COVID-19 thromboembolism is reduced in ambulatory, but not hospitalized patients, following COVID-19 vaccination

The risk of venous thromboembolism (VTE) is increased in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and is associated with higher mortality.[1-3] Despite changes to thromboprophylaxis regimens in patients hospitalized with coronavirus disease 2019 (COVID-19), high rates of VTE have been reported in the second and third waves of COVID-19.[1,3] With widespread COVID-19 vaccine availability, whether vaccination influences the risk of COVID-19-associated thromboembolism (COVID-19 TE) in ambulatory and hospitalized patients remains an important question.

Here, we use data from the large UK Biobank and perform a cohort study to investigate the association between COVID-19 vaccination and COVID-19 TE. The UK Biobank is a prospective population-based study with comprehensive health and genetic data for over 500,000 participants who were recruited to the Biobank between 2006 and 2010.[4] Data collection occurred from February 1, 2020 until September 30, 2021. We defined an early-pandemic, unvaccinated cohort (February 1, 2020 to December 31, 2020) and compared to patients who received a first or second dose of any COVID-19 vaccination, between January 1, 2021 and June 30, 2021 (Figure 1). Patients were characterized by age, sex, body mass index and smoking status. Participants were excluded if demographic or health data was incomplete.

Patients were evaluated for the development of COVID-19 infection, defined by a positive SARS-CoV-2 test more than 14 days after COVID-19 vaccination. COVID-19 test result data was provided to UK Biobank by Public Health England, Public Health Scotland and Secure Anonymized Information Linkage for England, Scotland and Wales, respectively. Participants were defined as hospitalized, if the SARS-CoV-2 test was ordered as a hospital inpatient (which includes Accident and Emergency, hospital ward inpatients and patients in Intensive Care Units), or if the test was flagged as a hospital acquired infection. Ambulatory participants were defined as anyone receiving a positive SARS-CoV-2 test that did not meet the criteria for hospitalization.

COVID-19 TE was defined as an International Classification of Diseases (ICD)-10 code for deep vein thrombosis (i.e., I801, I802, and I822) or pulmonary embolism (i.e., I260 and I269) occurring within 90 days of COVID-19 infection.

Statistical analysis was performed using R version 4.0.3. Data is available from researchers upon request. We performed logistic regression and calculated odds ratios (OR) with 95% confidence intervals (CI) for the outcome of COVID-19 TE, adjusted by the variables of age, sex and body mass index.

