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A Review on Suggested Mechanisms in Thrombocytopenia and Thrombosis Following ChAdOx1 nCoV-19 Vaccination

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ABSTRACT

Background: ChAdOx1 nCov-19 vaccine is a viral vector-based vaccine with desirable protection (about 70.4%, two weeks after the second dose). Few reports were released on thrombocytopenia associated with thrombotic events shortly after the ChAdOx1 nCov-19 vaccination. However, the exact pathophysiologic mechanism of this vaccine-induced thrombotic complication has not yet been elucidated. Vaccine-induced thrombotic thrombocytopenia syndrome (VITTS) is associated with detecting anti-platelet factor 4 (PF4) antibodies that are not yet linked to previous exposure to heparin.

Materials and Methods: In the current review, based on relevantly reported cases, possible mechanisms are suggested on the relationship between the anti-platelet factor 4 (anti-PF4) antibody assays, previous exposure to heparin, and the involved mechanisms of post-vaccination thrombocytopenia and thrombotic events, which might help the experts for selecting the appropriate therapeutic measures.

Results: Possibly involved mechanisms in VITTS after ChAdOx1 nCoV-19 vaccination include binding of anti-PF4 antibodies to heparin/PF4 complex or receptor-binding domain (RBD) protein-PF4 complex. Another mechanism could be the binding of anti-RBD antibodies to the RBD protein-PF4 complex. Finally, anti-RBD or anti-PF4 antibodies may bind to the heparin-RBD protein-PF4 complex. The binding of either of the mentioned antibodies to these complexes via the Fc/angiotensin-converting enzyme 2 receptors can cause activation/removal of platelets leading to thrombocytopenia and thrombosis.

Conclusion: The suggested mechanisms in this article provide a relationship between the results of anti-PF4 antibody assays, previous exposure to heparin, and the involved mechanisms of post-vaccination thrombocytopenia and thrombotic events, which might help the experts in selecting the therapeutic measures.

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Introduction

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one of the most critical global threats, has infected about 460 million individuals and killed more than 6 million cases (March 15, 2022; reported by Worldometers). Considerable efforts have been made to introduce different vaccines, including mRNA-based vaccines, subunit vaccines, and viral vector-based vaccines, to control the disease [1]. Although vaccination is regarded as the most efficacious approach to mitigate the virus, rare adverse complications may occur upon vaccination [2-4].

Vaccine-induced immune thrombotic thrombocytopenia syndrome (VITTS)

Vaccine-induced immune thrombotic thrombocytopenia syndrome (VITTS), also known as vaccine-induced prothrombotic immune thrombocytopenia or thrombosis with thrombocytopenia syndrome (TTS), has been reported following administration of adenoviral-based vaccines since February 2021 [5, 6]. This prothrombotic complication was observed in a couple of individuals vaccinated against COVID-19 with the ChAdOx1 nCov-19 vaccine from AstraZeneca and with less frequency in those who received Ad26.COV2-S from Janssen [7, 8]. The current review mainly focuses on ChAdOx1 nCov-19 as a recombinant chimpanzee adenoviral vector-based vaccine that encodes the SARS-CoV-2 spike protein. The immediate and accurate diagnosis at the preliminary stage is of vital importance due to the existence of some complications mimicking VITTS.

The pathophysiology of VITTS

The pathophysiology of VITTS is not yet fully understood but is comparable to that of heparin-induced thrombocytopenia (HIT), which is also caused by anti-platelet factor 4 (PF4) antibodies [9, 10]. It is worth noting that, in VITTS, there is no previous exposure to heparin. Although in most cases, HIT is induced following heparin exposure, in a non-frequent subtype known as autoimmune HIT, heparin exposure is not a prerequisite [11, 12]. Therefore, the mechanism of VITTS may overlap with autoimmune HIT. The clinical and laboratory features of VITTS cases are mainly similar to autoimmune HIT, previously reported after surgery, administration of specific medications, or some types of infections without receiving heparin [13, 14].

