and coagulative disorders

SMR 1.52 (0.97 to 2.25)

Bleeding events

SMR 1.23 (95% CI 0.97 to 1.55)

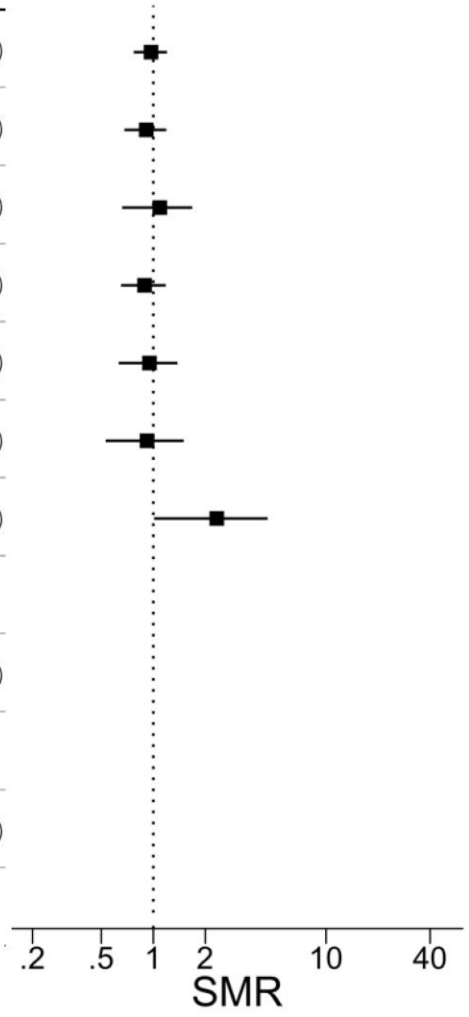
Cerebral venous thrombosis

+2.5 (0.9-5.2) / 100 000

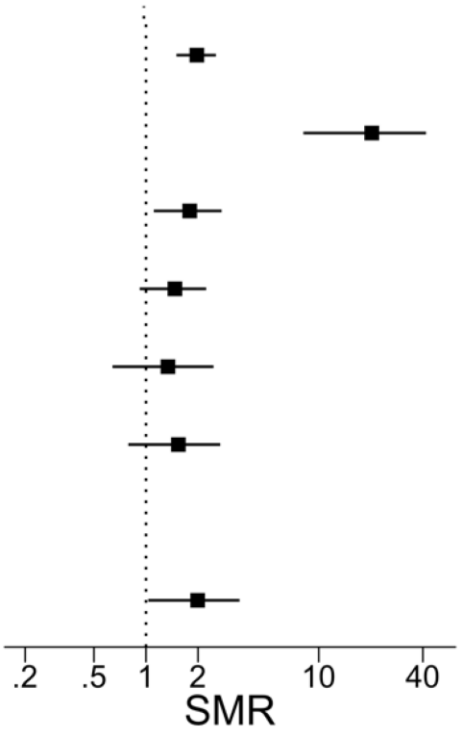
Venous thromboembolism

+10.8 (5.6-17.1) / 100 000

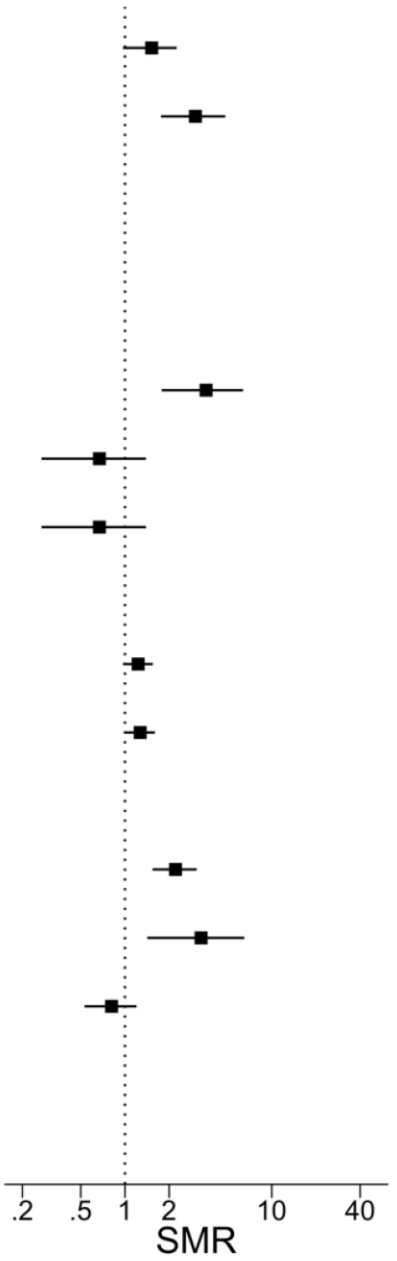
Outcome	Incidence rate DK / NO	Observed	Expected	Standardised morbidity difference /100,000 (95% CI)	Standardised morbidity ratio (95% CI)
ARTERIAL EVENTS	4.52 /4.71	83	86	-1.0 (-7.2 to 6.4)	0.97 (0.77 to 1.20)
Cardiac events	2.93 / 3.56	52	57	-1.9 (-6.8 to 4.1)	0.91 (0.68 to 1.19)
Acute myocardial infarction (AMI)	1.04 /1.21	20	18	0.6 (-2.3 to 4.6)	1.09 (0.66 to 1.68)
Ischaemic heart disease without AMI	2.58 / 3.35	46	52	-2.2 (-6.8 to 3.5)	0.89 (0.65 to 1.18)
Cerebrovascular events	1.62 / 1.21	27	28	-0.5 (-3.9 to 4.0)	0.95 (0.63 to 1.38)
Cerebral infarction	1.03 / 0.75	16	17	-0.5 (-3.0 to 3.2)	0.92 (0.53 to 1.50)
Intracerebral haemorrhage (ICH)	0.20 / 0.14	8	3	1.7 (0.0 to 4.6)	2.33 (1.01 to 4.59)
Occlusion and stenosis not resulting in cerebral infarction [d]	0.07 / 0.21	n<5	3	NR	NR
