Impact of vaccination on the association of COVID-19 with arterial and venous thrombotic diseases: an OpenSAFELY cohort study using linked electronic health records

Genevieve Cezard
gic30@medschl.cam.ac.uk
University of Cambridge https://orcid.org/0000-0002-3011-7416
Rachel Denholm
University of Bristol
Rochelle Knight
University of Bristol
Yinghui Wei
Plymouth University
Lucy Teece
University of Leicester
Renin Toms
Cardiff Metropolitan University
Harriet Forbes
London School of Hygiene & tropical Medicine
Alex Walker
University of Oxford https://orcid.org/0000-0002-5127-4728
Louis Fisher
University of Oxford
Jon Massey
Bennett Institute for Applied Data Science https://orcid.org/0000-0002-2497-4040
Lisa Hopcroft
University of Oxford
Elsie Horne
Population Health Sciences, University of Bristol
Kurt Taylor
University of Bristol
Tom Palmer
University of Bristol https://orcid.org/0000-0003-4655-4511
Marwa Al Arab
University of Bristol
Jose Cuitun Coronado
University of Bristol
Samantha Ip
University of Cambridge https://orcid.org/0000-0001-9162-6727
Simon Davy
Bennett Institute for Applied Data Science
Iain Dillingham
University of Oxford
Sebastian Bacon
Bennett Institute for Applied Data Science
Amir Mehrkar
Bennett Institute for Applied Data Science
Caroline Morton
Bennett Institute for Applied Data Science
Felix Greaves
National Institute for Health and Care Excellence
Catherine Hyams
University of Bristol https://orcid.org/0000-0003-3923-1773

George Davey Smith
University of Bristol https://orcid.org/0000-0002-1407-8314
John MacLeod
University of Bristol
Nishi Chaturvedi
University College London https://orcid.org/0000-0002-6211-2775
Ben Goldacre
Oxford University
William Whiteley
The University of Edinburgh https://orcid.org/0000-0002-4816-8991
Angela Wood
University of Cambridge https://orcid.org/0000-0002-7937-304X
Jonathan Sterne
University of Bristol https://orcid.org/0000-0001-8496-6053
Venexia Walker
University of Bristol https://orcid.org/0000-0001-5064-446X

Article

Keywords:

Posted Date: July 25th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3168263/v1

Additional Declarations: Yes there is potential Competing Interest. WW is supported by the Chief Scientist's Office, the Stroke Association, and the Alzheimer's Society; sits on data monitoring committees for academic trials (TEMPO-2, PROTECT-U, and CATIS-ICAD); and is an independent expert witness to UK courts. NC receives funds from AstraZeneca to support membership of Data Safety and Monitoring Committees for clinical trials. CH is the Principal Investigator of a study which is a collaboration sponsored by the University of Bristol and funded by Pfizer Inc. The other authors report no conflicts.

Version of Record: A version of this preprint was published at Nature Communications on March 11th, 2024. See the published version at https://doi.org/10.1038/s41467-024-46497-0.

Abstract

With the approval of NHS England, we quantified associations between COVID-19 diagnosis and cardiovascular diseases in different vaccination and variant eras using linked electronic health records for ~40% of the English population. We defined a 'pre-vaccination' cohort (18,210,937 people) in the wild-type/Alpha variant eras (January 2020-June 2021), and 'vaccinated' and 'unvaccinated' cohorts (13,572,399 and 3,161,485 people respectively) in the Delta variant era (June-December 2021). The incidence of each arterial thrombotic, venous thrombotic and other cardiovascular outcomes was substantially elevated during weeks 1-4 after COVID-19, compared with before or without COVID-19, but less markedly elevated in time periods beyond week 4. Hazard ratios were higher after hospitalized than non-hospitalized COVID-19 and higher in the pre-vaccination and unvaccinated than the vaccinated cohort. COVID-19 vaccination reduces the risk of cardiovascular events after COVID-19 infection. People who had COVID-19 before being vaccinated are at higher risk of cardiovascular events for at least two years.

INTRODUCTION

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) increases the risk of arterial thrombotic events (ATE), such as myocardial infarction (MI) and ischaemic stroke, and venous thrombotic events (VTE), such as pulmonary embolism (PE) and lower limb deep vein thrombosis (DVT)[1]. This elevation in risk is highest immediately after infection, and higher after severe COVID-19[1].

The dominant SARS-CoV-2 variant changed during the pandemic, and different variants may be associated with different subsequent risks of major vascular events. The Delta variant (B.1.617.2), which emerged in late 2020 and was dominant by mid-2021[2–6], was associated with a greater risk of hospitalization and death than the Alpha variant[7–11].

The UK's COVID-19 vaccine rollout started on December 8th, 2020, with eligibility in order of priority groups determined by the Joint Committee on Vaccination and Immunisation (JCVI), based on age, clinical vulnerability and health and social care occupation[12]. All adults in England became eligible to receive a first vaccination by June 18th 2021, and a second vaccination by August 2021[13].

Cohort studies have reported lower incidence of arterial and venous thrombotic events after COVID-19 vaccination than in unvaccinated people[14] and that rates of hospitalisation for acute MI and ischemic stroke 31–120 days after COVID-19 are lower in vaccinated than unvaccinated people[15]. Randomised trials suggest that seasonal influenza vaccination reduces rates of cardiovascular events and cardiovascular death[16]. However, uncertainties remain. In younger people, the rare complications of the Pfizer–BioNTech BNT162b2 and Moderna mRNA-1273 mRNA vaccines (myocarditis)[17,18] and the Oxford–AstraZeneca ChAdOx1 nCoV-19 AZD1222 vaccine (vaccine induced thrombotic thrombocytopenia)[19] are balanced by reduced risk of severe COVID-19, but the role of these vaccines in modifying the incidence of common vascular events after COVID-19 is less clear.

Using linked anonymised electronic health records on 18.2 million adults registered with English general practices (GP), we compared the incidence of vascular diseases after COVID-19 with the incidence before or without COVID-19, in a pre-vaccination cohort followed during the wild-type and Alpha variant eras; and in vaccinated and unvaccinated cohorts followed during the Delta variant era. Differences between associations in the pre-vaccination and unvaccinated cohorts should relate to effects of changing variants, while differences between the vaccinated and unvaccinated cohorts should relate to the effect of vaccination.

RESULTS

Characteristics of study cohorts

Among 18,210,937 people in the pre-vaccination cohort, 1,150,299 had a COVID-19 diagnosis during follow-up of whom 75,667 (6.6%) were hospitalized. There were 844,235 COVID-19 diagnoses (15,342 (1.8%) hospitalized) among 13,572,399 people in the vaccinated cohort and 162,103 (9,250 (5.7%) hospitalized) among 3,161,485 people in the unvaccinated cohort (Table 1). In the pre-vaccination cohort, the median age was 49 years (interquartile range (IQR) 34–64), a slight majority (50.2%) were female, and 78.0%, 6.4% and 2.2% were recorded as being of White, South Asian and Black ethnicities respectively. Differences between the vaccinated and unvaccinated cohorts reflected predictors of COVID-19 vaccine uptake[20]. The median (IQR) age was 54 (39–68) in the vaccinated cohort, compared with 36 (28–47) years in the unvaccinated cohort. The proportions of females were 52.1% and 42.0% in the vaccinated and unvaccinated cohorts respectively, while the proportions recorded as of White ethnicity were 82.1% and 61.6% respectively, and the proportions living in the most deprived areas were 16.4% and 29.8% respectively. Compared with the vaccinated cohort, people in the unvaccinated cohort were more likely to be smokers, less likely to consult their GPs and less likely to have prior medical problems recorded (Table S1).

Table 1
Patient characteristics in the pre-vaccination, vaccinated and unvaccinated cohorts.