Platelet activation and aggregation are induced by the IgG class of anti-PF4/polyanion antibody via forming a cross-link with the Fc-γ receptor on the surface of platelets and resulting in thrombosis [15, 16]. The binding sites of VITTS-associated antibodies on PF4 are, however, different from that of HIT-related antibodies [17]. Additionally, VITTS antibody binding to platelets is assessed to be much more potent than HIT antibody binding [11].

Most developed VITTS cases were younger than 60 years with superiority of female involvement. The high mortality rate of the complication (up to 40%) is of crucial significance. Severe thrombocytopenia and intracranial bleeding are mostly associated with high mortality of the TTS disorder [18].

Diagnosis of TTS

The diagnosis of TTS is confirmed after fulfilling its criteria: the onset of symptoms from 5 to 45 days upon vaccination, the existence of venous or arterial thrombosis, presence of thrombocytopenia, high levels of D-dimer and low titer of fibrinogen, both are suggestive of coagulation, as well as a positive test for anti-PF4 antibodies [19].

The site of thrombosis in VITTS varies in reported cases, ranging from specific sites or unusual ones. The former contains pulmonary embolism (PE) or deep vein thrombosis (DVT). Experimental data from reported cases recommend that cerebral venous sinus thrombosis accounts for up to 60% of thrombosis in VITTS following vaccination with the ChAdOx1 nCov-19 vaccine [20].

Medical interventions should be performed after vaccination if the patient complains of headache, visual disorders, pain in the abdomen, back, or leg, nausea/vomiting, petechiae, and bleeding [21]. To properly manage VITTS, various measures must be taken, including appropriate laboratory examinations besides imaging, such as a CT scan or MRI, to recognize thrombocytopenia and thrombosis. In the case of abnormal imaging and laboratory examinations, the patient should be hospitalized for immediate treatment and further follow-up.

Common laboratory tests include a complete blood count to inspect thrombocytopenia. In the most reported cases, no certain abnormalities were observed on the peripheral blood smear, such as platelet clumps and schistocytes [22].

There are various types of tests to detect PF4-antibody, including optical-density-based assays and functional assays. It is crucial to verify that the correct test has been performed and that outcomes are specifically analyzed. Enzyme-linked immunosorbent assay (ELISA) is the standard screening test [23]. Commercially available ELISA tests are often positive in VITTS cases [24]. It should also be highlighted that no individual ELISA method can detect all patients with VITT, and missing the case due to a false-negative result is likely. If high optical density (more than 2.00) is observed, functional assays will not be required. Functional assays, including serotonin release assays, are employed for a mechanistic understanding of VITTS [25].

Generally, the ELISA test to detect anti-PF4 antibodies is typically positive for both VITTS and HIT. However, rapid screening assays for HIT, such as latex-enhanced immunoassay, chemiluminescence immunoassay, particle gel immunoassay, and lateral flow immunoassay, are usually positive only for HIT, confirming the fact that different antigens target PF4 in VITTS compared to HIT [26-28].

Herein, we regard the potentially involved mechanisms upon Oxford-AstraZeneca COVID-19 vaccination. The global vaccination program against SARS-CoV-2 has been limited by the rare but highly lethal emergence of VITTS. Considering this challenge, a deeper mechanistic understanding of this event and rational treatment approaches have far-reaching implications.

Mechanism of thrombocytopenia and thrombosis after ChAdOx1 nCoV-19 vaccination

Figure 1 illustrates the possible mechanisms of thrombocytopenia and thrombosis after ChAdOx1 nCoV-19 vaccination.

(Heparin-PF4-Anti-PF4)-FcR mechanism

It has been demonstrated that binding anti-PF4 antibodies to the heparin-PF4 complex activate or removes the platelets via the Fc binding to the Fc receptor (FcR) on the platelets (Figure 1a). Removing the platelets by the macrophages can cause thrombocytopenia, and activating the platelets might lead to platelet aggregation and thrombosis [29]. Therefore, PF4 antibodies are thought to activate platelets via the platelet receptors leading to further platelet activation, causing thrombosis and thrombocytopenia [30]. Recently, binding of the SARS-CoV-2 receptor-binding domain (RBD) of the S1 subunit of the spike protein to heparin [31, 32] as well as interactions of SARS-CoV-2 spike-RBD protein and PF4 [33] has been demonstrated. In addition, after ChAdOx1 nCoV-19 vaccination, the RBD protein of SARS-CoV-2 is expressed in the vaccine recipients. Therefore, similar mechanisms could be possible after ChAdOx1 nCoV-19 vaccination in the patients who were previously exposed or not exposed to heparin.

