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Coagulation and inflammatory response after intramuscular or intradermal mRNA-1273 SARS-CoV-2 vaccine: secondary analysis of a randomized trial

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Abstract

Background: Fractional-dosed intradermal (i.d.) vaccination produces antibody concentrations above the proposed proxy for protection against severe disease as compared with intramuscular (i.m.) vaccination and may be associated with a decreased prothrombotic effect.

Objectives: To assess changes in coagulation following standard dosed i.m. or fractional-dosed i.d. (one-fifth of i.m.) mRNA-1273 SARS-CoV-2 vaccine and to determine the association between the inflammatory response and coagulation.

Methods: This study was embedded in a randomized controlled trial assessing the immunogenicity of an i.d. fractional-dosed mRNA-1273 vaccine. Healthy participants, aged 18 to 30 years, were randomized (2:1) to receive either 2 doses of i.d. or i.m. vaccine. Blood was drawn prior to first and second vaccination doses and 1 and 2 weeks after the second dose. The outcomes were changes in coagulation parameters (primary endpoint peak height of the thrombin generation curve) and inflammation (high-sensitivity C-reactive protein [hs-CRP]).

Results: One hundred twenty-three participants were included (81 i.d.; 42 i.m.). Peak height increased after vaccination (i.m., 28.8 nmol; 95% CI, 6.3-63.8; i.d., 17.3 nmol; 95% CI, 12.5-47.2) and recovered back to baseline within 2 weeks. I.m. vaccination showed a higher inflammatory response compared with i.d. vaccination (extra increase hs-CRP, 0.92 mg/L; 95% CI, 0.2-1.7). Change in endogenous thrombin potential was associated with change in hs-CRP (beta, 28.0; 95% CI, 7.6-48.3).

Conclusion: A transient increase in coagulability after mRNA-1273 SARS-CoV-2 vaccination occurred, which was associated with the inflammatory response. While i.d. administration showed antibody concentrations above the proposed proxy for protection against severe disease, it was associated with less systemic inflammation. Hence, i.d. vaccination may be safer.

Essentials

- Vaccination in the skin, instead of the muscle, produces antibodies at one-fifth of the dose.
- Vaccination in the skin gave less systemic inflammation than intramuscular vaccination.
- The larger the inflammatory response following vaccination, the larger the increase in coagulation.
- Intradermal vaccines may be more safe.

1 | INTRODUCTION

Vaccination against COVID-19 has played a pivotal role in containment of the COVID-19 pandemic [1]. Soon after the implementation of large-scale SARS-CoV-2 vaccination, thrombotic events were reported as possible side effects [2]. First reports described a pattern of thrombosis after vaccination with the vector-based ChAdOx1 nCoV-19 vaccine, associated with platelet factor 4 autoantibodies, a low platelet count, increased D-dimer, and decreased fibrinogen levels, and was named vaccine-induced thrombotic thrombocytopenia [3,4]. In addition, increased rates of venous thrombotic events without thrombocytopenia were reported in the weeks after vector-based (ChAdOx1 nCoV-19 or Ad26.COV2.S) and (to a lesser extent) mRNA-based vaccines (BNT162b2 or mRNA-1273) [5–9]. This resulted in several changes in vaccination campaigns across the world [10].

Several studies examining the effect of SARS-CoV-2 vaccination on coagulation parameters, such as the international normalized ratio and the activated partial thromboplastin time, showed contradictory results [11–20]. These parameters summarize only part of the coagulation system or are only relevant in patients receiving anticoagulant therapy and may not accurately reflect alterations in the coagulation cascade. The thrombin generation assay (TGA) provides a global overview of both procoagulant and anticoagulant pathways [21,22].

Intradermal (i.d.) vaccination is a dose-sparing strategy providing immune responses equivalent to intramuscular (i.m.) vaccination while using smaller vaccine doses with the benefits of fewer systemic side effects [23,24]. A dose-sparing technique may be particularly of interest to low- and middle-income countries [25,26]. I.d. administrations with fractional doses have been proven successful in the past for several vaccines, such as influenza, rabies, or hepatitis B vaccines [27]. During the COVID-19 pandemic, we conducted a randomized controlled trial, comparing the immunogenicity of 2 one-fifth fractional i.d. doses and 2 full-dose i.m. delivery of the mRNA-1273 (Moderna) vaccine, each 28 days apart, as a primary vaccination series [28]. Fractional dosing through i.d. vaccination showed antibody concentrations above the proposed proxy for protection against severe disease [29].