Characteristics		Pre-vaccination cohort (Jan 1 2020 to Dec 14 2021)		Vaccinated cohort (June 1 to Dec 14 2021)		Unvaccinated cohort (June 1 to Dec 14 2021)	
		N (%)	COVID-19 diagnoses	N (%)	COVID-19 diagnoses	N (%)	COVID-19 diagnoses
All		18,210,937	1,150,299	13,572,399	844,235	3,161,485	162,103
Sex	Female	9,144,881 (50.2%)	627,664	7,069,546 (52.1%)	469,430	1,328,645 (42.0%)	86,431
	Male	9,066,056 (49.8%)	522,635	6,502,853 (47.9%)	374,805	1,832,840 (58.0%)	75,672
Age, years	18–29	3,202,070 (17.6%)	261,713	1,676,216 (12.4%)	92,584	943,544 (29.8%)	43,264
	30–39	3,161,886 (17.4%)	220,784	1,885,074 (13.9%)	145,292	945,077 (29.9%)	54,772
	40–49	2,988,406 (16.4%)	207,475	2,136,224 (15.7%)	229,337	601,890 (19.0%)	36,422
	50–59	3,183,224 (17.5%)	203,992	2,632,224 (19.4%)	198,393	368,485 (11.7%)	18,297
	60–69	2,485,644 (13.6%)	105,671	2,238,772 (16.5%)	102,758	184,888 (5.8%)	6,092
	70–79	2,011,543 (11.0%)	68,179	1,927,005 (14.2%)	53,150	79,879 (2.5%)	2,045
	80–89	968,302 (5.3%)	59,078	891,437 (6.6%)	18,148	29,663 (0.9%)	968
	90+	209,862 (1.2%)	23,407	185,447 (1.4%)	4,573	8,059 (0.3%)	243
Ethnicity	White	14,199,514 (78.0%)	871,142	11,146,222 (82.1%)	716,017	1,947,330 (61.6%)	122,402
	Mixed	211,010 (1.2%)	15,545	122,352 (0.9%)	7,334	77,925 (2.5%)	4,074
	South Asian	1,168,451 (6.4%)	129,517	762,495 (5.6%)	40,741	314,718 (10.0%)	10,718
	Black	394,135 (2.2%)	30,176	210,470 (1.6%)	9,379	168,355 (5.3%)	8,227
	Other	408,705 (2.2%)	22,200	224,004 (1.7%)	10,288	181,162 (5.7%)	4,351
	Missing	1,829,122 (10.0%)	81,719	1,106,856 (8.2%)	60,476	471,995 (14.9%)	12,331
Index of multiple deprivation quintile	1: Most deprived	3,525,620 (19.4%)	279,926	2,222,818 (16.4%)	133,651	941,492 (29.8%)	49,101
	2	3,630,499 (19.9%)	249,597	2,549,290 (18.8%)	156,080	760,767 (24.1%)	38,474
	3	3,938,026 (21.6%)	231,601	3,000,854 (22.1%)	181,721	634,857 (20.1%)	32,075
	4	3,710,471 (20.4%)	208,451	2,959,981 (21.8%)	186,328	484,726 (15.3%)	24,590
	5: Least deprived	3,406,321 (18.7%)	180,724	2,839,456 (20.9%)	186,455	339,643 (10.7%)	17,863
Smoking status	Never smoker	8,362,691 (45.9%)	566,479	6,313,346 (46.5%)	411,248	1,312,958 (41.5%)	65,184
	Former smoker	5,973,167 (32.8%)	385,150	4,947,123 (36.4%)	324,969	632,484 (20.0%)	47,422
	Current smoker	3,119,113 (17.1%)	154,428	1,904,804 (14.0%)	91,978	858,703 (27.2%)	40,502
	Missing	755,966 (4.2%)	44,242	407,126 (3.0%)	16,040	357,340 (11.3%)	8,995

Characteristics		Pre-vaccination cohort (Jan 1 2020 to Dec 14 2021)		Vaccinated cohort (June 1 to Dec 14 2021)		Unvaccinated cohort (June 1 to Dec 14 2021)	
		N (%)	COVID-19 diagnoses	N (%)	COVID-19 diagnoses	N (%)	COVID-19 diagnoses
Region	East	4,222,601 (23.2%)	260,099	3,188,143 (23.5%)	179,633	710,839 (22.5%)	36,946
	East Midlands	3,163,448 (17.4%)	215,843	2,378,711 (17.5%)	155,625	514,154 (16.3%)	30,669
	London	1,250,376 (6.9%)	77,260	718,413 (5.3%)	37,512	458,007 (14.5%)	12,324
	North East	882,703 (4.8%)	68,550	656,311 (4.8%)	48,974	135,739 (4.3%)	7,890
	North West	1,613,534 (8.9%)	122,524	1,230,083 (9.1%)	85,666	213,099 (6.7%)	12,999
	South East	1,238,689 (6.8%)	60,689	952,166 (7.0%)	56,305	195,133 (6.2%)	9,821
	South West	2,543,525 (14.0%)	94,757	2,095,323 (15.4%)	126,893	313,208 (9.9%)	19,032
	West Midlands	742,813 (4.1%)	62,997	484,928 (3.6%)	29,502	174,477 (5.5%)	8,681
	Yorkshire/Humber	2,553,248 (14.0%)	187,580	1,868,321 (13.8%)	124,125	446,829 (14.1%)	23,741
Care home resident		89,607 (0.5%)	23,916	58,256 (0.4%)	2,883	2,988 (0.1%)	121

Number of events and incidence rates

The numbers, person-years, and incidence rates per 100,000 person-years of vascular events before any COVID-19 diagnosis, after hospitalized COVID-19 and after non-hospitalized COVID-19, are presented, for each cohort and outcome, in Table 2. There was a total of 212,557, 57,425 and 3,316 ATE in the pre-vaccination, vaccinated and unvaccinated cohorts respectively. The corresponding total numbers of VTE were 117,730, 29,107 and 3,178 respectively. In each cohort, the incidence of each arterial thrombotic and venous thrombotic event was higher after COVID-19 than before or without COVID-19. For each outcome and cohort, the highest incidence rates were after hospitalized COVID-19. Incidence rates were generally lower in the younger unvaccinated cohort than in the older vaccinated cohort.

Table 2
Number of arterial thrombotic, venous thrombotic, and other cardiovascular events in the pre-vaccination, vaccinated and unvaccinated cohorts, with person-years of follow-up, by COVID-19 severity. *Incidence rates are per 100,000 person-years

Event	COVID-19 severity	Pre-vaccination cohort (N = 18,210,937)		Vaccinated cohort (N = 13,572,399)		Unvaccinated cohort (N = 3,161,485)	
		Event/person-years	Incidence rate*	Event/person-years	Incidence rate*	Event/person-years	Incidence rate*
Arterial thrombotic events							
All arterial thrombotic events	No COVID-19	203,473/33,995,522	599	55,521/6,192,325	897	2,951/1,112,947	265
	Hospitalised COVID-19	2,304/47,431	4,858	407/2,679	15,191	169/1,649	10,250
	Non-hospitalised COVID-19	6,780/966,400	702	1,497/155,606	962	196/23,926	819
Acute myocardial infarction	No COVID-19	97,236/34,076,517	285	25,360/6,199,559	409	1,432/1,113,291	129
	Hospitalised COVID-19	1,150/48,545	2,369	197/2,717	7,252	72/1,661	4,335
	Non-hospitalised COVID-19	3,116/970,499	321	677/155,813	434	86/23,952	359
Ischaemic stroke	No COVID-19	100,350/34,072,265	295	28,194/6,198,458	455	1,377/1,113,278	124
	Hospitalised COVID-19	1,052/48,415	2,173	176/2,716	6,481	74/1,662	4,453
	Non-hospitalised COVID-19	3,517/970,028	363	799/155,793	513	93/23,949	388
Venous thrombotic events							
All venous thrombotic events	No COVID-19	108,798/34,065,305	319	27,303/6,198,810	440	2,265/1,113,091	203
	Hospitalised COVID-19	3,868/45,938	8,420	781/2,615	29,870	658/1,551	42,427
	Non-hospitalised COVID-19	5,064/968,526	523	1,023/155,742	657	255/23,918	1,066
Pulmonary embolism	No COVID-19	46,592/34,116,905	137	11,322/6,202,790	183	755/1,113,435	68
	Hospitalised COVID-19	3,093/46,783	6,611	663/2,639	25,120	587/1,566	37,481
	Non-hospitalised COVID-19	2,616/971,311	269	533/155,882	342	170/23,943	710
Deep vein thrombosis	No COVID-19	58,125/34,099,045	170	14,308/6,201,621	231	1,376/1,113,277	124
	Hospitalised COVID-19	826/48,540	1,702	124/2,723	4,554	76/1,657	4,588
	Non-hospitalised COVID-19	2,319/971,257	239	450/155,863	289	85/23,949	355
Other cardiovascular events							
Heart failure	No COVID-19	322,074/33,893,733	950	126,530/6,173,040	2,050	4,280/1,112,569	385
	Hospitalised COVID-19	4,998/44,622	11,201	1,591/2,399	66,313	303/1,621	18,693
	Non-hospitalised COVID-19	8,595/963,587	892	2,375/155,244	1,530	152/23,933	635
Angina	No COVID-19	238,660/33,922,822	704	81,037/6,182,983	1,311	2,530/1,112,942	227
	Hospitalised COVID-19	2,686/46,168	5,818	864/2,545	33,952	166/1,634	10,160
	Non-hospitalised COVID-19	5,675/965,281	588	1,452/155,417	934	88/23,943	368
Transient ischaemic attack	No COVID-19	46,617/34,105,801	137	12,707/6,201,839	205	463/1,113,466	42
	Hospitalised COVID-19	246/49,114	501	45/2,736	1,645	7/1,669	419
	Non-hospitalised COVID-19	1,070/972,505	110	222/155,906	142	13/23,967	54