To elucidate the etiopathogenesis of the ChAdOx1 nCoV-19 vaccine-induced TTS, three possible mechanisms are suggested. In the following mechanisms, the TTS can be induced through either the FcR or the angiotensin-converting enzyme 2 (ACE2).

(PF4-RBD-Anti-PF4)-FcR or -ACE2R mechanism

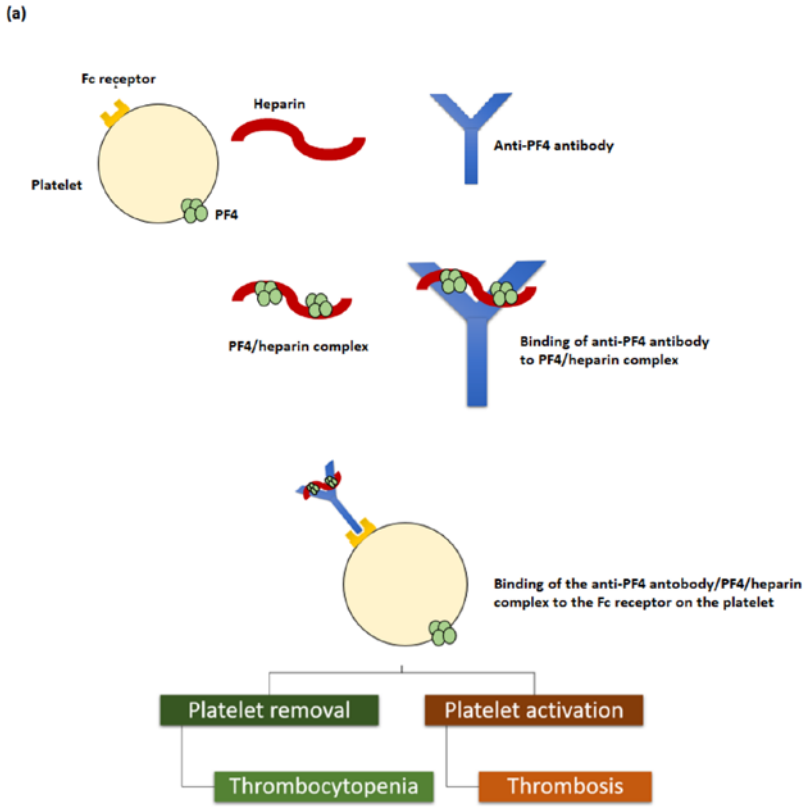
The first suggested mechanism is the binding of the post-vaccination-expressed RBD protein to the PF4, leading to the binding of ani-PF4 antibodies, as shown in Figure 1b. In this mechanism, the RBD protein plays the role of heparin in the induction of post-vaccination thrombocytopenia and thrombosis events. This mechanism justifies the TTS cases reported by Greinacher in which cases had previous exposure to heparin, but the anti-PF4 antibody assays were negative [5].