It is possible that a fractional dose confers a lower thrombotic risk than a full-dose vaccination. The aim of the present study was to assess the change proxies for a prothrombotic change, ie, levels of coagulation factor (F)VIII, fibrinogen, D-dimer, and thrombin generation parameters following mRNA-1273 vaccination by dose as well as the association between these changes and the inflammatory response.

2 | METHODS

2.1 | Trial design

This study was a secondary analysis of an open-label, randomized controlled trial at the Leiden University Medical Center in the Netherlands. The trial was approved by the Medical Ethical Committee Leiden, Den Haag, Delft (NL 76702.058.21) and registered in the International Clinical Trials Registry Platform (EUCTR2021-000454-26-NL). All participants provided written informed consent.

2.2 | Procedures

Eligible participants were adults aged 18 to 30 years and predominantly White or of European ancestry. Participants with a past or intercurrent SARS-CoV-2 infection, determined by a positive SARS-CoV-2 polymerase chain reaction or seropositivity (positivity SARS-CoV-2 anti-Nucleocapsid), were excluded. Other main exclusion criteria were prior SARS-CoV-2 vaccination, use of anticoagulants or steroids, hematologic disease, or pregnancy.

Participants were randomized into 3 groups. The control group received 2 standard doses of 100 µg 28 days apart in the deltoid muscle (standard administration technique). Two experimental groups received 2 fractional doses (one-fifth of the standard dose of 100 µg mRNA-1273) 28 days apart in the dermis of the deltoid region, one with the classical Mantoux technique and the other with a small needle (Bella-mu) designed for i.d. administration. Since both experimental groups showed similar immunogenicity results, they were combined in further analyses [29]. The randomization was done using sealed envelopes. The participant and site staff were unblinded as the administration route differs [29].

Blood was collected on days 1 (D1; before first dose), 29 (D29, before second dose), 36 (D36; 1 week after second dose), and 43 (D43). Fibrinogen, FVIII, and D-dimer (reported in ng/mL D-dimer

units) were measured to assess changes in coagulation using a coagulometric clot detection method on an ACL TOP 700 analyzer (Werfen) as previously described using designated reagent (D-dimer HS 500, HemosIL, Werfen) [30]. Thrombin generation (lag time, endogenous thrombin potential [ETP], peak height, time to peak, velocity index, and time until the start of the tail of the curve) was measured using the calibrated automated thrombogram (Diagnostica Stago) as previously described [31]. In the TGA, coagulation is activated in plasma samples according to manufacturer's instructions using a low amount of tissue factor and phospholipids, followed by continuous measurement of thrombin formation and degradation. The ETP, which is the net result of pro- and anticoagulant potentials, is described by the height of the peak and the area under the curve. A higher peak height, ETP, start tail time, or velocity index indicates hypercoagulability, while shorter lag time and time to peak represent hypercoagulability. The primary outcome of the TGA, measured in this study, was the peak height as this is the most strongly associated with venous thrombosis risk [32,33].

Inflammation was assessed by high-sensitivity C-reactive protein (hs-CRP) from serum using the immunoassay analyzer COBAS CORE (Roche Diagnostics GmbH).

2.3 | Statistical analysis

Outliers for coagulation and inflammation parameters (defined as 5 times the SD) were excluded. At baseline, we collected self-reported data on age, sex (biological male/female), medication use, body mass index, and comorbidities.

The change in coagulation parameters and inflammatory response was expressed as the difference between D1 and D36 (1 week after the second vaccination) as these are relatively "fast" processes and we expected that alterations in coagulation and inflammation normalize quickly. Participants with missing data on D1 or D36 were excluded from the analyses. To assess whether changes in coagulation or inflammation persist for a prolonged period, we determined the levels of the affected parameters again at D43. All changes relative to baseline were analyzed by univariate linear regression analyses. In addition, we compared changes in distribution, ie, the SDs of the parameters before and after vaccination, of all parameters. To assess whether there were differences between changes in coagulation or inflammation parameters after vaccination, stratified for type of vaccine administration (i.d. or i.m.), we adjusted for baseline values by using the difference between the post value (D36) and baseline value (D1) as the dependent variable and both the assigned type of administration (i.m. or i.d.) and baseline value (D1) as the independent variables in a linear regression analysis.