Event	COVID-19 severity	Pre-vaccination cohort (N = 18,210,937)		Vaccinated cohort (N = 13,572,399)		Unvaccinated cohort (N = 3,161,485)	
		Event/person-years	Incidence rate*	Event/person-years	Incidence rate*	Event/person-years	Incidence rate*
Arterial thrombotic events							
Subarachnoid haemorrhage / haemorrhagic stroke	No COVID-19	18,308/34,137,474	54	4,389/6,204,415	71	295/1,113,538	26
	Hospitalised COVID-19	222/49,235	451	24/2,743	875	9/1,670	539
	Non-hospitalised COVID-19	782/973,084	80	169/155,958	108	16/23,967	67

Comparisons of event rates after COVID-19 versus before or without COVID-19

Adjusted hazard ratios were estimated using Cox-proportional hazards models to quantify the associations between COVID-19 diagnosis (time-varying exposure) and cardiovascular events including arterial thrombotic, venous thrombotic and other cardiovascular events. Minimally adjusted models accounted for age, sex and region and maximally adjusted models accounted additionally for ethnicity, area deprivation, smoking status, number of GP-patient interactions and history of comorbidities. In each cohort, maximally adjusted HRs (aHRs) comparing the incidence of each outcome after COVID-19 with the incidence before or without COVID-19 were attenuated compared with age-, sex- and region-adjusted HRs (Table 3, Table S2). The incidence of each outcome in each cohort was substantially elevated during weeks 1–4 after COVID-19 diagnosis, compared with before or without COVID-19. aHRs were lower in subsequent time periods than during weeks 1–4 after COVID-19, though they were generally greater than 1 throughout follow-up in each cohort (Figs. 1–2, Table 3). aHRs during weeks 1–4 after COVID-19 were substantially lower in the vaccinated cohort than in the pre-vaccination and unvaccinated cohorts, and generally remained lower than in other cohorts during weeks 4–28 (Figs. 1–2, Table 3). For each outcome and in each cohort, aHRs were substantially higher after hospitalized than non-hospitalized COVID-19 (Fig. 1, Table 3, Table S2).

Table 3

Adjusted hazard ratios (95% CI) comparing the incidence of arterial thrombotic, venous thrombotic, and other vascular events after COVID-19 with the incidence before or without COVID-19, in the pre-vaccination, vaccinated and unvaccinated cohorts, overall and according to COVID-19 severity. Hazard ratios are maximally adjusted unless otherwise stated.

		Weeks since COVID-19	Pre-vaccination cohort	Vaccinated cohort	Unvaccinated cohort
Arterial thrombotic events					
All arterial thrombotic events	All, age/sex/region adjusted	1–4	14.7 (14.2–15.1)	4.95 (4.68–5.23)	21.4 (19.0-24.1)
		5–28	1.55 (1.49–1.61)	1.10 (1.01–1.20)	1.94 (1.47–2.57)
		29–52	1.28 (1.22–1.34)	-	-
		53–102	1.51 (1.41–1.62)	-	-
	All	1–4	12.7 (12.3–13.1)	4.91 (4.65–5.19)	17.2 (15.3–19.4)
		5–28	1.35 (1.30–1.41)	1.09 (1.00-1.18)	1.55 (1.17–2.05)
		29–52	1.12 (1.07–1.17)	-	-
		53–102	1.21 (1.13–1.30)	-	-
	Hospitalised COVID-19	1–4	22.5 (21.2–23.8)	12.8 (11.4–14.3)	32.8 (27.5–39.2)
		5–28	1.79 (1.64–1.96)	1.75 (1.39–2.20)	1.56 (0.88–2.78)
		29–52	1.34 (1.20–1.50)	-	-
		53–102	1.33 (1.16–1.53)	-	-
	Non-hospitalised COVID-19	1–4	10.3 (9.92–10.7)	4.06 (3.81–4.32)	10.9 (9.27–12.9)
		5–28	1.28 (1.22–1.34)	1.02 (0.93–1.11)	1.45 (1.06-2.00)
		29–52	1.08 (1.03–1.14)	-	-
		53–102	1.18 (1.10–1.28)	-	-
Acute myocardial infarction		1–4	11.1 (10.5–11.6)	4.48 (4.13–4.87)	13.4 (11.2–16.1)
		5–28	1.32 (1.25–1.40)	1.05 (0.93–1.19)	1.62 (1.12–2.35)
		29–52	1.16 (1.09–1.24)	-	-
		53–102	1.31 (1.19–1.44)	-	-
Ischaemic stroke		1–4	12.8 (12.2–13.4)	5.23 (4.84–5.64)	16.8 (14.1–20.0)
		5–28	1.40 (1.32–1.48)	1.09 (0.97–1.23)	1.28 (0.82-2.00)
		29–52	1.08 (1.01–1.15)	-	-
		53–102	1.15 (1.05–1.27)	-	-
Venous thrombotic events					
All venous thrombotic events	All, age/sex/region adjusted	1–4	31.5 (30.6–32.5)	8.05 (7.61–8.52)	56.8 (52.3–61.8)
		5–28	2.06 (1.97–2.15)	1.62 (1.48–1.77)	3.21 (2.55–4.05)
		29–52	1.20 (1.13–1.27)	-	-
		53–102	1.42 (1.29–1.56)	-	-
	All	1–4	28.2 (27.3–29.0)	7.69 (7.26–8.14)	45.4 (41.7–49.4)
		5–28	1.87 (1.79–1.95)	1.53 (1.40–1.67)	2.44 (1.94–3.07)
		29–52	1.10 (1.03–1.16)	-	-
		53–102	1.20 (1.09–1.32)	-	-
	Hospitalised COVID-19	1–4	128.5 (122.9-134.4)	64.9 (59.5–70.7)	302.8 (268.7-341.2)
		5–28	4.40 (4.02–4.81)	5.67 (4.63–6.95)	7.58 (5.12–11.2)
		29–52	1.39 (1.18–1.63)	-	-
		53–102	1.27 (1.02–1.58)	-	-
	Non-hospitalised COVID-19	1–4	13.3 (12.7–13.9)	3.91 (3.61–4.24)	12.0 (10.3–13.9)