(PF4-RBD-Anti-RBD)-FcR or -ACE2R mechanism

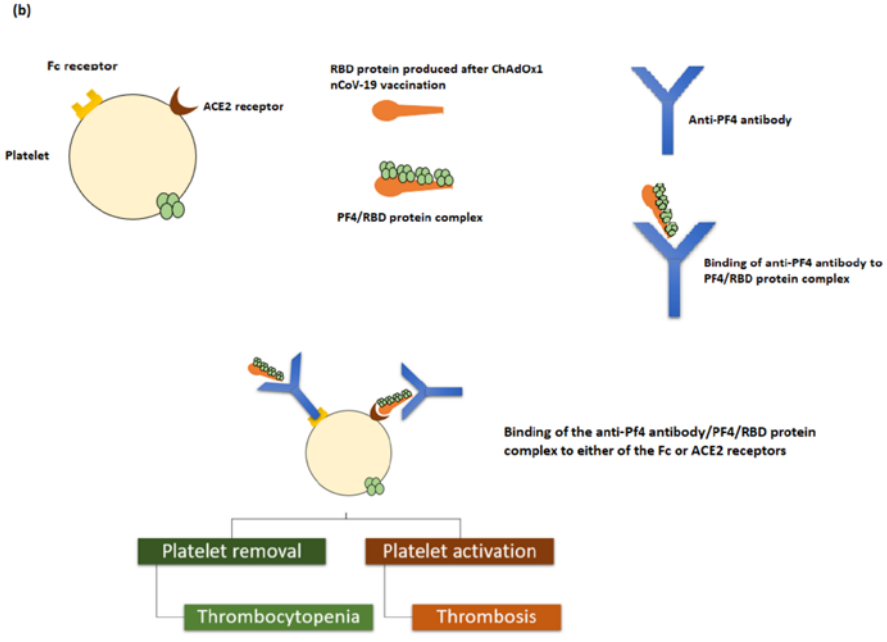
The second mechanism is the binding of post-vaccination-expressed RBD protein to the PF4. This complex formation leads to the binding of anti-RBD antibodies produced after the ChAdOx1 nCoV-19 vaccination, as shown in Figure 1c. In this mechanism, the RBD protein acts like heparin, and the anti-RBD antibodies play the role of anti-PF4 antibodies in the induction of post-vaccination thrombocytopenia and thrombosis events. This mechanism can justify thrombocytopenia and thrombotic events in the cases reported by Soleimani [34]. In these cases, the previous exposure to heparin and the anti-PF4 antibody assay is negative.

(PF4-RBD-Heparin-anti-RBD)-FcR/ACE2R and (PF4-RBD-Heparin-anti-PF4)-FcR/ACE2R mechanism

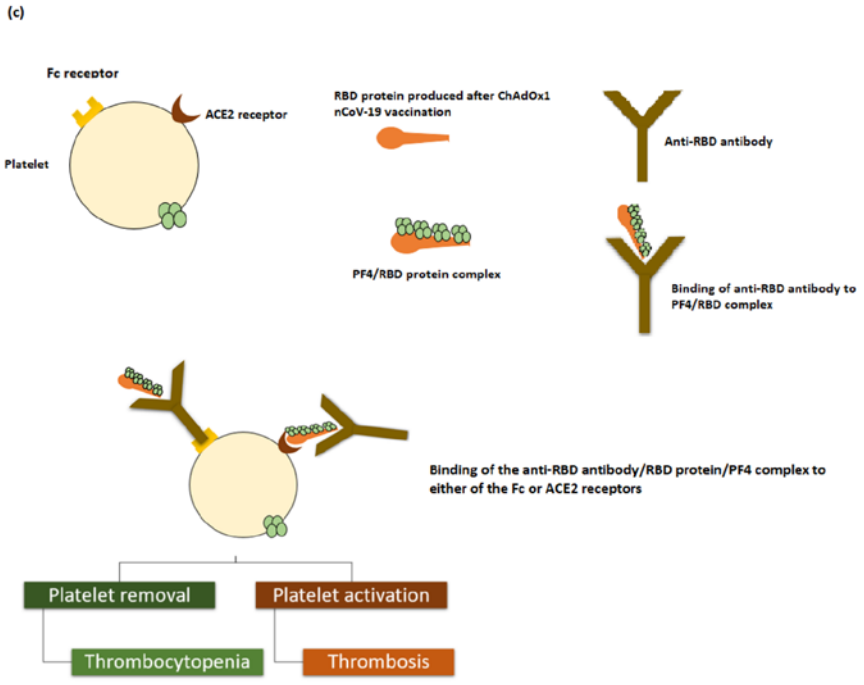
The third suggested mechanism is the formation of a complex composed of heparin, RBD protein, and PF4. This complex can either bind to anti-PF4 or anti-RBD antibodies, as shown in Figure 1d. This mechanism can justify the thrombocytopenia and thrombotic complications reported by Bourguignon [23]. In these cases, the previous exposure to heparin and anti-PF4 antibody assay is positive. The binding of all the antibodies men-



(a) (heparin-PF4-Anti-PF4)-FcR mechanism: anti-PF4 antibodies bind to heparin/PF4 complex and initiate the TTS via binding to the FcR.



(b) (heparin-PF4-Anti-PF4)-FcR mechanism: anti-PF4 antibodies bind to heparin/PF4 complex and initiate the TTS via binding to the FcR; **(b)** (PF4-RBD-Anti-PF4)-FcR or -ACE2R mechanism: anti-PF4 antibodies bind to the RBD protein/PF4 complex leading to the initiation of TTS through either the FcR or the ACE2R.



(c) (PF4-RBD-Anti-RBD)-FcR or -ACE2R mechanism: anti-RBD antibodies bind to the RBD protein/PF4 complex leading to the initiation of TTS via either the FcR or the ACE2R; and

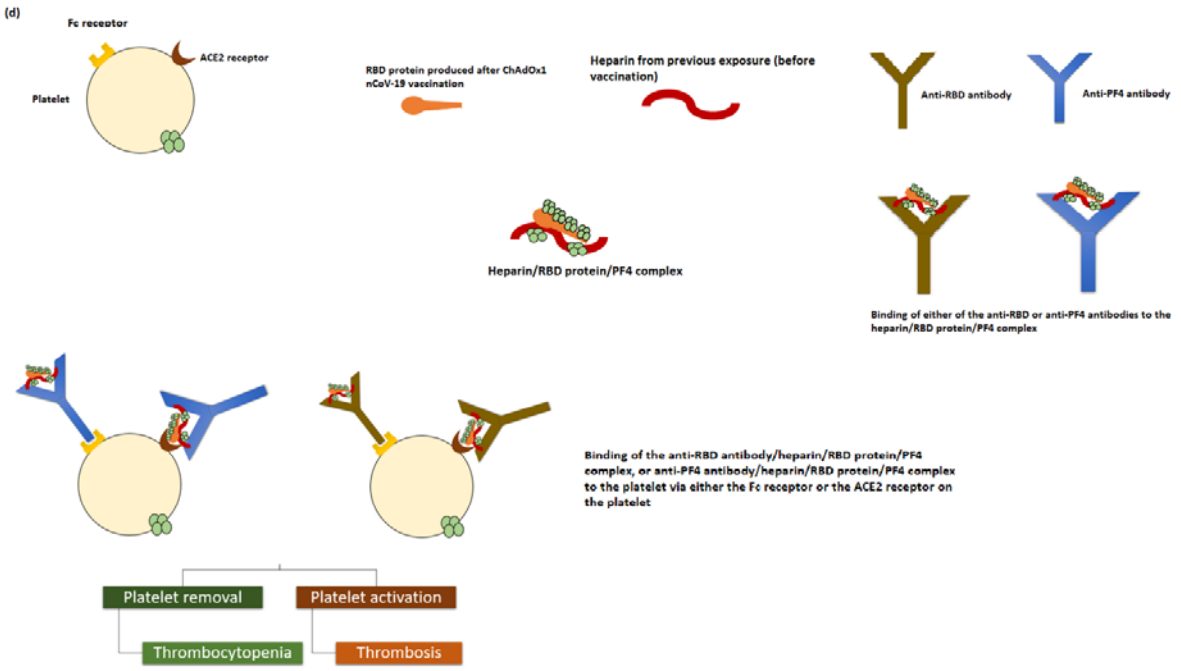


Figure 1. Recommended mechanisms of thrombocytopenia and thrombosis after ChAdOx1 nCoV-19 vaccination

(d) (PF4-RBD-heparin-Anti-RBD)-FcR/ACE2R and (PF4-RBD-heparin-anti-PF4)-FcR/ACE2R mechanism: anti-RBD or anti-PF4 antibodies bind to the heparin/RBD protein/PF4 complex which leads to the initiation of the TTS through either the FcR or ACE2R.

Table 1. Possible mechanisms involved in thrombocytopenia and thrombotic events after ChAdOx1 nCoV-19 vaccination based on Anti-PF4 antibody assays and previous exposure to heparin

Previous Exposure to Heparin	Anti-PF4 Antibody	Possible Mechanism	Case Reports*
Positive	Negative	(Heparin-PF4-Anti-PF4)-FcR mechanism (Figure 1a)	(5)
Negative	Positive	(PF4-RBD-Anti-PF4)-FcR or -ACE2R mechanism (Figure 1b)	(5)
Negative	Negative	(PF4-RBD-Anti-RBD)-FcR or -ACE2R mechanism (Figure 1c)	(34)
Positive	Positive	(PF4-RBD-heparin-Anti-RBD)-FcR/ACE2R and (PF4-RBD-heparin-anti-PF4)-FcR/ACE2R mechanism (Figure 1d)	(35)

* Details of the patients involved in these case reports are provided as three supplementary tables. These details include demographic data, laboratory tests, site of thrombosis, therapeutic measures, and immunoassays used for each patient in the case report.

tioned above to the complexes might lead to the removal/activation of the platelets, which can cause thrombocytopenia and thrombosis, respectively.

Table 1 summarises the relationship between a past medical history of exposure to heparin, the results of anti-PF4 antibody assays, and the involved mechanisms of post-vaccination thrombocytopenia and thrombotic events with the reported cases of post-vaccination thrombocytopenia with thrombotic events. The mechanism shown in Figure 1b might be the possible mechanism involved in the VITTS patients without previous exposure to heparin in which the anti-PF4 antibody is detected. However, in the VITTS patients without previous exposure to heparin and with a positive anti-PF4 antibody assay, the mechanism shown in Figure 1c might be the possible mechanism. Finally, the mechanism shown in Figure 1d might justify the severe condition in which the patients have previous exposure to heparin and positive results in the anti-PF4 antibody assay. In these cases, three binding conditions are possible: bindings of 1) the heparin to the PF4, 2) the RBD protein to the PF4, and 3) the heparin to the RBD protein. Two groups of antibodies are also available in this condition: the anti-PF4 and the anti-RBD antibodies. These antibodies have a high affinity for the complexes shown in Figure 1d. Therefore, the possibility of immune complex (ani-PF4 or anti-RBD antibodies/heparin/RBD protein/PF4) formation might be increased, leading to activation/removal of the target platelet, which can cause thrombosis and thrombocytopenia in the vaccine recipients.

Best treatment option for each mechanism of TTS following ChAdOx1 nCoV-19 Vaccination

If the tests for PF4-heparin antibodies are negative, heparins could be used. However, with a positive test for PF4/heparin antibodies, it needs to be studied further by functional assays, such as heparin-induced platelet activation (HIPA) assay or serotonin-release assay to detect pathophysiologically relevant antibodies. In cases with a positive result for anti-PF4/-RBD antibody in the existence of heparin (the first and the fourth mechanisms mentioned above), heparin could not be used as the treatment, and intravenous immunoglobulin (IVIG) should be considered in case of severe thromboembolic complications. However, in the second and third mechanisms mentioned, the test is positive for anti-PF4/-RBD antibodies in the absence of heparin, which could be used as a treatment option for the patients with consideration of IVIG for severe thromboembolic complications [35].

Conclusion

ChAdOx1 nCov-19, also called Oxford-AstraZeneca COVID-19 vaccine, is an approved viral vector-based vaccine to prevent COVID-19. Besides the common side effects of this vaccine, there were few case reports of patients with thrombocytopenia associated with thrombotic events shortly after the ChAdOx1 nCov-19 vaccination. The exact mechanism by which vector based-COVID-19 vaccines induce TTS has not yet been elucidated. Due to the unknown mechanism and pathophysiological basis of VITTS after ChAdOx1 nCoV-19 vaccination, careful consideration should be prompted for the treatment. Platelet transfusion can provide different substrates for coagulopathy through an antibody-mediated platelet activation mechanism. A comprehensive understanding of the exact mechanism involved in ChAdOx1 nCov-19 vaccine-associated TTS may allow for more targeted and efficient therapeutic measures.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Both authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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