Full Length Article

Absence of hypercoagulability after nCoV-19 vaccination: An observational pilot study

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ABSTRACT

Background: It is still unknown whether COVID-19 vaccines induce a prothrombotic state or increase the hypercoagulable condition in subjects with a predisposition to thrombosis.
Objectives: We evaluated the coagulation profile in a series of healthy subjects who received the first dose of the BNT162b2 or the ChAdOx1 vaccines and assessed whether hypercoagulability developed.
Patients/methods: Volunteers among the staff of the University of Padua or health care professionals in the Padua University Hospital who had received either the ChAdOx1 or BNT162b2 vaccine in the previous 10 ± 2 days were eligible. A cohort of unvaccinated volunteers among family members of the University staff acted as control group. Global coagulation monitoring was assessed by whole blood rotational thromboelastometry, whole blood impedance aggregometry and thrombin generation. Platelet count was also obtained.
Results: One hundred and ninety subjects were enrolled: 101 (53.2%) received the ChAdOx1 vaccine and 89 (46.8%) the BNT162b2 vaccine. Twenty-eight non-vaccinated subjects acted as controls. Thromboelastometry parameters were all comparable among groups. Thrombin receptor activating peptide (TRAP)-, ADP- and ASPI-induced platelet aggregation were similar among groups, as well as platelet count. Endogenous thrombin potential (ETP) was comparable among groups. The results were confirmed after controlling for age, gender and hormonal. Considering women taking combined oral contraceptives or thrombophilia carriers, no differences were detected in thromboelastometry or thrombin generation parameters between subjects who received ChAdOx1 vs. BNT162b2 vaccines.
Conclusions: No significant activation of fibrinogen-driven coagulation, plasma thrombin generation or clinically meaningful platelet aggregation after ChAdOx1 or BNT162b2 vaccination was observed.

1. Introduction

The European Medicines Agency (EMA) has approved five vaccines against coronavirus disease 2019 (COVID-19), and more than 85 million doses have already been administered across the European Union [1]. By April 12, 2021, a total of 13,125,458 persons had received a nCoV-19 vaccine in Italy: 8,689,796 BNT162b2-mRNA-COVID-19 (BNT162b2) (Pfizer–BioNTech) and 2,350,691 ChAdOx1-nCoV-19 (ChAdOx1) (AstraZeneca) vaccine [2].

Recent observations have documented several cases of unusual thrombotic events in combination with thrombocytopenia after receiving the ChAdOx1 vaccine [3,4]. The underlying mechanism is

partly understood as it appears, in many cases, to mimic that of an atypical Heparin-induced thrombocytopenia [5]. It is still unknown whether there may be a predisposition to develop this rare complication.

Although rare, these observations induced profound concern in people candidate to receive nCoV-19 vaccination. A large number of requests for medical examinations come every day from healthy subjects to the outpatients clinics in order to exclude possible risk factors for vaccination. Additionally, patients with thrombophilia conditions have further concern. To date it remains to be demonstrated whether COVID-19 vaccines may induce a transient hypercoagulable state or increase the hypercoagulable condition in subjects with a predisposition to thrombosis.

We performed an observational study to evaluate the coagulation profile in a series of healthy subjects who had received the first dose of the BNT162b2 or the ChAdOx1 vaccines and assessed whether hypercoagulability developed.

2. Methods

2.1. Study population

Volunteers among the staff of the University of Padua or health care professionals in the Padua University Hospital who had received either the ChAdOx1 or BNT162b2 vaccine in the previous 10 ± 2 days were eligible and offered coagulation monitoring. A cohort of unvaccinated volunteers among family members of the staff of the University of Padua acted as control group for coagulation monitoring. Exclusion criteria were: *i)* SARS-Cov2 infection within the previous three months; *ii)* infection, hospitalization, surgery within the previous month; *iii)* pregnancy/postpartum; *iv)* ongoing anticoagulant therapy; *v)* active cancer (recent diagnosis or radio-chemotherapy in the previous three months; vi) past venous thrombotic events.

2.2. Laboratory tests

Cases and controls underwent fasting venous sampling of 9 mL of blood into citrate-containing vacutainer tubes. Platelet-poor plasma (PPP) for thrombin generation was prepared within 1 h by double centrifugation (2×10 min at 1500g) at room temperature. Aliquots (1 mL) were immediately frozen and then stored at $-80°$.