† Insufficient events for estimation

	Weeks since COVID-19	Pre-vaccination cohort	Vaccinated cohort	Unvaccinated cohort
Arterial thrombotic events				
	5–28	1.55 (1.47–1.63)	1.28 (1.16–1.41)	1.63 (1.22–2.17)
	29–52	1.05 (0.99–1.12)	-	-
	53–102	1.16 (1.05–1.29)	-	-
Pulmonary embolism	1–4	52.8 (51.0-54.8)	14.4 (13.5–15.4)	130.9 (116.2-147.5)
	5–28	2.03 (1.90–2.17)	1.76 (1.54–2.01)	4.25 (3.08–5.88)
	29–52	1.03 (0.94–1.13)	-	-
	53–102	1.14 (0.99–1.32)	-	-
Deep vein thrombosis	1–4	11.3 (10.6–12.0)	3.42 (3.06–3.83)	9.52 (7.90–11.5)
	5–28	1.77 (1.67–1.89)	1.48 (1.30–1.68)	1.62 (1.16–2.25)
	29–52	1.17 (1.08–1.26)	-	-
	53–102	1.28 (1.13–1.45)	-	-
Other cardiovascular events				
Heart failure	1–4	16.5 (16.1–17.0)	5.81 (5.58–6.04)	17.4 (15.5–19.7)
	5–28	1.43 (1.38–1.49)	1.14 (1.07–1.21)	1.90 (1.48–2.43)
	29–52	1.09 (1.05–1.14)	-	-
	53–102	1.04 (0.98–1.11)	-	-
Angina	1–4	10.1 (9.75–10.5)	3.96 (3.76–4.17)	13.4 (11.6–15.4)
	5–28	1.23 (1.18–1.28)	1.12 (1.05–1.20)	1.35 (0.98–1.87)
	29–52	1.11 (1.06–1.16)	-	-
	53–102	1.16 (1.08–1.25)	-	-
Transient ischaemic attack	1–4	3.83 (3.38–4.34)	2.05 (1.72–2.44)	†
	5–28	1.23 (1.13–1.35)	1.16 (0.98–1.37)	†
	29–52	1.12 (1.02–1.24)	-	-
	53–102	1.10 (0.95–1.29)	-	-
Subarachnoid haemorrhage and haemorrhagic stroke	1–4	15.7 (14.2–17.3)	5.91 (4.98–7.02)	†
	5–28	1.45 (1.27–1.64)	1.17 (0.89–1.54)	†
	29–52	1.32 (1.14–1.52)	-	-
	53–102	1.42 (1.15–1.76)	-	-

† Insufficient events for estimation

The incidence of ATE during weeks 1–4 after COVID-19, compared with before or without COVID-19, was markedly elevated in the pre-vaccination and unvaccinated cohorts (aHRs 12.7 (95% CI 12.3–13.1) and 17.2 (15.3–19.4) respectively) but less markedly elevated in the vaccinated cohort (4.91 (4.65–5.19)) (Fig. 1, Table 3). The incidence of ATE remained elevated during weeks 5–28 in the unvaccinated cohort (1.55 (1.17–2.05)) and up to weeks 53–102 in the pre-vaccination cohort (1.21 (1.13–1.30)). aHRs for ATE were substantially higher during weeks 1–4 after hospitalized COVID-19, versus before or without COVID-19 (pre-vaccination cohort 22.5 (21.2–23.8), unvaccinated cohort 32.8 (27.5–39.2)) than after non-hospitalized COVID-19 (pre-vaccination cohort 10.3 (9.92–10.7), unvaccinated cohort 10.9 (9.27–12.9)). In sensitivity analyses restricted to primary diagnoses of ATE, aHRs during weeks 1–4 after hospitalized COVID-19 were attenuated compared with aHRs for all ATEs (Figure S1). Results were similar in sensitivity analyses removing censoring at first vaccination in the unvaccinated cohort (Table S3). When follow-up on the day of diagnosis (day 0) was separated from the rest of weeks 1–4, aHRs for ATE on day 0 were much higher than subsequently, particularly in the pre-vaccination and unvaccinated cohorts) (Table S4).

The aHRs for VTE during weeks 1–4 after COVID-19, versus before or without COVID-19, were substantially higher than for ATE, particularly in the pre-vaccination and unvaccinated cohorts (aHRs 28.2 (95% CI 27.3–29.0) and 45.42 (41.7–49.4) respectively), but less markedly in the vaccinated cohort (7.69 (7.26–8.14)) (Fig. 1, Table 3). The incidence of VTE remained elevated, compared with before or without COVID-19, during weeks 5–28 in all cohorts and up to weeks 53–102 in the pre-vaccination cohort (1.20 (1.09–1.32)). aHRs were substantially higher during weeks 1–4 after hospitalized COVID-19 (pre-vaccination cohort 128.5 (122.9-134.4), vaccinated cohort 64.9 (59.5–70.7), unvaccinated cohort 303 (269–341)) than after non-hospitalized COVID-19 (pre-vaccination cohort 13.3 (12.7–13.9), vaccinated cohort 3.91 (3.61–4.24), unvaccinated cohort 12.0 (10.3–13.9)). The incidence of VTE was still markedly

elevated during weeks 5–28 after hospitalized COVID-19 in the pre-vaccination, vaccinated and unvaccinated cohorts (aHRs 4.40 (4.02–4.81), 5.67 (4.63–6.95) and 7.58 (5.12–11.2) respectively). In sensitivity analyses restricted to primary diagnosis of VTE, aHRs after COVID-19 were attenuated compared with aHRs for all VTEs (Figure S2). This attenuation was particularly marked during weeks 1–4 and after hospitalized COVID-19. When separating day 0 from the rest of weeks 1–4, aHRs for day 0 were very high in the pre-vaccination and unvaccinated cohorts (Table S4).

In each cohort, aHRs for acute MI during weeks 1–4 after COVID-19, versus before or without COVID-19, were similar to those for ischaemic stroke (Fig. 2, Table 3). In the pre-vaccination cohort, aHRs for acute MI remained elevated during weeks 29–52 (1.16 (1.09–1.24)) and weeks 53–102 (1.31 (1.19–1.44)), but the incidence of ischaemic stroke was only slightly elevated from 29 weeks onwards (aHR 1.15 (1.05–1.27) during weeks 53–102). In all cohorts, aHRs during weeks 1–4 were markedly higher for PE (pre-vaccination 52.8 (51.0-54.8)), vaccinated cohort (14.4 (13.5–15.4), unvaccinated cohort 131 (116–148)) than for DVT, and aHRs for PE remained higher than for DVT during weeks 5–28. By contrast, in the pre-vaccination cohort aHRs for DVT during weeks 29–102 were higher than for PE.

The incidence of heart failure, angina, and subarachnoid haemorrhage and haemorrhagic stroke during weeks 1–4 after COVID-19 was substantially elevated in each cohort, versus before or without COVID-19, although aHRs were lower in the vaccinated cohort than the pre-vaccination or unvaccinated cohorts (Fig. 2, Table 3). Compared with these outcomes, the incidence of transient ischaemic attack was less markedly elevated during weeks 1–4. Though greater than 1, aHRs for these four outcomes were markedly lower during weeks 5–28 than weeks 1–4 after COVID-19. In the pre-vaccination cohort, the incidence of heart failure during weeks 53–102 was similar to the incidence before or without COVID-19 (aHR 1.04 (0.98–1.11)). The incidence of angina and transient ischaemic attack was slightly elevated (aHRs between 1.10 and 1.16) and remained elevated during weeks 29–102. aHRs for subarachnoid haemorrhage and haemorrhagic stroke were 1.32 (1.14–1.52) during weeks 29–52 and 1.42 (1.15–1.76) during weeks 53–102.

In subgroup analyses, aHRs for both ATE and VTE were generally lower in younger age groups, in females, and in those reporting white ethnicity (Tables S5-S6, Figures S3-S4). Estimated excess risks of ATE 6 months post-COVID-19 were 642, 229 and 718 per 100,000 people diagnosed with COVID-19 in the pre-vaccination, vaccinated and unvaccinated cohorts respectively (Figure S5, Table S7). Corresponding estimated excess risks of VTE were 797, 270, and 1,094 per 100,000 people diagnosed with COVID-19 respectively.