Stroke, unspecified	0.40 / 0.06	0	5	-1.8 (-1.8 to -0.4)	0.00 (0.00 to 0.78)
Subarachnoid haemorrhage (SAH)	0.14 / 0.09	n<5	3	NR	NR
Transitory cerebral ischemic attack	0.07 / 0.09	0	2	-0.6 (-0.6 to 0.8)	0.00 (0.00 to 2.24)
Other arterial events [e]	0.11 / 0.10	n<5	3	NR	NR



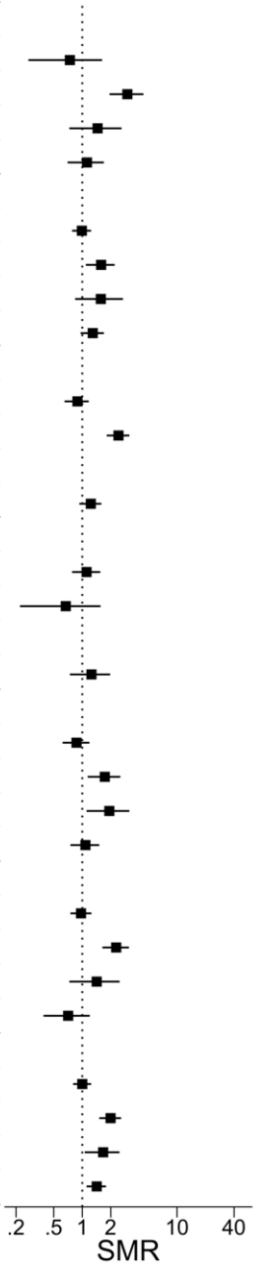
Outcome	Incidence rate DK / NO	Observed	Expected	Standardised morbidity difference /100,000 (95% CI)	Standardised morbidity ratio (95% CI)
VENOUS THROMBOEMBOLISM	1.58 / 1.26	59	30	10.8 (5.6 to 17.1)	1.97 (1.50 to 2.54)
Cerebral venous thrombosis	0.02/ 0.01	7	0	2.5 (0.9 to 5.2)	20.25 (8.14 to 41.73)
Pulmonary embolism (PE)	0.57/ 0.57	21	12	3.4 (0.5 to 7.5)	1.79 (1.11 to 2.74)
Lower limb venous thrombosis	0.94 / 0.48	22	15	2.6 (-0.4 to 6.8)	1.47 (0.92 to 2.23)
Deep thrombophlebitis of veins in legs	0.35 / 0.38	10	7	0.9 (-1.0 to 4.0)	1.34 (0.64 to 2.46)
Unspecified deep thrombophlebitis in lower limb	0.66 / 0.05	12	8	1.6 (-0.6 to 4.9)	1.54 (0.79 to 2.69)
Splanchnic thrombosis	0.04 / 0.06	n<5	1	NR	NR
Other venous thrombosis [f]	0.22 / 0.36	12	6	2.2 (0.1 to 5.5)	1.99 (1.03 to 3.48)