Platelet count was obtained by an automated cell counter (CELL-DYN Emerald 22, Abbott, Milan, Italy).

Global coagulation monitoring was assessed by whole blood rotational thromboelastometry (ROTEM® Instrumentation Laboratory, Werfen, Milan, Italy), whole blood impedance aggregometry by MULTIPLATE® analyzer (Roche Diagnostics, Milan, Italy) and thrombin generation in platelet-poor plasma (PPP) by calibrated automated thrombogram (CAT, Thrombinoscope BV, Maastricht, The Netherlands).

Rotational thromboelastometry-ROTEM is based on the viscoelastic method. Upon activation by calcium, phospholipids and ellagic acid or tissue factor, clot formation is achieved and thereby decreases the rotational potential of a pin (i.e., viscoelastometry) [6]. The increase in viscoelastic force is proportional to the capability of clot formation in intrinsic (INTEM), extrinsic coagulation (EXTEM) pathways and fibrinogen contribution to blood clot (FIBTEM).

Evaluation of platelet aggregation by Multiplate® is based on the impedance method. Upon activation by different agonists, platelets adhere to the sensor wires and thereby increase the electrical resistance (i.e., impedance). The increase is proportional to the capability of platelets to aggregate on each wire. Results are expressed as Area Under the Curve (AUC, AU*min) [7]. The higher the AUC value, the greater the capability of platelets to aggregate. Particularly, platelets were stimulated with 3 different agonists: (1) thrombin receptor activating peptide-6 (TRAP-6) 32 μmol/L, which is the most potent platelet activator and stimulates platelet aggregation via the thrombin receptor PAR-1 (TRAP test-Roche Diagnostics GmbH, Mannheim, Germany); (2) ADP 6.5 μmol/L (ADP test-Roche Diagnostics GmbH); (3) arachidonic acid 500 μmol/L, which allows the evaluation of cyclooxygenase-dependent aggregation (ASPI test-Roche Diagnostics GmbH).

Thromboelastometry and platelet aggregometry were performed in whole blood within 2 h after sample draw by trained members of the research team, as previously reported [7,8].

Thrombin generation was assessed in PPP with the CAT method (Thrombinoscope BV) [8,9]. Briefly, 80 μL of plasma were dispensed into the wells of a 96-well microtiter plate and coagulation was triggered with 20 μL of PPP-Reagent (Diagnostica Stago, Asnieres sur Seine, France), a mixture of TF (5 pmol/L final concentration) and synthetic phospholipids (4 μmol/L final concentration). The reaction was initiated by adding 20 μL of a mixture composed of a thrombin fluorogenic substrate and CaCl2 (FluCa kit, Diagnostica Stago). Thrombin Calibrator (Diagnostica Stago) was used to correct each curve for inner filter effects and substrate consumption. Fluorescence was read in a Fluoroskan Ascent® reader (Thermo Labsystems, Helsinki, Finland) and thrombin generation curves were calculated using the Thrombinoscope Software version 5.0.0.742 (Thrombinoscope BV). The following parameters were assessed: lag time, peak height and endogenous thrombin potential (ETP). Thrombin generation tests were performed in the presence of the absence of 5 nmol/L thrombomodulin (TM) (rabbit TM, Sekisui Diagnostics, Stamford, CT, USA). TM is the main cofactor in the thrombin-induced activation of the natural anticoagulant protein C. In normal plasma, the addition of TM leads to reduced thrombin generation (reduction of ETP). In this study, the concentration of TM (5 nmol/L) was to reduce the ETP by 51 ± 13% in normal pool plasma (resulting in an ETP ratio of 0.49 ± 0.13). Plasma from 45 healthy subjects was also tested to evaluate the effects of TM on ETP and acted as controls for TGA. This group consisted of 22 males and 23 females without history of cardiovascular, autoimmune and acute diseases and not taking antithrombotic, antibiotic, or hormonal therapy. All tests were performed in duplicate. The ETP ratio was calculated as follows: ETP with TM/ETP without TM, and it reflects the "resistance" to the anticoagulant effect of protein C. The lower the ETP ratio, the better preserved the level and the function of protein C. Conversely, a higher ETP ratio means more severe protein C resistance and a potentially greater predisposition to thrombosis.