DISCUSSION

These cohort studies of up to ~ 18.2 million people demonstrate that COVID-19 vaccination substantially attenuates the elevated incidence of arterial and venous thrombotic events after COVID-19. This attenuation appears mainly attributable to the reductions in severity of COVID-19 caused by vaccination. Among people diagnosed with COVID-19 before availability of vaccination the incidence of ATEs and VTEs remained elevated by around 20% during the second year after COVID-19, and more so after hospitalized COVID-19, compared with the incidence before or without COVID-19. The associations of VTEs, and particularly PE, with hospitalized COVID-19 were stronger than those for ATEs. The magnitude of elevations in incidence of arterial and venous thrombotic events after COVID-19 was of similar magnitude in the pre-vaccination and unvaccinated cohorts, suggesting that changes in the dominant SARS-CoV-2 variant had little impact compared with that of vaccination.

Most previous studies of cardiovascular events following SARS-CoV-2 infections were conducted prior to the delta era and widespread availability of COVID-19 vaccination[1,21–23]. For example, a study of over 6 million patients from the US Department of Veterans Affairs healthcare system, including over 162,000 who had a positive COVID-19 test between March 2020 and January 2021 estimated HRs 30 days to 12 month post COVID-19 for several outcomes we considered, including MI (HR: 1.63, 95% CI: 1.51–1.75), DVT (2.09, 1.94–2.24), and heart failure (1.72, 1.65–1.80)[23].

Many pathways have been postulated to explain the increased risk of vascular events after infection[24]. Respiratory infections including SARS-CoV-2 activate immune responses beyond the respiratory epithelium. Influenza leads to inflammation, smooth muscle proliferation and fibrin deposition in atherosclerotic plaques in mice, which may increase risks of MI if replicated in human infection[25]. SARS-CoV-2 infection generally increases inflammatory cytokines, activating endothelium and increasing biomarkers of thrombosis, but probably does not directly infect the vascular epithelium (although this is contested)[26]. Agents that attenuate the inflammatory response (dexamethasone, tociluzamab and baricitinib) reduce mortality from SARS-CoV-2, but it is unclear whether these reduce vascular-specific mortality[27–30]. Cardiovascular sequalae of SARS and MERS are not well defined due to the small number of patients who have been followed up and lack of appropriate control groups, but the evidence points to potentially substantial post-infection cardiovascular risks[31].

Although the risk of thrombotic events is high soon after infection, clinical trials have not demonstrated clear benefit from antithrombotic agents to most people with COVID-19. In RECOVERY, aspirin did not reduce the chance of death at 28 days after randomisation (rate ratio 0.96, 95%CI: 0.89–1.04), but did modestly reduce hospital stay[32]. In ATTACC, ACTIV-4a, and REMAP-CAP, therapeutic anticoagulation with heparins did not clearly increase organ-support free days in patients who were hospitalized with COVID-19 and were critically unwell (OR: 0.83, CrInt 0.67–1.03), but did in patients who were not critically unwell (4% (CrInt 0.5–7.2))[33,34]. Oral anticoagulation after admission did not clearly reduce mortality in people after hospital admission in HEALCOVID (n = 402)[35] and ACTION (n = 615)[36], but there was a suggestion of benefit (and no evidence of bleeding) in MICHELLE (n = 320)[37].

We analysed comprehensive linked electronic health record data on ~ 40% of the English population. The large dataset size allowed us to estimate associations in important subgroups as well as overall, and we controlled for a substantial range of potential confounding factors. Limitations of our study include first that we did not have access to SARS-CoV-2 sequencing data so could not confirm the SARS-CoV-2 variant for individual infections. Second, we could not analyse an Omicron-era cohort as mandatory testing for SARS-CoV-2 in England stopped at the end of March 2022. Third, a substantial proportion of cardiovascular events during weeks 1–4 were recorded on the day of COVID-19 diagnosis, and so it is possible that some COVID-19 diagnoses were made because patients with cardiovascular events were examined in hospital or in other healthcare settings, rather than because COVID-19 caused these cardiovascular events. However, the substantial differences between aHRs in the vaccinated and unvaccinated cohorts suggest that such reverse causation

was not the main reason for the very high hazard ratios during weeks 1–4. Fourth, although we adjusted for a broad range of potential confounders, our results may be biased by unmeasured confounding due to missing information or measurement error. For example, body mass index is not systematically recorded in electronic health records and may be incorrect in some instances. In addition, we did not adjust for potential time-varying confounders that varied after the cohort start date and may have predicted both COVID-19 and cardiovascular outcomes. Fifth, we did not account for reinfections, although these will have been rare until the Omicron variant became dominant. Sixth, older people in the vaccinated cohort were eligible for booster vaccination from September 2021 so associations between COVID-19 and CVD in that cohort will relate to effects of booster as well as second vaccination. Finally, outcome misclassification or delays in diagnosis can occur because individuals with mild symptoms do not present to healthcare or because it is difficult to identify a thrombotic disorder in individuals who are very unwell with COVID-19.

The absence of clear benefit for antithrombotic strategies after infection, and the clear reduction in thrombotic complication after vaccination means that vaccination is critical to prevent severe COVID-19 disease and its cardiovascular sequelae, particularly in population groups at highest risk and in which coverage is currently low. In conclusion, COVID-19 vaccination reduces the risk of arterial thrombotic, venous thrombotic and other cardiovascular events after COVID-19 infection. People who had COVID-19 before being vaccinated are at higher risk of these events for an extended period of at least two years: further follow-up is required to establish the duration of this higher risk.

ONLINE METHODS

The study design and pre-determined methods are described in detail in a publicly available protocol: https://github.com/opensafely/post-covid-vaccinated/tree/main/protocol.

Study design and data source

Using a cohort study design, linked electronic health records were analysed through OpenSAFELY (https://opensafely.org), a data analytics platform created to address COVID-19-related research questions[38]. The platform provides secure access to primary care records managed by the GP software provider, The Phoenix Partnership (TPP) SystmOne software, which covers around 40% of the population in England. This OpenSAFELY-TPP population is representative of the general population of England in terms of age, sex, ethnicity, index of multiple deprivation, and causes of death[39]. The TPP primary care data is securely linked at individual level to the Second Generation Surveillance System for Pillars 1 and 2 SARS-COV-2 infection laboratory testing data, COVID-19 vaccination records (National Immunisation Management System), National Health Service (NHS) hospitalisations (Secondary Uses Services data) and the Office of National Statistics (ONS) death registry, including causes of death.

Outcomes were derived from primary care records, hospital admissions and causes of death. Clinically verified SNOMED-CT (Systematized Nomenclature of Medicine-Clinical Terms) and ICD-10 (International Classification of Disease, 10th revision) rule-based phenotyping algorithms were used to define arterial thrombosis outcomes (acute MI, ischaemic stroke and a composite 'arterial thrombotic event' (ATE)), venous thrombosis outcomes (PE, DVT and a composite 'venous thrombotic event' (VTE)), and other cardiovascular outcomes (heart failure, angina, transient ischaemic attack, subarachnoid haemorrhage and haemorrhagic stroke) (see protocol: https://github.com/opensafely/post-covid-vaccinated/tree/main/protocol).

The date of COVID-19 diagnosis was defined as the earliest of the date of a positive SARS-COV-2 test, the date of a confirmed COVID-19 diagnosis in primary or secondary care or the date of death with SARS-COV-2 infection listed as primary or underlying cause. Individuals who were hospitalized with a COVID-19 primary diagnosis within 28 days of first COVID-19 diagnosis were categorised as 'hospitalized COVID-19', otherwise they were categorised as 'non-hospitalized COVID-19'. Covariates identified as potential confounders included age; sex; ethnicity; region; area socioeconomic deprivation; smoking status; number of GP-patient interactions in the last 12 months; and previous history of a specific comorbidity (binary) for a range of diseases (details in Table S8).