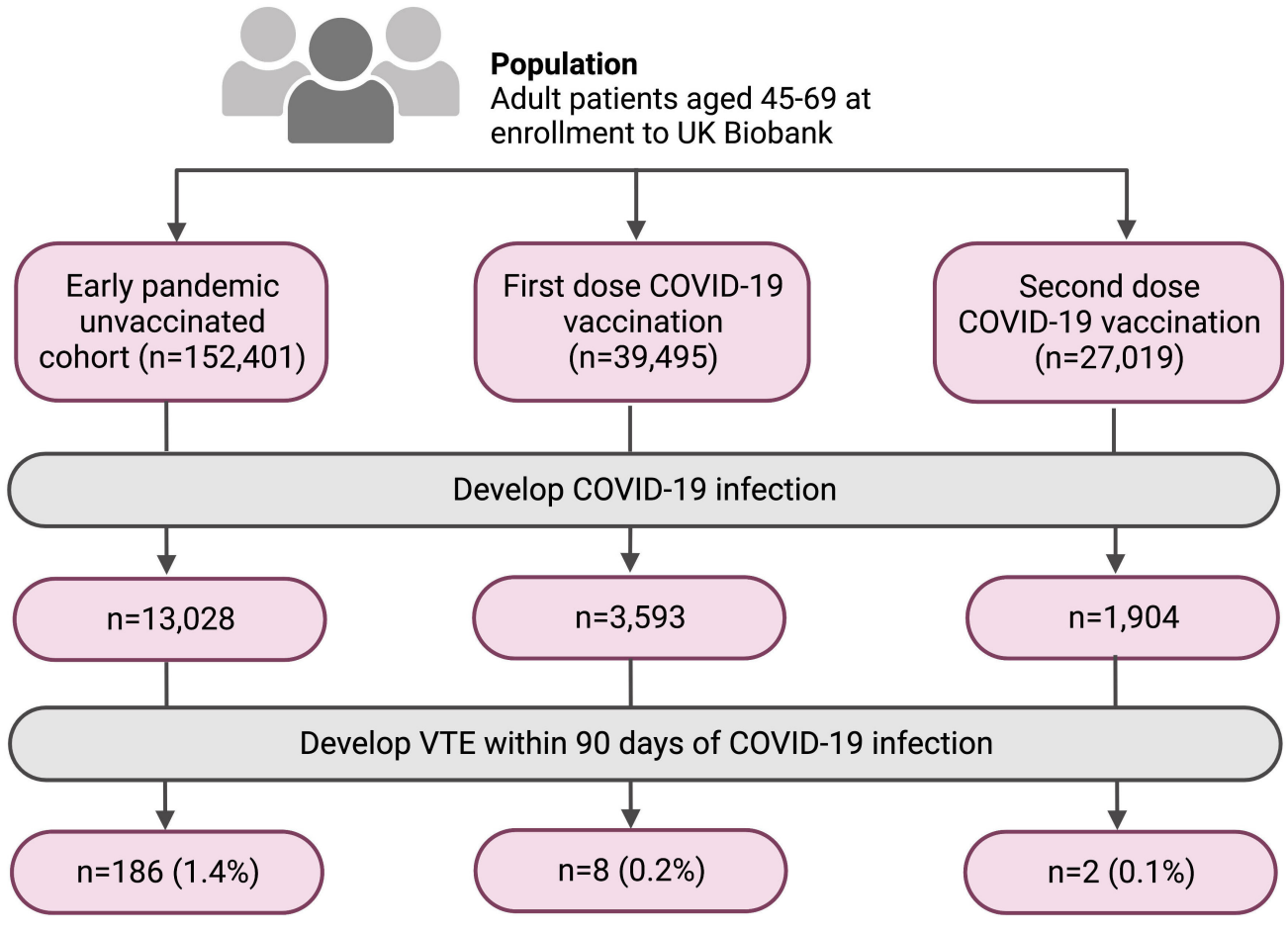

Figure 1. Study design. Created with BioRender.com. COVID-19: coronavirus disease 2019; VTE: venous thromboembolism.

The UK Biobank received ethical approval from the North West Multicenter Research Ethics Committee (11/NW/0382). All participants gave written informed consent. This research has been conducted using the UK Biobank Resource under application number 55469.

Overall, 218,915 individuals were included in the analysis, with 152,401 individuals in the early-pandemic unvaccinated cohort, 39,495 individuals in the first dose cohort, and 27,019 individuals in the second dose cohort. Demographic information is shown in Table 1. Within the unvaccinated cohort, COVID-19 was diagnosed in 13,028 patients (8.5%), compared with 3,593 (9.1%) individuals following first dose of COVID-19 vaccination, and 1,904 (7.0%) individuals following the second dose of vaccination (Table 1).

COVID-19 infection resulting in hospitalization occurred in 2,703 (20.7%) of the unvaccinated cohort, 54 (1.5%) of the first dose cohort and 39 (2%) patients of the second dose cohort. Death from COVID-19 occurred in 1.1% of the unvaccinated cohort, and 0.1% patients of both the first and second dose cohorts (Table 1).