The association between the inflammatory response and change in coagulation was assessed for i.d. and i.m. vaccination combined and visualized by scatter plots and tested using univariate linear regression analysis.

Statistical analyses were done using STATA 16.1 for Windows (StataCorp). Sample size was calculated based on the original trial.

TABLE 1 Characteristics of participants.

Characteristic of participants	Intradermal n (%)	Intramuscular n (%)
N	81	42
Age, mean (SD)	22.1 (3.2)	23.5 (3.7)
Sex (female)	34 (42)	17 (40)
BMI, mean (SD)	24.4 (4.7)	23.4 (3.7)
Comorbidity	38 (47)	17 (40)
Psychiatric	16 (20)	8 (19)
Pulmonal	2 (2)	0 (0)
Allergy	16 (20)	5 (12)
Neurologic	5 (6)	1 (2)
Other	11 (14)	5 (12)
Medication use	27 (33)	13 (31)
Antihistamine	9 (11)	4 (10)
Methamphetamine	8 (10)	3 (7)
Oral contraceptives	21 (26)	6 (14)
Other	8 (10)	5 (12)

BMI, body mass index.

3 | RESULTS

Between June 14 and July 8, 2021, 150 participants were enrolled, of whom 15 were excluded due to SARS-CoV-2 seropositivity at baseline or because of intercurrent SARS-CoV-2 infection before D29. Eleven additional participants were excluded because of missing coagulation data at baseline or D36, and 1 participant was excluded because of self-reported homozygosity for the FV Leiden mutation. Therefore, a total of 123 (82%) participants were included in the analyses of coagulation. Demographic characteristics of these participants are shown in Table 1, stratified by group (i.d. vs i.m.). No major differences were observed between the i.d. and i.m. groups, except a higher proportion of oral contraceptive use in the i.d. group than that in the i.m. group (26% vs 14%). For the analyses involving inflammatory markers, 10 participants were excluded because of missing inflammation data at baseline or D36, and 1 participant was excluded because of a hs-CRP over 5 SDs from the mean. The remaining 112 participants (75%) were included in the analysis of the association between coagulation and inflammation.

Differences between pre- and postvaccination (D36-D1) for the coagulation and inflammation parameters are listed in Table 2 and Figure 1. The peak height increased in both the i.m. and i.d. groups (change in i.d. group, 17.3 nmol [95% CI, −12.5 to 47.2]; change in i.m. group, 28.8 nmol [95% CI, −6.3 to 63.8]). The SDs were larger at D36 than at D1 and differed between the measurements and the 2 groups (peak height SD in i.m. group: before vaccination [D1], 69.2; after vaccination [D36], 90.9; and peak height SD in i.d. group: before vaccination [D1], 93.1; after vaccination [D36], 99.1), indicating that

TABLE 2 Coagulation and inflammation at baseline, before the second vaccine, and 1 and 2 weeks after the second vaccine.