All participants gave written informed consent for coagulation monitoring and the use of data for research purposes.

2.3. Statistical analysis

Qualitative data were described as frequencies and percentages. Quantitative data were described as mean ± standard deviation (SD). Comparisons between the independent groups were performed by the Mann Whitney *U* test and Kruskal- Wallis test with post-hoc analysis (Dunn) for quantitative variables, and the Chi-square test or Fisher's exact test for categorical variables. Multiple linear regression analysis was run in order to control for potential confounding factors (i.e. age, gender, and hormonal therapy). Statistical significance was set at $p \leq 0.05$. All analyses were completed using SPSS software version 26.0.

3. Results

One hundred and ninety subjects who met the inclusion criteria were enrolled: 101 (53.2%) received the ChAdOx1 vaccine and 89 (46.8%) the BNT162b2 vaccine. Twenty-eight non-vaccinated subjects acted as control group. The clinical characteristics of the study population are reported in Table 1. The three groups were comparable for gender and body mass index. The subjects who received the BNT162b2 vaccine were slightly younger (p = ns). The prevalence of known thrombophilia was similar among groups. A higher proportion of patients in the BNT162b2 group was taking combined oral contraceptive therapy (COC). Finally, a higher proportion of subjects vaccinated with ChAdOx1 were taking aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Mean time after vaccination was comparable between groups.

3.1. Platelet count

We detected no difference in platelet count after receiving the vaccine (ChAdOx1 213,000 ± 57,200/μL; BNT162b2 216,000 ± 55,000/μL; controls 208,000 ± 43,800/μL, p = 0.83). The difference remained no significant after controlling for age, gender and hormonal therapy by regression analysis.

Table 1

Clinical characteristics of the study population.

	ChAdOx1	BNT162b2	Controls	p
Number of subjects	101	89	28	
Age - years	49.5 ± 12.6	42.5 ± 18.0	47.1 ± 14.5	ns
Gender – female n (%)	67 (66.3)	64 (71.9)	15 (53.5)	ns
BMI – kg/m^2	24.3 ± 3.8	24.4 ± 3.9	25.4 ± 4.1	ns
Comorbidities – (%)				
Hypertension	17 (16.8)	17 (19.1)	5 (17.8)	ns
Diabetes	2 (2)	4 (4.5)	1 (3.6)	
Dyslipidemia	11 (10.9)	8 (8.9)	3 (10.7)	
Autoimmune diseases	13 (12.9)[†]	13 (14.6)[††]	3 (10.7)[†††]	
Known thrombophilia – n (%)	12 (11.8)[*]	10 (11.2)[**]	3 (10.7%)[***]	ns
COC therapy – n (%)	5 (5)	13 (14.6)	2 (7.1)	<0.001
Antiplatelet therapy – n (%)	3 (3)	4 (4.5)	2 (7.1)	ns
NSAIDs – n (%)	10 (9.9)	–	–	–
Time from vaccination – days	9 [8–12]	8.5 [7–10.5]	–	ns
Symptoms – n (%)				ns
Local	4 (4)	5 (5.6)		
Fever[a]	21 (20.8)	16 (18)	–	
Headache	10 (9.9)	5 (5.6)		
Myalgia/arthralgia	14 (13.9)	9 (10.1)		

Data are reported as mean and standard deviation or frequencies. p are calculated by Kruskal-Wallis test for quantitative variables and Fisher-Freeman-Halton Test for qualitative variables.

BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; COC: combined oral contraceptives.

[a] Fever was defined as body temperature ≥ 38 °C.

[†] 1 celiac disease, 1 primary biliary cirrhosis, 2 Raynaud syndrome, 9 Hashimoto's thyroiditis.

[††] 6 Hashimoto's thyroiditis, 1 atopic dermatitis, 1 Sjögren's syndrome, 1 psoriasis, 1 spondyloarthritis, 2 immune thrombocytopenia, 1 autoimmune enteropathy.

[†††] 2 Hashimoto's thyroiditis and 1 psoriasis.

[*] 8 heterozygous prothrombin mutation, 3 heterozygous factor V Leiden, 1 proteins S deficiency.

[**] 8 heterozygous factor V Leiden, 1 heterozygous prothrombin mutation, 1 combined heterozygous (prothrombin mutation and factor V Leiden).

