Supplementary Material

For “Safety of heterologous primary and booster schedules with ChAdOx1-S and BNT162b2 or mRNA-1273 vaccines: a nationwide cohort study”

Table S1. Definitions and ICD-10 codes for the main and secondary outcomes and the comorbidity covariate[a]

Main outcomes	**ICD-10 codes**
Ischemic cardiac events	I20, I21, I23, I24, I251
Cerebrovascular events	I60-66, G450-453
Cerebrovascular infarction (incl. TIA)[b]	I63, I64, G450-453
Intracranial bleeding[b]	I60-62
Arterial thromboembolism	I74
Venous thromboembolism	I26, I676, I80-82 (not I800, I808C, or I821)
Cerebral venous thrombosis[b]	I676
Pulmonary embolism[b]	I26
Myocarditis or pericarditis	I300, I301E, I308, I309, I400, I401, I409, I411, I418, I514
Thrombocytopenia and coagulative disorders	D65, D683-684 (not D684A-C), D686, D688-689, D690, D693, D694, D695, D696, D698 (not D698A), D699
Other bleeding events[c]	D55, D59, D62, D629, I850, J942, K226, K250, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276 K280, K282, K284, K286, K290, K625, K661, K920-922, N029, R04, R31 (not R319B), R58
Secondary outcomes	**ICD-10 codes**
Guillain-Barré syndrome	G610
Bell's palsy	G510
Transverse myelitis	G373
Encephalomyelitis/encephalitis	G04, G040, G040A, G048, G049, G051, G058, G361
Narcolepsy	G474
Anaphylaxis	T782, T783, T805, T886
Appendicitis	K35, K36, K37
All-cause mortality	NA
Comorbidity covariate[d]	**ICD-10 codes**
Cardiac conditions Diabetes mellitus Malignancy Cerebrovascular disease Venous thromboembolisms	I20-25, I110, I130, I132, I42, I48, I50 E10-E14 C00–96 (not C44) G45-46, I60-I69 I26, I676, I80-82 (not I800, I808C, or I821)

ICD-10 denotes International Classification of Diseases System, version 10, TIA transient ischemic attack, and NA not applicable. [a]Diagnoses were identified through use of the Danish National Patient Register. Deaths were identified through use of the Danish Civil Registration System. [b]Also examined separately (included as secondary outcomes). [c]Bleeding events other than intracranial hemorrhages. [d]Defined as hospital contact where the diagnoses were registered with a 5-year look back period from the respective index dates.

Figure S1. Cumulative distributions of the examined vaccine schedules and risk periods by calendar months

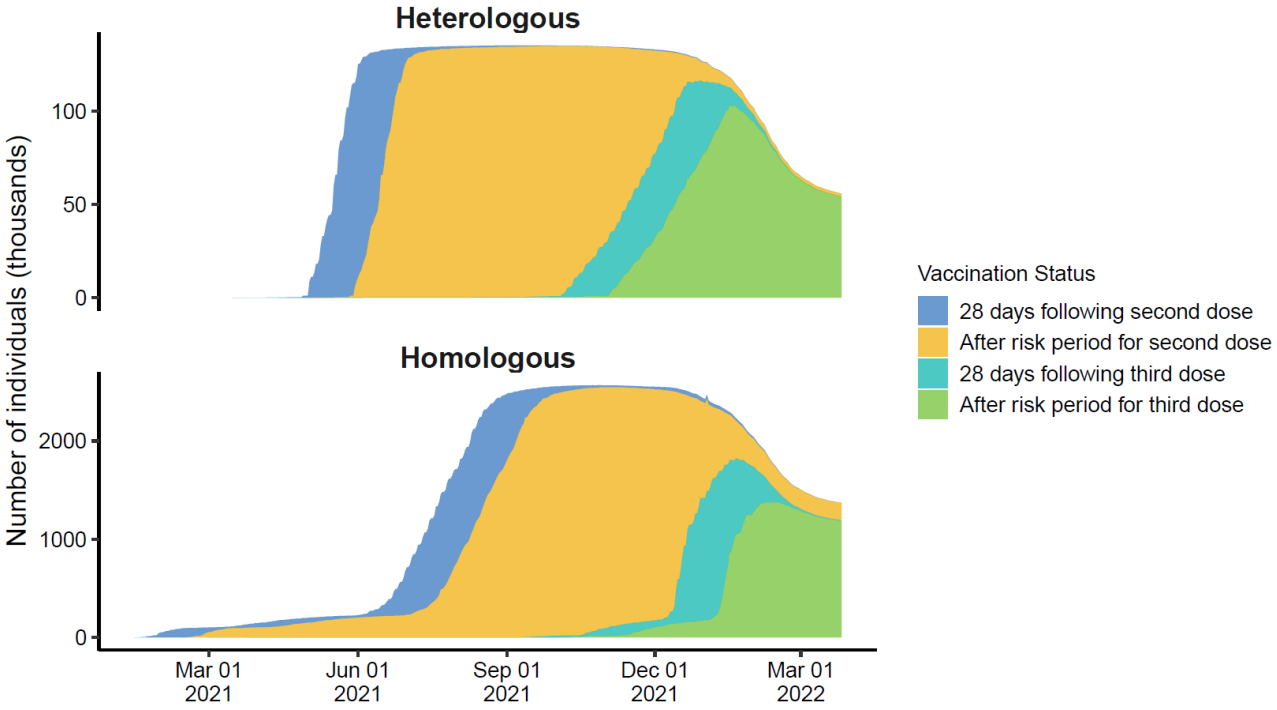
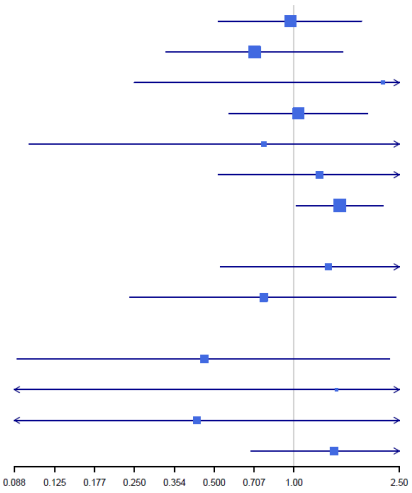


Figure shows the cumulative number of individuals (thousands) vaccinated with heterologous (ChAdOx1-S/mRNA) and homologous (mRNA/mRNA) primary and booster vaccine schedules by calendar months from 1 January 2021 to 26 March 2022. The 28-day periods following the second and third dose (in blue colors) denote the main risk periods for the primary and booster vaccine schedule comparisons, respectively. The decline in the number of individuals in the respective periods after vaccination in right part of the figure is owing to greater censoring because of positive PCR test results for SARS-CoV-2 (censoring criteria were: an outcome event, death, emigration, disappearance, positive PCR test for SARS-CoV-2, or end of data [26 March 2022], whichever occurred first).

Figure S2. Associated risk of cardiovascular or hemostatic adverse events with the individual heterologous primary vaccine schedules for covid-19 compared to respective homologous mRNA vaccine schedules counterpart