Coagulation parameter	Day 1 Baseline	Day 29 Before second vaccine	Day 36 7 days after second vaccine	Day 43 14 days after second vaccine	Change between baseline and day 36 (95% CI)
N	81	80	81	81	
Peak height (nmol)	219.4 (93.1)	223.9 (87.5)	236.7 (99.1)	223.6 (94.2)	17.3 (−12.5 to 47.2)
Lag time (min)	5.8 (1.0)	5.9 (1.0)	5.6 (0.9)	5.7 (0.9)	−0.3 (−0.6 to 0.03)
ETP (nmol × min)	1719.2 (467.4)	1687.5 (433.5)	1760.0 (515.1)	1690.9 (439.5)	40.7 (−111.9 to 193.4)
Time to peak (min)	10.5 (1.7)	10.4 (1.8)	9.9 (1.7)	10.3 (1.9)	−0.6 (−1.1 to −0.03)
Start tail time (min)	27.6 (3.2)	27.0 (3.0)	26.9 (3.4)	27.1 (3.0)	−0.8 (−1.8 to 0.3)
Velocity index (nmol/min)	52.2 (32.1)	56.5 (35.1)	63.9 (41.6)	58.5 (40.9)	11.7 (0.11 to 23.3)
Fibrinogen (mg/dL)	273.4 (57.9)	272.5 (60.3)	284.3 (64.8)	277.9 (71.5)	10.9 (−8.2 to 30.0)
FVIII (%)	100.1 (23.4)	101.5 (25.9)	99.6 (26.4)	100.8 (34.0)	−0.5 (−8.2 to 7.3)
D-dimer (ng/mL)	258.6 (236.6)	266.7 (242.4)	274.7 (253.2)	279.9 (300.1)	16.1 (−60 to 92.1)
Hs-CRP (ng/mL)	1.7 (2.5)	1.4 (1.8)	1.6 (2.0)	1.7 (2.4)	−0.1 (−0.8 to 0.6)
Coagulation parameter	Day 1 Baseline	Day 29 Before second vaccine	Day 36 7 days after second vaccine	Day 43 14 days after second vaccine	Change between baseline and day 36 (95% CI)
N	42	42	42	42	
Peak height (nmol)	202.9 (69.2)	210.0 (76.6)	231.7 (90.9)	222.0 (77.4)	28.8 (−6.3 to 63.8)
Lag time (min)	5.8 (1.0)	5.9 (1.0)	6.0 (1.1)	5.8 (1.0)	0.1 (−0.3 to 0.6)
ETP (nmol × min)	1648.7 (386.0)	1666.7 (369.9)	1761.7 (433.7)	1748.2 (413.0)	113 (−65.2 to 291.2)
Time to peak (min)	10.8 (2.0)	10.8 (2.1)	10.4 (1.8)	10.4 (1.6)	−0.3 (−1.2 to 0.5)
Start tail time (min)	27.7 (3.0)	27.6 (3.1)	27.4 (2.8)	27.2 (2.7)	−0.2 (−1.6 to 1.1)
Velocity index (nmol/min)	46.8 (28.9)	51.2 (33.0)	59.8 (39.1)	53.8 (31.5)	13.0 (−1.9 to 27.9)
Fibrinogen (mg/dL)	263.8 (57.4)	269.1 (58.7)	295.9 (59.0)	263.1 (43.7)	32.1 (6.8 to 57.4)
FVIII (%)	106.5 (24.1)	107.7 (25.4)	105.3 (25.9)	97.6 (26.9)	−1.1 (−12.0 to 9.7)
D-dimer (ng/mL)	215.8 (187.3)	233.2 (180.0)	299.2 (188.8)	261.6 (180.4)	83.5 (0.8 to 166.1)
Hs-CRP (ng/mL)	1.2 (2.0)	1.1 (1.5)	2.3 (2.3)	1.1 (1.1)	1.1 (0.1 to 2.1)

ETP, endogenous thrombin potential; FVIII, factor VIII; Hs-CRP, high-sensitivity C-reactive protein.

the magnitude of the change in peak height is variable between study participants.

Changes between D1 and D36 were observed for other parameters of thrombin potential, fibrinogen, and D-dimer but not for FVIII levels (Supplementary Figure S1). Most parameters were back to baseline levels at D43 (peak height at D1, 219.4 nmol; at D36, 236.7 nmol; at D43, 223.6 nmol). Additionally, to confirm the quick normalization of coagulation after vaccination, we also compared coagulation parameters of D29 (just before second dose) with those of D1 and D43 to confirm whether they were similar (Table 2 and Supplementary Table S1). Hs-CRP increased in i.m. vaccinated participants (D36 relative to D1) but remained stable after i.d. vaccination (change in i.d. group, −0.1 mg/L [95% CI, −0.8 to 0.6]; change in the i.m. group, 1.1 mg/L [95% CI, 0.1-2.1]; Table 2 and Figure 1).

After adjustment for baseline values, i.m. administration was associated with mild increase in all coagulation parameters and with an increase in hs-CRP compared with i.d. administration (extra increase peak height, 8.4 nmol [95% CI, −16.9 to 33.7]; extra increase hs-CRP, 0.92 mg/L [95% CI, 0.2-1.7]; Table 3).

Excluding participants using oral contraceptives did not alter these results (Supplementary Tables S3 and S4).