Outcome	Incidence rate DK / NO	Observed	Expected	Standardised morbidity difference /100,000 (95% CI)	Standardized morbidity ratio (95% CI)
THROMBOCYTOPENIA AND COAGULATIVE DISORDERS	0.60 / 0.75	24	16	3.0 (-0.2 to 7.4)	1.52 (0.97 to 2.25)
Thrombocytopenia	0.15 / 0.38	17	6	4.2 (1.6 to 8.0)	3.02 (1.76 to 4.83)
Idiopathic thrombocytopenic purpura	0.07 / 0.06	n<5	1	NR	NR
Other primary thrombocytopenia	0.00 / 0.01	0	0	-0.0 (-0.0 to 1.3)	0.00 (0.00 to 35.70)
Secondary thrombocytopenia	0.01 / 0.18	NR	2	NR	NR
Thrombocytopenia unspecified	0.09 / 0.20	11	3	2.9 (0.9 to 6.1)	3.57 (1.78 to 6.38)
Coagulative disorders	0.45 / 0.38	7	10	-1.3 (-2.8 to 1.5)	0.67 (0.27 to 1.39)
Coagulative disorders, purpura	0.45 / 0.38	7	10	-1.3 (-2.8 to 1.5)	0.67 (0.27 to 1.39)
Disseminated intravascular coagulation (DIC)	0.01 / 0.02	0	0	-0.1 (-0.1 to 1.3)	0.00 (0.00 to 12.20)
BLEEDING EVENTS	2.75 / 3.04	74	60	5.1 (-0.7 to 12.2)	1.23 (0.97 to 1.55)
Bleedings	2.67 / 2.96	74	58	5.9 (0.0 to 12.9)	1.27 (1.00 to 1.60)
Anemia from bleeding	0.11 / 0.60	n<5	8	NR	NR
Bleeding from respiratory tract	0.85 / 0.87	35	16	7.1 (3.2 to 12.2)	2.21 (1.54 to 3.08)
Bleeding, not specified	0.15 / 0.05	8	2	2.1 (0.4 to 4.9)	3.30 (1.42 to 6.50)
Hematuria	1.43 / 1.50	25	31	-2.1 (-5.4 to 2.3)	0.81 (0.53 to 1.20)
Intestinal bleeding	0.18 / - [d]	n<5	2	NR	NR
Hemolytic anemias [e]	0.09 / 0.09	0	2	-0.8 (-0.8 to 0.5)	0.00 (0.00 to 1.66)