Study population

Three cohorts were defined. In the 'pre-vaccination' cohort, follow-up started on January 1st 2020 (baseline) and ended on the earliest of December 14th 2021 (when the Omicron variant became dominant in England[40]), date that the outcome event of interest was recorded, and date of death. Exposure was defined as a recorded COVID-19 diagnosis between baseline and the earliest of eligibility for COVID-19 vaccination, date of first vaccination and June 18th 2021 (when all adults became eligible for vaccination): this exposure period was before the Delta variant became dominant in England. The other two cohorts were followed during the period when the Delta variant was dominant in England: between June 1st 2021 (baseline) and December 14th 2021 (study end date). Follow-up in the 'vaccinated' cohort started at the later of baseline and two weeks after a second COVID-19 vaccination and ended at the earliest of the study end date, outcome event date, and date of death. The 'unvaccinated' cohort had not received a COVID-19 vaccine by 12 weeks after they became eligible for vaccination. Follow-up started at the later of baseline and 12 weeks after vaccination eligibility and ended at the earliest of the study end date, outcome event date, date of death, and date of first vaccination.

Individuals eligible for each cohort had been registered with an English GP for at least six months before the cohort baseline, were alive and aged between 18 and 110 years at baseline, and had known sex, region and area deprivation. Individuals with a history of COVID-19 before the cohort baseline were excluded. In the vaccinated cohort, individuals who received a COVID-19 vaccination before December 8th 2020, or a second dose before or less than three weeks after their first dose, or received more than one type of vaccine before May 7th 2021, were excluded. In the unvaccinated cohort, individuals who could not be assigned to a vaccination priority group as defined by JCVI were excluded.

Statistical analyses

For each cohort, baseline demographic and clinical characteristics were described, and the number of events per outcome, person-years of follow-up and incidence rates (per 100,000 person-years) of events before and after all, hospitalized and non-hospitalized COVID-19 were calculated. Time to first event was analysed for each outcome. Cox models were fitted with calendar time scale using the cohort-specific baseline as the origin (time zero). Hazard ratios (HRs) for follow-up after versus before or without COVID-19 were estimated, splitting follow-up into periods 1-4 and 5-28 weeks after COVID-19 for all cohorts and additionally 29-52 and 53-102 weeks after COVID-19 for the pre-vaccination cohort. For each outcome and cohort, we estimated: (i) age and sex; and (ii) maximally (including all potential confounders) adjusted HRs. Subgroup analyses were conducted according to whether individuals had been hospitalized for COVID-19 within 28 days of COVID-19 diagnosis. Absolute excess risks (AER) of any ATE and any VTE after COVID-19, weighted by the proportions of individuals in age and sex strata in the pre-vaccination cohort, were derived. Further details of the statistical analyses and AER calculations are provided in the supplementary material.

For the outcomes ATE and VTE, we conducted additional subgroup analyses by age group, sex, ethnicity, and prior history of the outcome. Further sensitivity analyses included separating events on day 0 (day of COVID-19 diagnosis) from the rest of weeks 1-4, removing censoring at first vaccination in the unvaccinated cohort, and identifying outcomes using primary position only (main diagnosis or cause of death).

Data management and analyses were conducted in Python version 3.8.10 and R version 4.0.2.

Declarations

Data availability statement

All data were linked, stored and analysed securely within the OpenSAFELY platform: https://opensafely.org/. Data include pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. All code and code lists are shared openly for review and re-use under an MIT open license (pre-vaccination cohort: https://github.com/opensafely/post-covid-Pre-vaccination-cardiovascular; vaccinated and unvaccinated cohorts: https://github.com/opensafely/post-covid-vaccinated). Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared.

Ethical approval and information governance

This study was approved by the Health Research Authority [REC reference 22/PR/0095] and by the University of Bristol's Faculty of Health Sciences Ethics Committee [reference 117269]. Authors involved in data management/analysis successfully passed information governance training and obtained ONS safe researcher accreditation. NHS England is the data controller of OpenSAFELY-TPP. All outputs underwent disclosure checks and were approved by NHS England. Further details of OpenSAFELY information governance are provided in supplemental methods.

Acknowledgements

We are very grateful for all the support received from the TPP Technical Operations team throughout this work, and for generous assistance from the information governance and database teams at NHS England and the NHS England Transformation Directorate. We thank the CONVALESCENCE Study Long Covid PPIE group for their input and for sharing their experiences and expertise throughout the duration of the project.

Author contributions are reported below in line with the Contributor Roles Taxonomy (CRediT).

Conceptualization: Rachel Denholm, Angela M Wood, Jonathan A C Sterne, Venexia Walker

Methodology: Rachel Denholm, Angela M Wood, Jonathan A C Sterne, Venexia Walker

Software: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Alex J Walker, Louis Fisher, Jon Massey, Lisa E M Hopcroft, Elsie M F Horne, Kurt Taylor, Tom Palmer, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Sam Ip, Simon Davy, Iain Dillingham, Sebastian Bacon, Amir Mehrkar, Catherine Morton, Catherine Hyams, Ben Goldacre, Venexia Walker

Validation: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Alex J Walker, Louis Fisher, Jon Massey, Lisa E M Hopcroft, Elsie M F Horne, Kurt Taylor, Tom Palmer, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Sam Ip, Simon Davy, Iain Dillingham, Sebastian Bacon, Amir Mehrkar, Catherine Morton, Catherine Hyams, Ben Goldacre, Venexia Walker

Formal analysis: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Kurt Taylor, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Venexia Walker

Investigation: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Kurt Taylor, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Venexia Walker

Resources: Alex J Walker, Louis Fisher, Jon Massey, Lisa E M Hopcroft, Simon Davy, Iain Dillingham, Sebastian Bacon, Amir Mehrkar, Catherine Morton, Catherine Hyams, Ben Goldacre

Data curation: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Kurt Taylor, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Venexia Walker

Writing - Original Draft: Genevieve I Cezard, William N Whiteley, Jonathan A C Sterne, Venexia Walker

Writing - Review & Editing: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Alex J Walker, Louis Fisher, Jon Massey, Lisa E M Hopcroft, Elsie M F Horne, Kurt Taylor, Tom Palmer, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Sam Ip, Simon Davy, Iain Dillingham, Sebastian Bacon, Amir Mehrkar, Catherine Morton, Felix Greaves, Catherine Hyams, George Davey Smith, John Macleod, Nishi Chaturvedi, Ben Goldacre, William N Whiteley, Angela M Wood, Jonathan A C Sterne, Venexia Walker

Visualization: Genevieve I Cezard, Rachel Denholm, Rochelle Knight, Yinghui Wei, Lucy Teece, Renin Toms, Harriet J Forbes, Kurt Taylor, Marwa Al Arab, Jose Ignacio Cuitun Coronado, Venexia Walker

Project administration: Genevieve I Cezard, Rachel Denholm, Angela M Wood, Jonathan A C Sterne, Venexia Walker

Funding acquisition: Nishi Chaturvedi, Angela M Wood, Jonathan A C Sterne

Sources of Funding

This study was supported by the COVID-19 Longitudinal Health and Wellbeing National Core Study, funded by the UKRI Medical Research Council (MC_PC_20059); the COVID-19 Data and Connectivity National Core Study, funded by the UKRI Medical Research Council; and by the CONVALESCENCE long COVID study, funded by the UK National Institute for Health and Care Research (COVID-LT-009). This work was also supported by Health Data Research UK, which is funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and Wellcome. GC, SI and AWo are supported by the British Heart Foundation (RG/13/13/30194; RG/18/13/33946), BHF Cambridge Centre of Research Excellence **(RE/18/1/34212) and** NIHR Cambridge Biomedical Research Centre (BRC-1215-20014; NIHR203312). RK, GDS, and VW are supported by the Medical Research Council Integrative Epidemiology Unit at the University of Bristol [MC_UU_00011/1; MC_UU_00011/4]. RK and JACS are supported by the NIHR Bristol Biomedical Research Centre and by Health Data Research UK South-West. YW was supported by an UKRI MRC Fellowship (MC/W021358/1) and received funding from UKRI EPSRC Impact Acceleration Account (EP/X525789/1). SI and AWo were funded by a British Heart Foundation–Turing Cardiovascular Data Science Award (BCDSA/100005). SI is funded by the International Alliance for Cancer Early Detection, a partnership among Cancer Research UK C18081/A31373, Canary Center at Stanford University, the University of Cambridge, OHSU Knight Cancer Institute, University College London, and the University of Manchester. RK and JM were supported by NIHR ARC West. RD and JACS were supported by Health Data Research UK. WW is supported by the Chief Scientist's Office (CAF/01/17). AWo and WW are supported by the Stroke Association (SA CV 20/100018). AWo is part of the BigData@Heart Consortium, funded by the Innovative Medicines Initiative-2 Joint Undertaking under grant agreement No 116074. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Disclosures

WW is supported by the Chief Scientist's Office, the Stroke Association, and the Alzheimer's Society; sits on data monitoring committees for academic trials (TEMPO-2, PROTECT-U, and CATIS-ICAD); and is an independent expert witness to UK courts. NC receives funds from AstraZeneca to support membership of Data Safety and Monitoring Committees for clinical trials. CH is the Principal Investigator of a study which is a collaboration sponsored by the University of Bristol and funded by Pfizer Inc. The other authors report no conflicts.