3.1 | Association between coagulation and inflammation

The association between changes (eg, delta) of coagulation parameters and change in hs-CRP between D1 and D36 are shown in Table 4
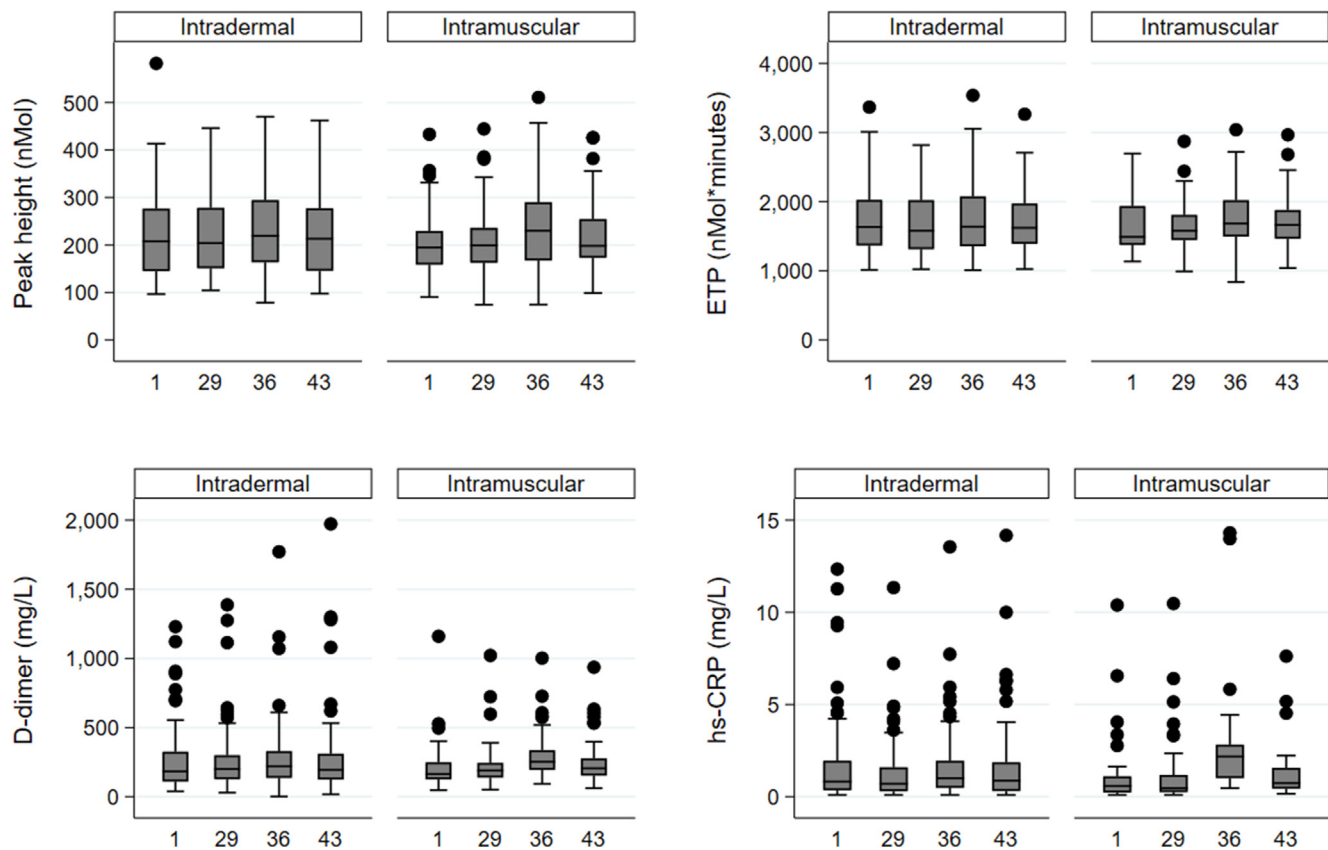
FIGURE 1 Distribution of peak height, endogenous thrombin potential (ETP), D-dimer, and high-sensitivity C-reactive protein (hs-CRP) at each time point (1: baseline; 29: before second dose; 36: 1 week after second dose; 43: 2 weeks after second dose), stratified for administration technique.

and Figure 2. A positive association was found of delta lag time (beta, 0.13; 95% CI, 0.06-0.2), delta ETP (beta, 28.0; 95% CI, 7.6-48.3), delta time to peak (beta, 0.13; 95% CI, 0.01-0.27), delta time to tail (beta,

TABLE 3 Difference in change after vaccination (day 1 vs day 36) between intramuscular and intradermal vaccination; adjusted for baseline.

Coagulation parameter	Extra increase i.m. vs i.d. (95% CI) Adjusted for difference in baseline
Peak height (nmol)	8.4 (−16.9 to 33.7)
Lag time (min)	0.35 (0.04 to 0.7)
ETP (nmol × min)	66.7 (−36.0 to 169.5)
Time to peak (min)	0.35 (−0.2 to 0.9)
Start tail time (min)	0.54 (−0.6 to 1.7)
Velocity index (nmol/min)	1.76 (−9.5 to 13.0)
Fibrinogen (mg/dL)	17.8 (−1.4 to 36.9)
Factor VIII (%)	0.46 (−6.2 to 7.1)
D-dimer (ng/mL)	49.9 (−24.1 to 124.0)
Hs-CRP (ng/mL)	0.93 (0.2 to 1.7)

ETP, endogenous thrombin potential; Hs-CRP, high-sensitivity C-reactive protein; i.d., intradermal; i.m., intramuscular.

0.26; 95% CI, 0.003-0.51), delta fibrinogen (beta, 14.6; 95% CI, 11.4-17.7), and delta FVIII (beta, 2.2; 95% CI, 0.8-3.6) with delta hs-CRP. No association was found between the changes in the other coagulation parameters and the change in hs-CRP. Excluding participants with a delta hs-CRP under −5 or above 5 did not alter these results (results are shown in Supplementary Table S2).

4 | DISCUSSION

SARS-CoV-2 vaccination with full-dose i.m. or fractional-dose (one-fifth of standard dose) i.d. of the mRNA-1273 vaccine results in a transient prothrombotic state as evidenced by changes in peak height, ETP, levels of fibrinogen, and D-dimer. Particularly, the systemic inflammatory response was most pronounced in participants receiving the full dose of the vaccine intramuscularly as compared with the participants receiving the fractional dose intradermally. These changes in coagulation were associated with the inflammatory response.

Although no association was seen between the change in coagulation (D36-D1) and the inflammatory response after vaccination (D36-D1) in the primary coagulation endpoint (peak height), this was observed for multiple other coagulation endpoints, ie, lag time, ETP,

TABLE 4 The association between the change in coagulation parameter and the change in the inflammatory response (delta high-sensitivity C-reactive protein) in all participants.

Coagulation parameter	Units increase in the change in coagulation factors associated with 1 mmol increase in the change of hs-CRP (95% CI)
Peak height (nmol)	1.6 (−3.5 to 6.6)
Lag time (min)	0.13 (0.06 to 0.2)
ETP (nmol × min)	28.0 (7.6 to 48.3)
Time to peak (min)	0.13 (0.01 to 0.27)
Velocity index (nmol/min)	−0.43 (−2.6 to 1.7)
Start tail time (min)	0.26 (0.003 to 0.51)
Fibrinogen (mg/dL)	14.6 (11.4 to 17.7)
Factor VIII (%)	2.2 (0.8 to 3.6)
D-dimer (ng/mL)	4.7 (−8.5 to 17.8)

ETP, endogenous thrombin potential; Hs-CRP, high-sensitivity C-reactive protein.

time to peak, the start tail time, fibrinogen, and FVIII. Particularly, the change in ETP was positively associated with the change in inflammation. This is most likely due to a longer time to complete inhibition of thrombin generation than a stronger and faster propagation of thrombin caused by inflammation (relatively stronger association of start tail time with inflammation than lag time or time to peak or peak height). This suggests that inflammation causes the same amount of thrombin to be produced; however, the inhibition of thrombin is slower. Fibrinogen and FVIII are acute-phase proteins, which explains their association with inflammation. D-dimer was not associated with inflammation. This could be due to the relatively shorter half-life of D-dimer (5 hours) as compared with CRP (19 hours), fibrinogen (40 hours), and FVIII (12 hours) and therefore a possible change due to vaccination was not detectable anymore after 1 week of vaccinations. It may seem contradictory that mean levels of FVIII do not change following vaccination (between D1 and D36), while there was an association between changes (eg, delta) of FVIII and change in hs-CRP between D1 and D36. However, mean FVIII levels are measured on group level, while the association between changes in FVIII and hs-CRP is assessed on an individual level.

Prior studies that evaluated coagulation parameters in SARS-CoV-2 vaccinated individuals using an unvaccinated control group also reported a change in the thrombohemorrhagic balance toward hypercoagulability [16,18,19]. Campello et al. [14] showed a transient increase in TGA at 3 days after vaccination, which normalized within 10 days. Brambilla et al. [13] observed increased thrombin generation in 30 participants 8 days after receiving a mRNA vaccine. Garabet
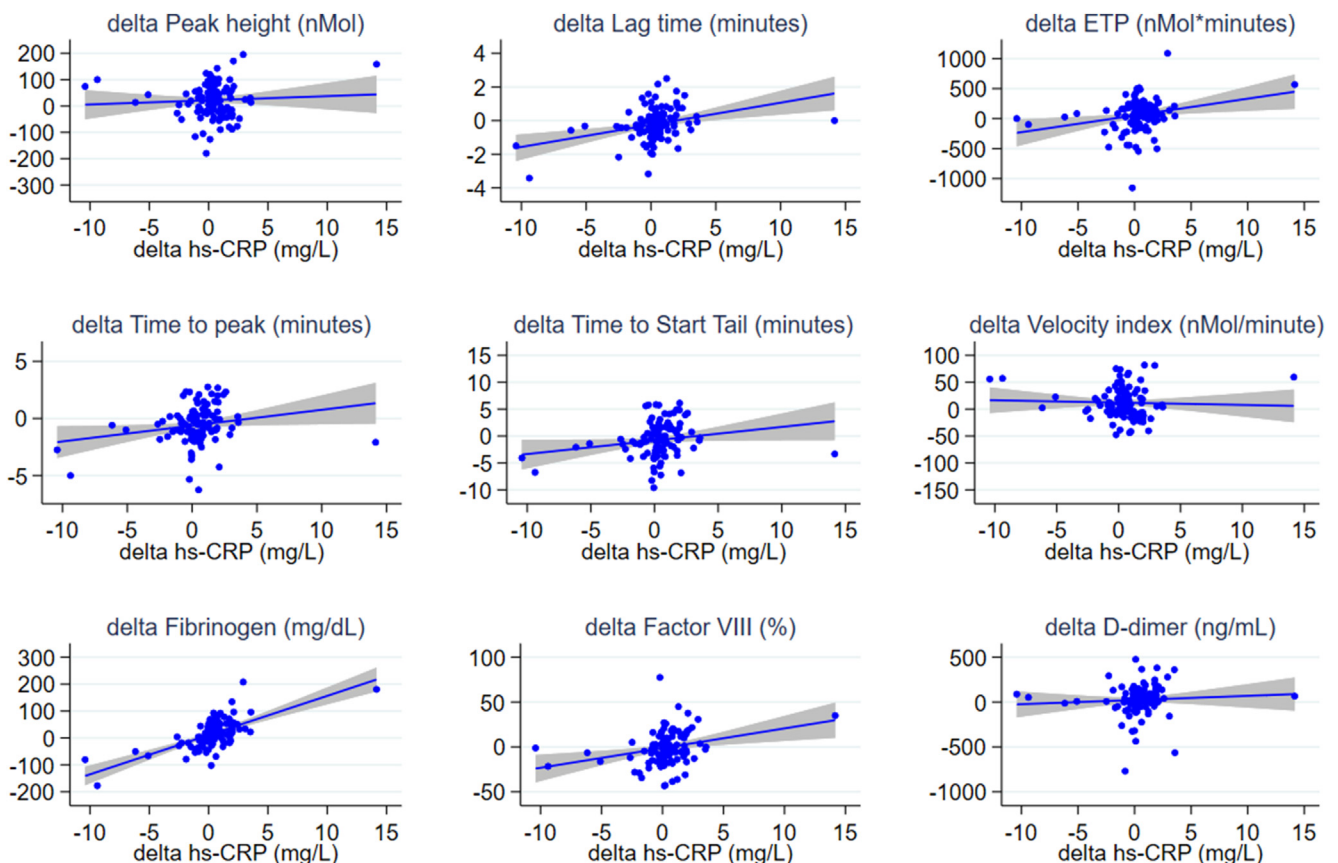
FIGURE 2 Scatter graphs for the association between the inflammatory response and changes after vaccination for each coagulation parameter with fitted linear regression line. ETP, endogenous thrombin potential; Hs-CRP, high-sensitivity C-reactive protein.

et al. [17] found no changes in thrombin generation or D-dimer on average 11 days after vaccination, which might (similar to Campello et al. [14]) be too long after vaccination to detect small and transient changes. Despite an increased inflammatory response, Willems et al. [20] found no changes in several activated coagulation factors in older participants in the 48 hours after vector-based vaccines. However, all studies that reported an increase in coagulation parameters after vaccination concluded that these transient changes were not strong enough to be clinically relevant in an unselected population, and (similar to our study) no venous thrombotic events were observed.

The strengths of this study include the pre- and postrandomized design, preventing several possibilities of confounding. The only factor that could intervene in intraindividual change of coagulation may be an event of noticeable impact (eg, infections and trauma). No such events were registered in the adverse event registration of the original randomized controlled trial, and participants with a SARS-CoV-2 infection were excluded. In addition, the route of vaccine administration (i.d. or i.m.) was randomized. The only difference by chance between the 2 groups (oral contraceptive use) did not affect the conclusions.

Our study has limitations. The limited sample size did not allow a stratified analysis for low- and high-risk venous thrombosis groups. This is particularly evident in the analyses comparing i.d. with i.m., in which CIs were wide. In addition, the time points on which coagulation and inflammation were measured (7 days after second dose of vaccination) could be too late, especially for the inflammatory response. Potentially, the effects of vaccination on coagulation and inflammation are different in the week directly after vaccination; however, our blood sample was drawn not earlier than 7 days after the vaccination. Furthermore, loss to follow-up was about 25%. However, this was evenly distributed between the i.d. and i.m. groups and is unlikely to have been related to these laboratory analyses. Additionally, the cohort consisted of young individuals (<30 years of age), limiting generalizability to middle-aged and older individuals. However, (thrombotic) side effects of SARS-CoV-2 vaccinations are more often reported in young people and are of relatively higher importance for young people because of a lower risk of severe COVID-19 infection in the young [34]. The cohort was predominantly White or of European ancestry; therefore, we are unsure if our results apply to other ethnicities. It is known that thrombin generation (TG) is affected by differences in blood collection, sample preparation, and storage [35]. One might say that this lack of official standardization and reference values of TG results in limited external replicability of our results. However, all blood collections and analyses were standardized and performed in a single laboratory, preventing biased measurements. In addition, by focusing on within-individual changes, we expect that the lack of standardization of TG does not influence external replicability of our results. No measurement of coagulation and inflammation was performed in the first week after the first vaccine dose. Therefore, we do not know the effect of a single vaccination on coagulation and inflammation. However, most systemic side effects of the mRNA-1273 vaccine are reported especially after the second dose [34]. von Willebrand factor plays a key role in

vascular inflammation and coagulation [36]. Unfortunately, von Willebrand factor was not measured in our study, which could have aided in the interpretation of our results. Because of the design of this study, we cannot conclude whether the smaller effect of i.d. vaccination than i.m. vaccination on coagulation and inflammation is caused by the administration technique, the fractional vaccine dose, or both. Lastly, these results are only applicable to the mRNA-1273 vaccine. However, prior research suggests an even stronger effect on coagulation and inflammation after viral-vector-based vaccines [14,19,37].

5 | CONCLUSION

We conclude that vaccination results in a transient prothrombotic state, which is associated with the inflammatory response. I.d. vaccination with a one-fifth vaccine dose provokes a smaller systemic inflammatory response and might have a smaller effect on coagulation than i.m. vaccination, which indicates a benefit for i.d.-administered or fractional dose (SARS-CoV-2) vaccines. Combined with other advantages of using i.d. fractional dose vaccines, eg, economic, ecologic, and on public health domains, our results support the additional potential benefit of further implementation of i.d.-administered vaccines. Further research, using larger cohorts, should be performed on the identification of subgroups with higher risk of vaccine-induced thrombosis. These groups could potentially benefit the most from i.d.-administered vaccines.

AUTHOR CONTRIBUTIONS

L.G.V. and A.H.E.R. designed the original study. F.R.R. advised on the design of the study. W.J.v.D. analyzed the data and wrote the manuscript. M.L.M.P. and G.V.T.R. were responsible for the site work, including recruitment, follow-up, and data collection. L.G.V., A.H.E.R., F.R.R., M.L.M.P., G.V.T.R., M.R., and A.v.H.V. revised the manuscript.

RELATIONSHIP DISCLOSURE

All authors declare no financial or nonfinancial competing interests.

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SUPPLEMENTARY MATERIAL

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