	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
ChAd/BNT vs. BNT/BNT					
Ischemic cardiac events	11	6764	403	172422	0.97 (0.52−1.80)
Cerebrovascular events	7	6766	295	172530	0.71 (0.33−1.53)
Arterial thromboembolism	<3	6771	19	172773	2.17 (0.25−18.86)
Venous thromboembolism	<14	6763	362	172486	1.04 (0.57−1.90)
Myocarditis or pericarditis	<3	6771	63	172757	0.77 (0.10−6.25)
Thrombocytopenia or coagulative disorders	<8	6768	99	172698	1.25 (0.52−3.01)
Other bleeding events	32	6757	628	172370	1.49 (1.02−2.17)
ChAd/m1273 vs. m1273/m1273					
Ischemic cardiac events	12	3754	28	32688	1.35 (0.53−3.46)
Cerebrovascular events	5	3755	31	32693	0.77 (0.24−2.43)
Arterial thromboembolism	0	3758	<3	32712	NE
Venous thromboembolism	<14	3754	30	32678	0.46 (0.09−2.30)
Myocarditis or pericarditis	<3	3758	30	32708	1.45 (0.03−75.65)
Thrombocytopenia or coagulative disorders	<8	3757	11	32701	0.43 (0.07−2.64)
Other bleeding events	16	3750	101	32652	1.42 (0.69−2.92)



Incidence rate ratios (IRRs) for the outcomes within 28 days were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Cell counts less than three (but not zero) are not reported. If a subgroup analysis yielded cell counts less than three (but not zero), the number of cases are reported as less than (<) the sum of the subgroup cell counts, ie, the number of cases reported in the main analysis. Other bleeding events includes a composite of bleeding-related diagnoses other than intracranial hemorrhages. BNT denotes BNT162b2, ChAd ChAdOx1-S, CI confidence interval, m1273 mRNA-1273, and NE not estimated.

Figure S3. Associated risk of cardiovascular or hemostatic adverse events with the individual heterologous booster vaccine schedules for covid-19 compared to respective homologous mRNA vaccine schedules counterpart

	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
ChAd/BNT/BNT vs. BNT/BNT/BNT					
Ischemic cardiac events	11	6064	331	130164	1.32 (0.72−2.44)
Cerebrovascular events	<9	6066	265	130323	0.91 (0.42−1.96)
Arterial thromboembolism	<3	6074	11	130644	4.59 (0.54−39.25)
Venous thromboembolism	8	6062	249	130291	1.15 (0.56−2.35)
Myocarditis or pericarditis	<3	6073	34	130632	0.90 (0.12−6.94)
Thrombocytopenia or coagulative disorders	<3	6070	42	130564	1.48 (0.35−6.26)
Other bleeding events	17	6053	564	130081	0.89 (0.55−1.46)
ChAd/m1273/m1273 vs. m1273/m1273/m1273					
Ischemic cardiac events	3	3415	29	20628	0.41 (0.11−1.46)
Cerebrovascular events	<9	3419	19	20637	0.44 (0.09−2.09)
Arterial thromboembolism	<3	3423	<3	20663	7.03 (0.08−596.23)
Venous thromboembolism	4	3417	16	20626	1.21 (0.36−4.13)
Myocarditis or pericarditis	<3	3423	7	20661	0.65 (0.04−10.05)
Thrombocytopenia or coagulative disorders	0	3422	5	20654	NE
Other bleeding events	14	3410	68	20594	1.24 (0.63−2.43)

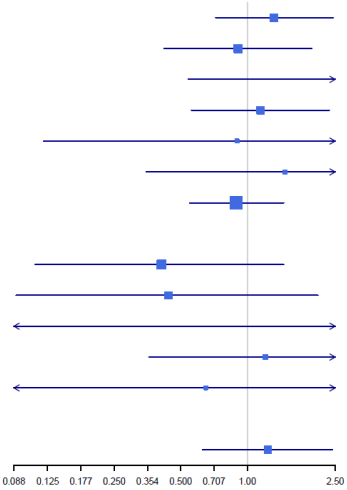


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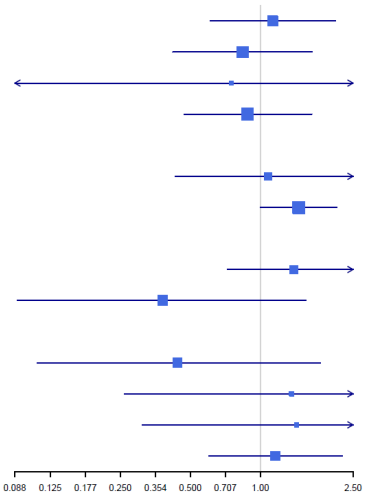
Figure S4. Association between heterologous primary vaccine schedules and cardiovascular or hemostatic adverse events by sex

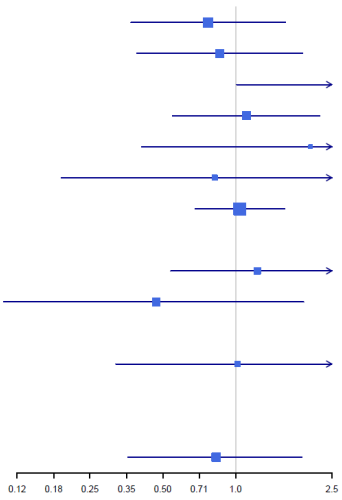
	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
Female					
Ischemic cardiac events	13	8421	126	100552	1.13 (0.61−2.10)
Cerebrovascular events	<12	8422	118	100557	0.84 (0.42−1.67)
Arterial thromboembolism	<3	8429	10	100649	0.75 (0.08−7.47)
Venous thromboembolism	<14	8418	165	100513	0.88 (0.47−1.66)
Myocarditis or pericarditis	0	8428	25	100645	NE
Thrombocytopenia and other coagulative disorders	<8	8425	50	100592	1.08 (0.43−2.71)
Other bleeding events	38	8412	314	100452	1.46 (1.00−2.13)
Male					
Ischemic cardiac events	10	2096	305	104558	1.39 (0.72−2.71)
Cerebrovascular events	<12	2098	208	104666	0.38 (0.09−1.57)
Arterial thromboembolism	0	2101	10	104836	NE
Venous thromboembolism	<14	2098	227	104651	0.44 (0.11−1.81)
Myocarditis or pericarditis	<3	2100	68	104820	1.36 (0.26−7.08)
Thrombocytopenia and other coagulative disorders	<8	2100	60	104807	1.43 (0.31−6.66)
Other bleeding events	10	2095	415	104571	1.16 (0.60−2.24)



Incidence rate ratios (IRRs) for the outcomes within 28 days were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Cell counts less than three (but not zero) are not reported. If a subgroup analysis yielded cell counts less than three (but not zero), the number of cases are reported as less than (<) the sum of the subgroup cell counts, i.e., the number of cases reported in the main analysis. Other bleeding events includes a composite of bleeding-related diagnoses other than intracranial hemorrhages. CI denotes confidence interval and NE not estimated.

Figure S5. Association between heterologous booster vaccine schedules and cardiovascular or hemostatic adverse events by sex

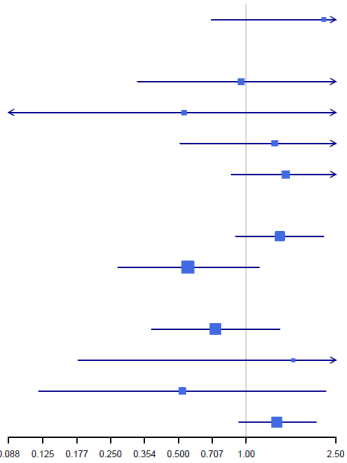
	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
Female					
Ischemic cardiac events	8	7614	109	74167	0.77 (0.37−1.61)
Cerebrovascular events	<9	7616	97	74183	0.86 (0.39−1.89)
Arterial thromboembolism	<3	7626	3	74304	7.20 (1.01−51.49)
Venous thromboembolism	9	7611	101	74145	1.11 (0.55−2.23)
Myocarditis or pericarditis	<3	7625	13	74301	2.04 (0.41−10.13)
Thrombocytopenia and other coagulative disorders	<3	7620	33	74246	0.82 (0.19−3.51)
Other bleeding events	25	7600	277	74031	1.04 (0.68−1.59)
Male					
Ischemic cardiac events	6	1865	251	76625	1.23 (0.54−2.82)
Cerebrovascular events	<9	1868	187	76777	0.47 (0.11−1.91)
Arterial thromboembolism	0	1872	9	77004	NE
Venous thromboembolism	3	1868	164	76773	1.02 (0.32−3.27)
Myocarditis or pericarditis	0	1871	28	76992	NE
Thrombocytopenia and other coagulative disorders	0	1871	14	76972	NE
Other bleeding events	6	1863	355	76643	0.83 (0.36−1.88)



Incidence rate ratios (IRRs) for the outcomes within 28 days were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Cell counts less than three (but not zero) are not reported. If a subgroup analysis yielded cell counts less than three (but not zero), the number of cases are reported as less than (<) the sum of the subgroup cell counts, i.e., the number of cases reported in the main analysis. Other bleeding events includes a composite of bleeding-related diagnoses other than intracranial hemorrhages. CI denotes confidence interval and NE not estimated.

Figure S6. Association between heterologous primary vaccine schedules and cardiovascular or hemostatic adverse events by birth year.

	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
Birth year > 1975					
Ischemic cardiac events	0	5333	48	112755	NE
Cerebrovascular events	4	5332	35	112746	2.21 (0.70−7.03)
Arterial thromboembolism	<3	5333	<3	112784	NE
Venous thromboembolism	4	5328	108	112692	0.95 (0.33−2.76)
Myocarditis or pericarditis	<3	5333	72	112767	0.53 (0.06−4.80)
Thrombocytopenia and other coagulative disorders	<8	5330	50	112735	1.34 (0.51−3.51)
Other bleeding events	17	5326	285	112612	1.50 (0.86−2.61)
Birth year < 1975					
Ischemic cardiac events	23	5185	383	92355	1.41 (0.90−2.21)
Cerebrovascular events	8	5189	291	92477	0.55 (0.27−1.14)
Arterial thromboembolism	0	5196	19	92701	NE
Venous thromboembolism	10	5188	284	92472	0.73 (0.38−1.41)
Myocarditis or pericarditis	<3	5196	21	92698	1.62 (0.18−14.77)
Thrombocytopenia and other coagulative disorders	<8	5195	60	92664	0.52 (0.12−2.26)
Other bleeding events	31	5182	444	92411	1.37 (0.93−2.04)



Individuals were subgrouped according to whether born in year 1975 or later or before year 1975. Birth year of 1975 corresponds to turning 46 years of age in year 2021. Incidence rate ratios (IRRs) for the outcomes within 28 days were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Cell counts less than three (but not zero) are not reported. If a subgroup analysis yielded cell counts less than three (but not zero), the number of cases are reported as less than (<) the sum of the subgroup cell counts, i.e., the number of cases reported in the main analysis. Other bleeding events includes a composite of bleeding-related diagnoses other than intracranial hemorrhages. CI denotes confidence interval and NE not estimated.

Figure S7. Association between heterologous booster vaccine schedules and cardiovascular or hemostatic adverse events by birth year

	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
Birth year > 1975					
Ischemic cardiac events	<14	4589	27	70652	0.78 (0.10−6.02)
Cerebrovascular events	<9	4589	37	70647	0.53 (0.07−4.01)
Arterial thromboembolism	0	4590	<3	70686	NE
Venous thromboembolism	4	4584	63	70596	1.10 (0.39−3.14)
Myocarditis or pericarditis	<3	4589	25	70673	0.75 (0.09−6.00)
Thrombocytopenia and other coagulative disorders	<3	4587	21	70640	0.93 (0.12−7.22)
Other bleeding events	15	4578	183	70499	1.62 (0.94−2.82)
Birth year < 1975					
Ischemic cardiac events	<14	4889	333	80140	1.02 (0.58−1.80)
Cerebrovascular events	<9	4896	247	80313	0.75 (0.36−1.53)
Arterial thromboembolism	<3	4907	11	80622	4.86 (0.94−25.17)
Venous thromboembolism	8	4895	202	80321	1.05 (0.51−2.16)
Myocarditis or pericarditis	<3	4907	16	80620	1.52 (0.18−12.55)
Thrombocytopenia and other coagulative disorders	<3	4905	26	80578	0.93 (0.12−7.07)
Other bleeding events	16	4885	449	80176	0.75 (0.45−1.25)

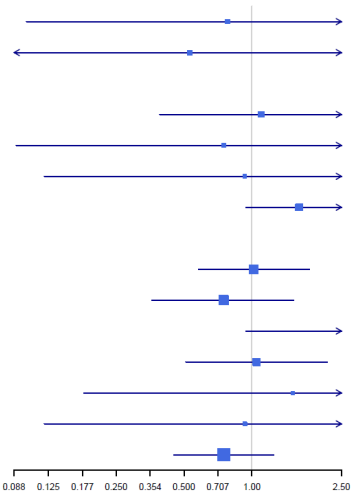


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Figure S8. Sensitivity analyses of the associated risk with heterologous primary vaccine schedules by use of different follow-up definitions

	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
Exposure period restricted to 2 weeks					
Ischemic cardiac events	13	5261	218	102704	1.37 (0.76−2.48)
Cerebrovascular events	7	5262	171	102759	0.80 (0.37−1.76)
Arterial thromboembolism	<3	5267	7	102888	2.90 (0.30−27.65)
Venous thromboembolism	12	5261	195	102731	1.45 (0.78−2.68)
Myocarditis or pericarditis	<3	5266	64	102878	1.29 (0.25−6.57)
Thrombocytopenia and other coagulative disorders	6	5264	48	102845	1.76 (0.71−4.37)
Other bleeding events	25	5256	365	102663	1.40 (0.91−2.15)
Exposure period extended to 180 days after index date					
Ischemic cardiac events	115	66903	2926	1248799	1.12 (0.90−1.38)
Cerebrovascular events	82	66929	2241	1249688	0.90 (0.70−1.16)
Arterial thromboembolism	3	67000	107	1251738	1.06 (0.30−3.80)
Venous thromboembolism	96	66901	2334	1249310	1.10 (0.87−1.38)
Myocarditis or pericarditis	15	66992	312	1251588	1.29 (0.70−2.38)
Thrombocytopenia and other coagulative disorders	27	66967	551	1251125	1.00 (0.65−1.55)
Other bleeding events	215	66816	4930	1247964	1.08 (0.92−1.26)
Guillain Barré syndrom	<3	67002	44	1251818	0.44 (0.05−3.69)
Narcolepsy	7	66996	89	1251712	2.18 (0.79−5.99)
Death	40	67004	2678	1251849	0.70 (0.50−0.97)

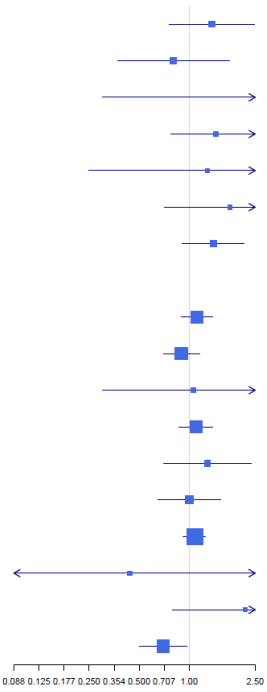

Figure shows the results of the sensitivity analyses where assessing a shorter follow-up of two weeks and extending the follow-up to 180 days after the day of the respective second (ie, index date). For the latter, the outcomes of Guillain-Barré syndrome and narcolepsy were studied post hoc. Incidence rate ratios (IRRs) were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Other bleeding events includes a composite of bleeding-related diagnoses other than intracranial hemorrhages. CI denotes confidence interval.

Figure S9. Sensitivity analyses of the associated risk with heterologous booster vaccine schedules by use of different follow-up definitions

	Heterologous		Homologous		
Outcome	No. of events	Person years	No. of events	Person years	IRR (95% CI)
Exposure period restricted to 2 weeks					
Ischemic cardiac events	8	4791	167	77670	1.21 (0.59−2.48)
Cerebrovascular events	3	4794	138	77754	0.48 (0.15−1.51)
Arterial thromboembolism	0	4801	6	77928	NE
Venous thromboembolism	8	4792	110	77732	1.70 (0.82−3.52)
Myocarditis or pericarditis	<3	4800	26	77920	0.84 (0.11−6.47)
Thrombocytopenia and other coagulative disorders	0	4798	21	77882	NE
Other bleeding events	8	4783	306	77610	0.54 (0.26−1.09)
Exposure period extended to 180 days after index date					
Ischemic cardiac events	56	30445	1067	323996	1.11 (0.83−1.48)
Cerebrovascular events	46	30470	819	324596	1.06 (0.77−1.46)
Arterial thromboembolism	3	30516	41	325724	1.98 (0.54−7.32)
Venous thromboembolism	44	30452	728	324519	1.19 (0.86−1.65)
Myocarditis or pericarditis	5	30512	63	325697	1.28 (0.48−3.43)
Thrombocytopenia and other coagulative disorders	8	30499	116	325447	1.09 (0.52−2.32)
Other bleeding events	115	30387	1581	323879	1.15 (0.94−1.42)
Guillain Barré syndrom	0	30518	5	325772	NE
Narcolepsy	0	30514	9	325748	NE
Death	25	30519	1258	325789	0.59 (0.38−0.92)

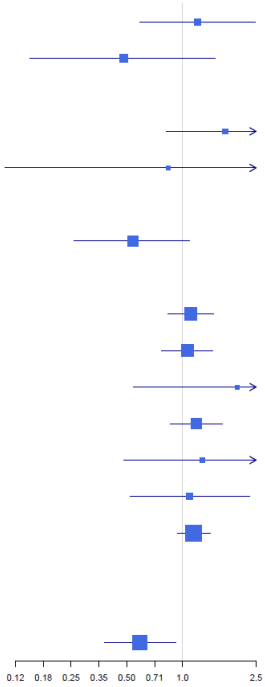

Figure shows the results of the sensitivity analyses where assessing a shorter follow-up of two weeks and extending the follow-up to 180 days after the day of the respective third dose (ie, index date). For the latter, the outcomes of Guillain-Barré syndrome and narcolepsy were studied post hoc. Incidence rate ratios (IRRs) were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Other bleeding events includes a composite of bleeding-related diagnoses other than intracranial hemorrhages. CI denotes confidence interval and NE not estimated.

Table S2. Post-hoc analysis for the outcome of other bleeding events according to the specific site of bleeding among heterologous primary vaccinated

Subtypes of bleeding events	Heterologous (ChAdOx1-S/mRNA)		Homologous (mRNA/mRNA)		IRR (95% CI)
	Events, No.	Person-years	Events, No.	Person-years	
Anemia	3	10509.01	37	205048.25	1.59 (0.43-5.86)
Gastrointestinal bleedings	16	10508.54	311	205037.92	1.09 (0.64-1.87)
Respiratory bleedings	12	10508.73	154	205043.56	1.86 (0.97-3.55)
Urogenital bleedings	11	10508.68	192	205042.39	1.34 (0.69-2.59)
Bleedings, unspecified	6	10508.85	38	205047.97	1.31 (0.49-3.50)

Incidence rate ratios (IRRs) were adjusted for calendar period, sex, birth year (proxy for age), region of residency, birth country, vaccine priority group, hospital contact in the last 6 months, and comorbidities. Individuals with any other bleeding event during the washout period of 6 months prior to index date were excluded. CI denotes confidence interval.