References

1. Knight R, Walker V, Ip S, Cooper JA, Bolton T, Keene S, Denholm R, Akbari A, Abbasizanjani H, Torabi F, et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales. Circulation. 2022;146:892–906.
2. Singh J, Rahman SA, Ehtesham NZ, Hira S, Hasnain SE. SARS-CoV-2 variants of concern are emerging in India. Nat Med. 2021;27:1131–1133.
3. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, Pavlin B, Vandemaele K, Van Kerkhove MD, Jombart T, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. *Eurosurveillance* [Internet]. 2021;26. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.24.2100509
4. World Health Organisation. Weekly epidemiological update on COVID-19–20 July 2021 [Internet]. 2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—20-july-2021
5. Public Health England. SARS-CoV-2 variants of concern and variants under investigation: technical briefing 14. [Internet]. 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/991343/Variants_of_Concern_VOC_Technical_Briefi
6. Bolze A, Luo S, White S, Cirulli ET, Wyman D, Dei Rossi A, Machado H, Cassens T, Jacobs S, Schiabor Barrett KM, et al. SARS-CoV-2 variant Delta rapidly displaced variant Alpha in the United States and led to higher viral loads. Cell Reports Medicine. 2022;3:100564.
7. Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, Aliabadi S, Seaman SR, Harris RJ, Hope R, Lopez-Bernal J, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. The Lancet Infectious Diseases. 2022;22:35–42.
8. Rodrigues EF, Moreno J, Leite PP, Casaca P, Nunes B, Gomes JP, Ferreira R, Isidro J, Borges V, Vieira L, et al. B.1.617.2 SARS-CoV-2 (Delta) variant is associated with increased risk of hospitalization and death compared with B.1.1.7 SARS-CoV-2 (Alpha) variant [Internet]. Infectious Diseases (except HIV/AIDS); 2022 [cited 2023 Jan 4]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.01.21.22268602

9. Bast E, Tang F, Dahn J, Palacio A. Increased risk of hospitalisation and death with the delta variant in the USA. The Lancet Infectious Diseases. 2021;21:1629–1630.
10. Bager P, Wohlfahrt J, Rasmussen M, Albertsen M, Krause TG. Hospitalisation associated with SARS-CoV-2 delta variant in Denmark. The Lancet Infectious Diseases. 2021;21:1351.
11. Thelwall S, Aiano F, Harman K, Dabrera G, Ladhani SN. Risk of hospitalisation and death in children with SARS-CoV-2 delta (B.1.612.2) infection. The Lancet Child & Adolescent Health. 2022;6:e16–e17.
12. UK Health Security Agency. COVID-19: the green book, Chap. 14a [Internet]. 2022. Available from: https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a
13. Horne EMF, Hulme WJ, Keogh RH, Palmer TM, Williamson EJ, Parker EPK, Green A, Walker V, Walker AJ, Curtis H, et al. Waning effectiveness of BNT162b2 and ChAdOx1 covid-19 vaccines over six months since second dose: OpenSAFELY cohort study using linked electronic health records. *BMJ*. 2022;e071249.
14. Whiteley WN, Ip S, Cooper JA, Bolton T, Keene S, Walker V, Denholm R, Akbari A, Omigie E, Hollings S, et al. Association of COVID-19 vaccines ChAdOx1 and BNT162b2 with major venous, arterial, or thrombocytopenic events: A population-based cohort study of 46 million adults in England. PLoS Med. 2022;19:e1003926.
15. Kim Y-E, Huh K, Park Y-J, Peck KR, Jung J. Association Between Vaccination and Acute Myocardial Infarction and Ischemic Stroke After COVID-19 Infection. JAMA. 2022;328:887.
16. Behrouzi B, Bhatt DL, Cannon CP, Vardeny O, Lee DS, Solomon SD, Udell JA. Association of Influenza Vaccination With Cardiovascular Risk: A Meta-analysis. JAMA Network Open. 2022;5:e228873–e228873.
17. Larson KF, Ammirati E, Adler ED, Cooper LT, Hong KN, Saponara G, Couri D, Cereda A, Procopio A, Cavalotti C, et al. Myocarditis After BNT162b2 and mRNA-1273 Vaccination. Circulation. 2021;144:506–508.
18. Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021;385:2132–2139.
19. Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, Rampotas A, Ambler G, Makris M. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N Engl J Med. 2021;385:1680–1689.
20. Curtis HJ, Inglesby P, Morton CE, MacKenna B, Green A, Hulme W, Walker AJ, Morley J, Mehrkar A, Bacon S, et al. Trends and clinical characteristics of COVID-19 vaccine recipients: a federated analysis of 57.9 million patients' primary care records *in situ* using OpenSAFELY. Br J Gen Pract. 2022;72:e51–e62.
21. Chilazi M, Duffy EY, Thakkar A, Michos ED. COVID and Cardiovascular Disease: What We Know in 2021. Curr Atheroscler Rep. 2021;23:37.
22. Shakil SS, Emmons-Bell S, Rutan C, Walchok J, Navi B, Sharma R, Sheth K, Roth GA, Elkind MSV. Stroke Among Patients Hospitalized With COVID-19: Results From the American Heart Association COVID-19 Cardiovascular Disease Registry. Stroke. 2022;53:800–807.
23. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nature Medicine. 2022;28:583–590.
24. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. The Lancet Infectious Diseases. 2010;10:83–92.
25. Naghavi M, Wyde P, Litovsky S, Madjid M, Akhtar A, Naguib S, Siadaty MS, Sanati S, Casscells W. Influenza Infection Exerts Prominent Inflammatory and Thrombotic Effects on the Atherosclerotic Plaques of Apolipoprotein E–Deficient Mice. Circulation. 2003;107:762–768.
26. Martínez-Salazar B, Holwerda M, Stüdle C, Piragyte I, Mercader N, Engelhardt B, Rieben R, Döring Y. COVID-19 and the Vasculature: Current Aspects and Long-Term Consequences. Front. Cell Dev. Biol. 2022;10:824851.
27. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384:693–704.
28. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, Abbott A, Abdallah N, Abdelaziz A, Abdelfattah M, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2021;397:1637–1645.
29. Abani O, Abbas A, Abbas F, Abbas J, Abbas K, Abbas M, Abbasi S, Abbass H, Abbott A, Abbott A, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. The Lancet. 2022;400:359–368.
30. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Domingo P, Mur I, Mateo GM, Gutierrez M del M, Pomar V, de Benito N, Corbacho N, Herrera S, Millan L, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021;326:499.
31. Zhao M, Wang M, Zhang J, Ye J, Xu Y, Wang Z, Ye D, Liu J, Wan J. Advances in the relationship between coronavirus infection and cardiovascular diseases. Biomedicine & Pharmacotherapy. 2020;127:110230.
32. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, Abbott A, Abdallah N, Abdelaziz A, Abdelfattah M, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2022;399:143–151.
33. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021;385:777–789.
34. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med*. 2021;385:790–802.
35. Toshner MR, Gamble C, Baillie JK, Best A, Bedson E, Bradley J, Calvert M, Davies EH, Docherty AB, Gkioni E, et al. Apixaban following discharge in hospitalised adults with COVID-19: Preliminary results from a multicentre, open-label, randomised controlled platform clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 [cited 2023 Mar 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.12.07.22283175