The incidence of COVID-19 TE in the unvaccinated cohort was 1.4%, which decreased to 0.2% following the first dose of COVID-19 vaccination (OR: 0.18, 95% CI: 0.09-0.36; *P*<0.001) and to 0.1% after the second dose of vaccination (OR: 0.06, 95% CI: 0.02-0.26; *P*<0.001) (Table 1). Across the three cohorts, PE rather than DVT was the predominant type of venous thrombotic event diagnosed, and accounted for 80.1%, 87.5% and 100% of all events in the unvaccinated, first dose and second dose cohorts, respectively. Despite the marked reduction in overall COVID-19 TE, the incidence of COVID-19 TE in hospitalized patients remained elevated. In the unvaccinated cohort, the incidence of COVID-19 TE following hospitalization for COVID-19 infection was 163 of 2,703 (6%), compared with six of 54 (11.1%) in the first dose cohort and two of 39 (5.1%) in the second dose cohort. By contrast, COVID-19 TE rates in ambulatory patients remained low across all cohorts, being diagnosed in 0.2% of the unvaccinated cohort, 0.1% of the first dose cohort, with no events diagnosed in the second dose cohort (Table 1).

Our study demonstrates a marked reduction in the rate of COVID-19 TE following one or two doses of COVID-19 vaccination compared to an unvaccinated cohort. However, this reduction in COVID-19 TE appears to be largely driven by a reduction in severe COVID-19 infection requiring hospitalization. Indeed, although the number of patients requiring hospitalization for COVID-19 was markedly reduced, the incidence of COVID-19 TE in hospitalized patients remained relatively stable and was diagnosed in 6% of the early pandemic cohort, 11.1% of the first dose cohort and 5.1% of the second dose cohort. Conversely, we demonstrate that the incidence of COVID-19 TE in the first 90 days after COVID-19 infection in ambulatory patients is low.

To our knowledge, this is the first study to evaluate COVID-19 TE in vaccinated individuals in both ambulatory and hospitalized patients. Recently, Xie and colleagues demonstrated that COVID-19 vaccination attenuates the

Table 1. Study cohort clinical characteristics and results.

	Unvaccinated	Vaccinated	
		First dose	Second dose
Total study participants, N	152,401	39,495	27,019
Individuals diagnosed with COVID-19, N (%)	13,028 (8.5)	3,593 (9.1)	1,904 (7.0)
Age in years, mean (SD)	65.1 (8.6)	63.8 (7.8)	67.4 (7.5)
Female sex, N (%)	80,010 (52.5)	21,011 (53.2)	14,887 (55.1)
BMI (kg/m^2) ≥30, N (%)	46,482 (30.5)	8,886 (22.5)	6,971 (25.8)
Current/previous smoker, N (%)	72,390 (47.5)	16,943 (42.9)	12,267 (45.4)
COVID-19 infection details			
Mean time from vaccination to infection, days (SD)		176.4 (56.7)	140.8 (45.3)
Hospitalization status, N (%)			
Hospitalized	2,703 (20.7)	54 (1.5)	39 (2)
Ambulatory	10,325 (79.3)	3,539 (98.5)	1,865 (98)
Death from COVID-19, N (%)	143 (1.1)	2 (0.1)	2 (0.1)
Venous thromboembolism			
COVID-19 TE (all patients), N (%)	186 (1.4)	8 (0.2)	2 (0.1)
Pulmonary embolism	149/186 (80.1)	7/8 (87.5)	2/2 (100)
Deep vein thrombosis	37/186 (19.9)	1 (12.5)	0
COVID-19 TE by hospitalization status for COVID-19 infection, N (%)			
Hospitalized	163/2,703 (6)	6/54 (11.1)	2/39 (5.1)
Ambulatory	23/10,325 (0.2)	2/3,539 (0.1)	0/1,865
OR* for COVID-19 TE (all patients), (95% CI), *P* value	Reference	0.18 (0.09-0.36), *P*<0.001	0.06 (0.02-0.26), *P*<0.001

*Odds ratio adjusted by age, sex and body mass index. BMI: body mass index; CI: confidence interval; COVID-19: coronavirus disease 2019; COVID-19 TE: COVID-19-associated thromboembolism; OR: odds ratio; SD: standard deviation; TE: thromboembolism.

risk of COVID-19 TE in the first 30 days following infection in ambulatory patients, but no hospitalized individuals were included.[5] Our study, which evaluated patients until 90 days post COVID-19 infection, supports that COVID-19 vaccination is associated with a reduced risk of COVID-19 TE, which appears to be predominantly due the lower rate of hospitalization with COVID-19 infection. These findings also support the recently published randomized clinical trials evaluating the use of thromboprophylaxis in outpatients with COVID-19, that demonstrated low rates of VTE regardless of thromboprophylaxis or vaccination status.[6,7]

Whether COVID-19 vaccination mitigates the risk of COVID-19 TE in hospitalized patients remains to be fully elucidated. Although the majority of VTE events in our study across all cohorts were diagnosed in patients who were hospitalized for COVID-19 infection, the absolute event rate was low due to a reduction in severe COVID-19 infection. Currently, several international professional society guidelines recommend therapeutic anti-coagulation for non-intensive care unit patients hospitalized with COVID-19 acute illness to prevent major thromboembolism and reduce mortality.[8,9] Our results suggest that patients hospitalized with COVID-19 have an elevated risk of VTE independent of vaccination status, and, thus are supportive of these guidelines. However, it will be important to prospectively validate the benefit of such anticoagulant strategies in populations with high vaccine coverage.

The strengths of this study include the large study size with access to free universal healthcare through the UK National Health Service, increasing the likelihood that COVID-19 therapies were consistent between cohorts. Limitations include the lack of available data regarding vaccination type, COVID-19-specific therapeutics and anticoagulation regimens prescribed to COVID-19 cases. Due to the retrospective nature of the study and the use of ICD-10 codes, the study did not capture several patient factors, such as medical comorbidities and current medical therapies, or further information regarding VTE, which includes the type of diagnostic imaging used for VTE, the specific location of DVT, or whether the events were symptomatic in nature. Moreover, our definition of hospitalization for COVID-19 may include cases where COVID-19 was an incidental finding on routine hospital testing, and not the cause for hospitalization. Whether vaccine-induced immune thrombotic thrombocytopenia (VITT) or other vaccine-related thrombotic events were captured in the vaccinated population in this study is not known. However, the mean time from COVID-19 vaccination to COVID-19 infection was 176.4 days and 140.8 days in the first and second dose cohorts, respectively, and COVID-19 TE was diagnosed up to 90 days post infection. Given that VITT is extremely rare (reported incidence ranging from 1 in 26,000 to 2.1 in 100,000 individuals following 1 dose of ChAdOx1 nCov-19 [AstraZeneca, Sydney, NSW, Australia]), and vaccine-related thrombotic events and VITT typically present within 30 days of vaccination, the likelihood of capturing these events is extremely low.[10-12] Finally, the inclusion of a contemporaneous unvaccinated cohort is unable to be included due to the high vaccine coverage in the UK.

In summary, these findings demonstrate that the rate of COVID-19 TE is low in a large population with high vaccination rates and access to COVID-19 therapeutics. Moreover, this reduction in COVID-19 TE appears to be driven by significantly lower rates of hospitalization with COVID-19 infection. Our findings suggest that the rate of COVID-19 TE is very low in ambulatory patients, but that the risk of COVID-19 TE persists in individuals requiring hospitalization with COVID-19, regardless of vaccination status. Further clinical trials should address optimal anticoagulation strategies in the era of widespread COVID-19 vaccination.

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Contributions

HS contributed to the study design, analysis and interpretation of data, drafting and revision of the manuscript. SRC contributed to the study design, acquisition and analysis of data, and drafting and

revision of the manuscript. JDM contributed to the study design, interpretation of data, and drafting and revision of the manuscript. KP contributed to the study design, interpretation of data, and drafting and revision of the manuscript.

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Data-sharing statement

Data is available from researchers upon request.

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