[***] 1 homozygous prothrombin mutation, 1 heterozygous factor V Leiden, 1 protein S deficiency.

3.2. Thromboelastometry

Thromboelastometry parameters were all comparable among groups (Table 2). Particularly, maximum clotting firmness (MCF) was within the normal range in all subjects regardless of the type of vaccine and comparable to MCF in controls for all assays (INTEM, EXTEM and FIB-TEM). No significant association between thromboelastometry parameters and vaccination type after controlling for age, gender, or hormonal therapy was detected by regression analysis.

3.3. Platelet aggregometry in whole blood (multiplate)

Data of platelet aggregometry in whole blood were analyzed after excluding patients under treatment with antithrombotic or NSAIDs. Thrombin receptor activating peptide (TRAP)-, ADP- and ASPI-induced platelet aggregation were similar among groups (Table 2). The difference remained no significant after controlling for age, gender and hormonal therapy by regression analysis. Additionally, patients taking antiplatelet drugs as anti-thrombotic therapy (cardioaspirin) showed a significant reduction in ASPI-induced platelet aggregation which was similar among groups (data not showed).

3.4. Thrombin generation

Thrombin generation was performed in 132 vaccinated subjects

Table 2

Thromboelastometry and platelet aggregometry data in the study population according to the type of vaccine administered.

	ChAdOx1	BNT162b2	Controls	p
Number of subjects	101	89	28	
Clotting time (CT) – sec				ns
INTEM	188 ± 26	184 ± 24	186 ± 22.2	
EXTEM	67 ± 9.7	64 ± 14.5	67 ± 10.8	
Clotting formation time (CFT) – sec				ns
INTEM	73 ± 15.2	75 ± 19.2	81 ± 22.6	
EXTEM	83 ± 19	84 ± 19	90.5 ± 25	
Maximum clotting firmness (MCF) – mm				ns
INTEM	61 ± 5.8	62 ± 4.3	61 ± 4.8	
EXTEM	64 ± 4.6	64 ± 4.5	63 ± 4.4	
FIBTEM	17.5 ± 5.1	16.8 ± 4.7	15.7 ± 3.3	
Area under the curve (AUC)				ns
INTEM	6146 ± 548	6131 ± 474	6166 ± 472	
EXTEM	6355 ± 545	6354 ± 487	6392 ± 391	
FIBTEM	1671 ± 621	1622 ± 548	1626 ± 306	
Number of subjects[a]	88	85	26	
TRAP AUC	115 ± 23	120 ± 20.9	114 ± 19.3	ns
ADP AUC	75.7 ± 22.3	73.5 ± 22.7	74 ± 21	ns
ASPI AUC	74.1 ± 24.8	76.9 ± 20.1	70.8 ± 22.6	ns

Reference ranges: INTEM CT 100–240 s; INTEM CFT 30–110 s; INTEM MCF 50–72 mm; EXTEM CT 38–79 s; EXTEM CFT 34–159 s; EXTEM MCF 50–72 mm; FIBTEM MCF 9–25 mm.

Reference ranges: TRAP [thrombin receptor activating peptide] 69–117 AUC; ADP 38–85 AUC; ASPI 39–79 AUC

[a] Analyzed only in subjects without treatment with antithrombotic agents or NSAIDs.

(70% of the cohort) and in all the non-vaccinated subjects. ETP was similar among groups (Fig. 1, panel A) even after controlling for age, gender and hormonal therapy. ETP with TM was slightly increased in subjects vaccinated with BNT162b2 as compared to the other two groups (p = 0.037), leading to a slightly increased in the ETP ratio (p = 0.007; Fig. 1, panels B and C, Supplementary Table 1). After controlling for the use of COC, no differences were detected in the ETP ratio among groups (Fig. 1 panel D, Supplementary Table 1).

3.5. Sub-analyses in special subgroups

Among women taking COC therapy (9.5% of the vaccinated population), no differences were detected in thromboelastometry (MCF in FIBTEM) or in thrombin generation parameters (ETP and ETP ratio) between subjects who received ChAdOx1 vs. BNT162b2 vaccines (Table 3).

Among thrombophilia carriers (11.6% of the vaccinated population), no differences were detected in thromboelastometry (MCF in FIBTEM) or in thrombin generation parameters (ETP and ETP ratio) between subjects who received ChAdOx1 vs. BNT162b2 vaccines (Table 3). Finally, among subjects with autoimmune diseases – mostly Hashimoto's thyroiditis — (13.7% of the vaccinated population) no differences were detected in coagulation parameters between subjects who received ChAdOx1 vs. BNT162b2 vaccines (Table 3).

4. Discussion

The COVID-19 vaccine ChAdOx1 (AstraZeneca) has been associated with rare thrombotic complications such as cerebral venous sinus thrombosis (CVST) [3,4,10]. It has been reported that these rare complications may occur approximately 5 to 20 days after vaccination and are immune-related leading to severe thrombocytopenia mediated by
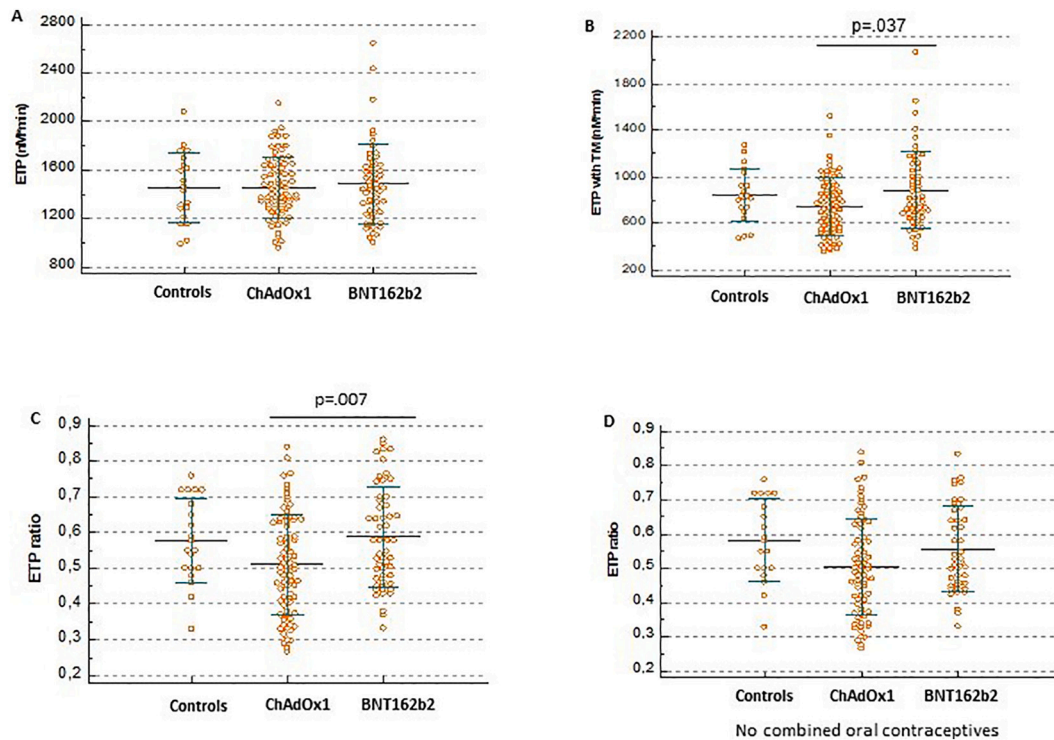
Fig. 1. Endogenous Thrombin Potential (ETP) levels in the study population according with the type of vaccine administered.
Panel A. ETP; Panel B. ETP with TM; Panel C. ETP ratio; Panel D. ETP ratio after the exclusion of women taking combined oral contraceptives (COCs). TM stands for thrombomodulin.

Table 3
Thromboelastometry and thrombin generation data in specific groups of subjects.

Combined oral contraceptives (COC)				
	ChAdOx1 n 5	BNT162b2 n 13	Controls n 2	p
FIBTEM MCF – mm	16.8 ± 2.1	19.5 ± 1.3		ns
ETP – nM*min	1641 ± 132	1767 ± 80	–	ns
ETP ratio	0.62 ± 0.07	0.71 ± 0.04		ns
Inherited thrombophilia				
	ChAdOx1 n 12	BNT162b2 n 10	Controls n 3	p
FIBTEM MCF – mm	17.9 ± 1.4	16.5 ± 1.5		ns
ETP – nM*min	1698 ± 86	1690 ± 122	–	ns
ETP ratio	0.51 ± 0.04	0.53 ± 0.06		ns
Autoimmune diseases				
	ChAdOx1 n 13	BNT162b2 n 13	Controls n 3	p
FIBTEM MCF – mm	17.3 ± 1.3	16.8 ± 1.3		ns
ETP – nM*min	1379 ± 85	1532 ± 127	–	ns
ETP ratio	0.51 ± 0.04	0.56 ± 0.06		ns

MCF: maximum clotting firmness; ETP: Endogenous thrombin potential.

platelet-activating antibodies and thrombotic manifestations [3,4,11]. This mechanism is rather peculiar and dissimilar to those commonly involved in the development of venous or arterial thrombosis due to more common prothrombotic conditions, such as congenital or acquired thrombophilia [12]. The possible occurrence of severe thrombosis as a complication of the nCoV-19 vaccination arose great concern among people waiting to be called for the vaccination. In order to reassure people about the safety of the vaccination, we performed an observational pilot study to evaluate the potential presence of hypercoagulability after nCoV-19 vaccination using global coagulation assays.

The coagulation monitoring of this pilot cohort of vaccinated subjects excluded the presence of hypercoagulability at a mean time of nine days after ChAdOx1 or BNT162b2 vaccination. Using thromboelastometry, impedance aggregometry and thrombin generation, we can exclude the presence of fibrinogen-driven hypercoagulability, platelet hyperactivity and increased plasma thrombin generation induced by the vaccination. In addition, no reduction in platelet count was detected.

Although the sample size was very low, we can beckon that a few females showed increased thrombin generation linked to combined oral contraceptives [13], regardless of the type of vaccine received. Additionally, the comparison of a small cohort of carriers of inherited thrombophilia showed a similar coagulation profile between the two types of vaccination. The same is true for subjects suffering from autoimmune conditions, mainly thyroiditis.

We would be remiss if we did not mention some of the limitations of our study. Firstly, though the number of subjects included is small, it is representative of the population eligible for COVID-19 vaccines in Italy at this time. Additionally, we agree that a longitudinal design of the study with coagulation evaluation before and after the vaccine would have been stronger; however, the presence of a non-vaccinated control group can compensate for the lack of pre-vaccine coagulation determinations. Besides the enrollment of a non-vaccinated group as control, we showed that thromboelastometry, aggregometry, as well as thrombin generation parameters in vaccinated subjects were all within the reference ranges. Secondly, our conclusions should be limited to ChAdOx1 or BNT162b2, the only two vaccines considered in our study. Thirdly, we did not perform coagulation tests in order to exclude other possible mechanisms of vaccine-induced hypercoagulability (e.g. D-dimer or coagulation inhibitors levels) but we chose to only perform global coagulation tests in order to explore overall whole blood and plasma coagulation profile, as well as platelet function. Lastly, subjects were recruited on a voluntary basis for coagulation monitoring and this

may account for the relatively high prevalence of inherited thrombophilia in the otherwise asymptomatic cohort (11.6%) vs. the general population (2–4%) [14]. Following news of a possible association between vaccination and thrombosis, subjects with known thrombophilia might have adhered more promptly to our coagulation monitoring on a voluntary basis. Needless to say, the absence of hypercoagulability also shown in this small subgroup of thrombophilic patients after vaccination appears reassuring. The same holds true of women taking oral contraceptives in whom vaccination had no additional effect in increasing the expected mild hypercoagulability related to the hormonal treatment [13].

In conclusion, we observed no significant activation of fibrinogen-driven coagulation, plasma thrombin generation or clinically meaningful platelet aggregation after ChAdOx1 or BNT162b2 vaccination. We observed no onset of hypercoagulability in healthy subjects nor increased hypercoagulability in subjects with inherited or acquired thrombophilia after vaccination, which suggests that other pathogenetic mechanisms may contribute to the development of CVST. Although this is a pilot study, these preliminary results may be useful for Clinicians to reassure people referring to our Centres every day for an opinion on the prothrombotic risk associated with the nCoV-19 vaccination.

We acknowledge that longitudinal studies are needed to better understand to what extent second doses of ChAdOx1 or BNT162b2, as well as other available COVID-19 vaccines may cause hypercoagulability in healthy subjects or increase hypercoagulability in those with inherited or acquired thrombophilia, and to clarify the underlying mechanisms.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.06.016.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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