	Observed	Expected	Standardised morbidity difference /100,000 (95% CI)	Standardised morbidity ratio (95% CI)
AGE 18-44 YEARS				
Arterial events	6	8	-1.6 (-4.4 to 3.8)	0.74 (0.27 to 1.62)
Venous thromboembolism	25	8	12.6 (5.9 to 21.5)	2.99 (1.94 to 4.42)
Thrombocytopenia and coagulative disorders	11	8	2.6 (-1.6 to 9.1)	1.45 (0.73 to 2.60)
Bleeding events	22	20	1.8 (-4.4 to 10.3)	1.12 (0.70 to 1.69)
AGE 45-65 YEARS				
Arterial events	77	78	-0.4 (-12.3 to 13.7)	0.99 (0.78 to 1.24)
Venous thromboembolism	34	22	9.1 (1.5 to 18.9)	1.58 (1.09 to 2.20)
Thrombocytopenia and coagulative disorders	13	8	3.4 (-1.0 to 10.1)	1.57 (0.84 to 2.69)
Bleeding events	52	40	3.4 (-1.0 to 10.1)	1.29 (0.96 to 1.69)
FEMALES ONLY				
Arterial events	48	54	-2.9 (-8.8 to 4.4)	0.89 (0.65 to 1.17)
Venous thromboembolism	54	22	14.8 (8.5 to 22.5)	2.41 (1.81 to 3.14)
Thrombocytopenia and coagulative disorders	NR	13	NR	NR
Bleeding events	56	46	4.8 (-1.6 to 12.7)	1.23 (0.93 to 1.59)
MALES ONLY				
Arterial events	35	31	6.5 (-12.6 to 31.0)	1.11 (0.78 to 1.55)
Venous thromboembolism	5	7	-4.4 (-10.4 to 7.4)	0.67 (0.22 to 1.56)
Thrombocytopenia and coagulative disorders	n<5	3	NR	NR
Bleeding events	18	14	6.3 (-6.7 to 24.9)	1.25 (0.74 to 1.97)
14-DAY FOLLOW-UP				
Arterial events	39	45	-4.3 (-12.3 to 6.0)	0.87 (0.62 to 1.19)
Venous thromboembolism	27	16	8.1 (1.6 to 16.9)	1.73 (1.14 to 2.52)
Thrombocytopenia and coagulative disorders	16	8	5.5 (0.6 to 12.6)	1.93 (1.11 to 3.14)
Bleeding events	34	31	1.8 (-5.6 to 11.5)	1.08 (0.75 to 1.51)
EXCLUDING. BRIEF HOSPITAL CONTACTS				
Arterial events	62	64	-0.7 (-6.0 to 5.8)	0.97 (0.75 to 1.25)
Venous thromboembolism	40	18	8.3 (4.1 to 13.7)	2.28 (1.63 to 3.11)
Thrombocytopenia and coagulative disorders	12	8	1.3 (-0.8 to 4.6)	1.42 (0.73 to 2.48)
Bleeding events	14	20	-2.1 (-4.4 to 1.4)	0.71 (0.39 to 1.20)
USING A MORE RECENT GENERAL POPULATION COMPARISON COHORT				
Arterial events	83	83	0.1 (-6.2 to 7.5)	1.00 (0.80 to 1.24)
Venous thromboembolism	59	30	10.9 (5.6 to 17.2)	1.99 (1.51 to 2.57)
Thrombocytopenia and coagulative disorders	24	14	3.5 (0.3 to 7.9)	1.66 (1.06 to 2.47)
Bleeding events	74	52	8.1 (2.2 to 15.1)	1.42 (1.11 to 1.78)



Main strength

Population-based

Main weaknesses

'Healthy vaccinee' effect

Potential increased surveillance

Limitations

No data on individuals >65 years

No data on risks after second jab

Insufficient data on non-Caucasian individuals

Risk : Benefit

Conclusions. Among recipients of the Oxford-AstraZeneca COVID-19 vaccine, we observed increased rates of venous thromboembolic events, including cerebral venous thrombosis. For the remaining safety outcomes, results were largely reassuring, with slightly higher rates of thrombocytopenia/coagulative disorders and bleeding, which could be influenced by increased surveillance of vaccine recipients. Importantly, the absolute risks of venous thromboembolic events were small, and the findings should be interpreted in the light of the proven beneficial effects of the vaccine, the context of the given country, and the limitations to the generalisability of our study findings.

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