36. Lopes RD, de Barros e Silva PGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, Barbosa LM, de Aveiro Morata J, Ramacciotti E, de Aquino Martins P, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. The Lancet. 2021;397:2253–2263.
37. Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, Lins dos Santos J, Volpiani GG, Sobreira ML, Joviliano EE, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. The Lancet. 2022;399:50–59.
38. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430–436.
39. Andrews C, Schultze A, Curtis H, Hulme W, Tazare J, Evans S, Mehrkar A, Bacon S, Hickman G, Bates C, et al. OpenSAFELY: Representativeness of electronic health record platform OpenSAFELY-TPP data compared to the population of England. Wellcome Open Res. 2022;7:191.
40. UK Health Security Agency. Omicron daily overview: 17 December 2021 [Internet]. 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042100/20211217_OS_Daily_Omicron_Overview.p

Figures

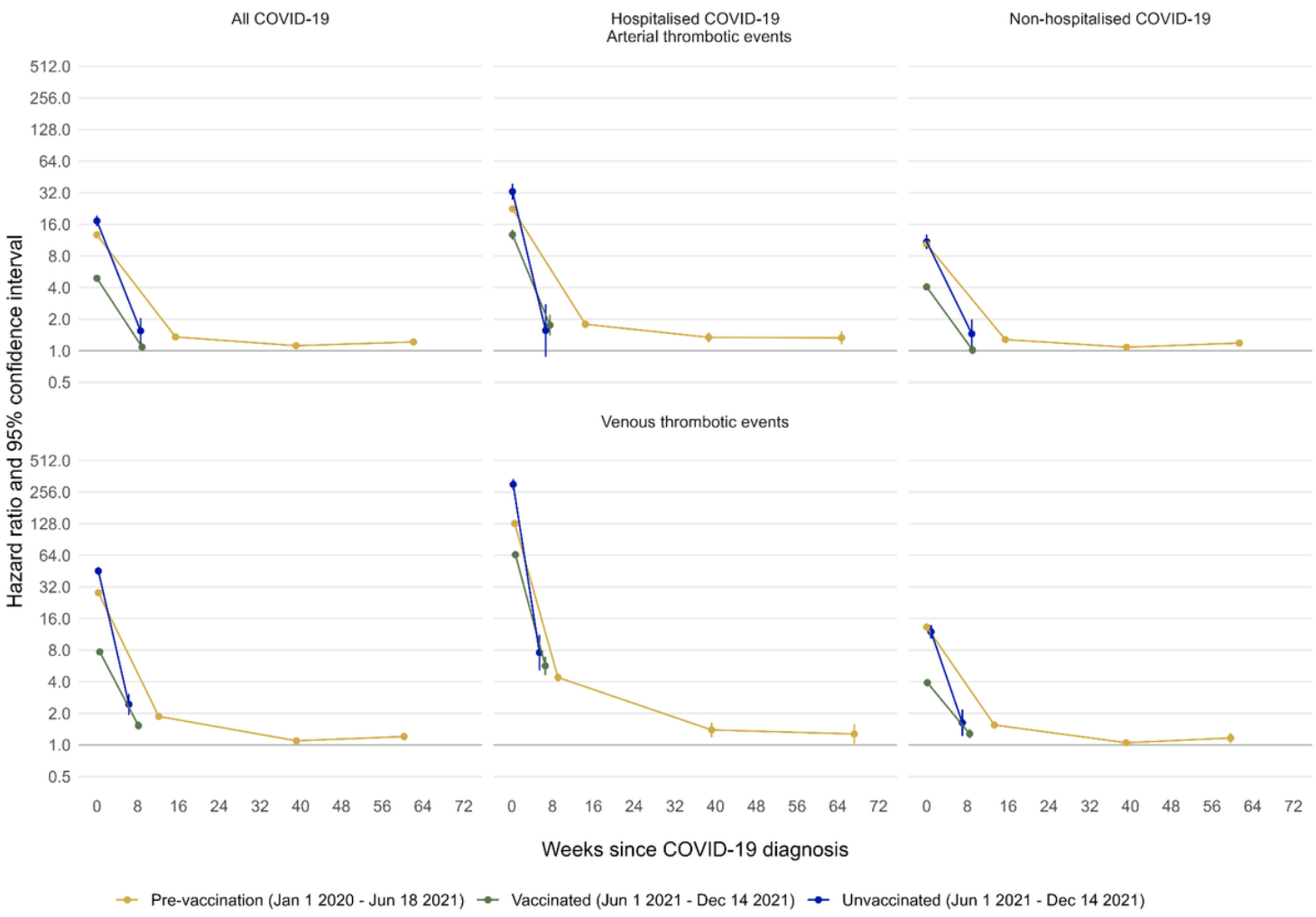

Figure 1

Maximally adjusted hazard ratios and 95% CIs comparing the incidence of arterial thrombotic and venous thrombotic events after COVID-19 with the incidence before or without COVID-19, in the pre-vaccination, vaccinated and unvaccinated cohorts, overall and by COVID-19 severity. Points are plotted at the median time of the outcome event within each follow up period in each cohort.

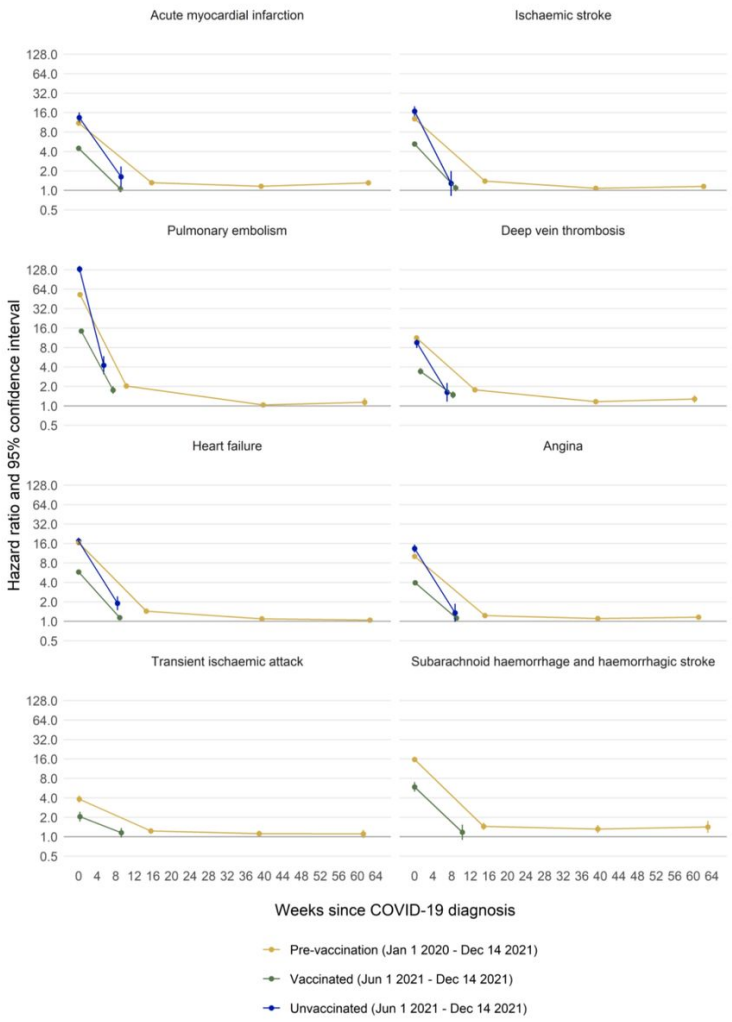

Figure 2

Maximally adjusted hazard ratios and 95% CIs comparing the incidence of arterial thrombotic, venous thrombotic, and other vascular events after COVID-19 with the incidence before or without COVID-19, in the pre-vaccination, vaccinated and unvaccinated cohorts. Points are plotted at the median time of the outcome event within each follow up period in each cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarymaterialpostcovidcardiovascular.docx