BioTechnology: An Indian Journal

**Editorial**|Vol18Iss01

# Thrombosis with COVID-19 Vaccines: An opinion

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**Received date:** January 12, 2022; **Accepted date:** January 15, 2022; **Published date:** January 28, 2022

## Abstract

**The European Medicines Agency (EMA) has approved two adenovirus-based vaccines, ChAdOx1 nCoV-19 and Ad26.COV2.S, as well as two mRNA-based vaccines, BNT162b2 and mRNA.1273, to prevent and reduce the incidence of coronavirus disease-2019 (COVID-19). Recent publications have shown thrombosis with thrombocytopenia as an adverse event that occurs infrequently in some people following vaccination. The interactions of the SARS-CoV-2 spike protein with different C-type lectin receptors, heparan sulphate proteoglycans (HSPGs), and the CD147 receptor, as well as different soluble splice variants of the spike protein, adenovirus vector interactions with the CD46 receptor, and platelet factor 4 antibodies, may be the cause of such events. Following vaccination, similar findings have been observed for a variety of viral illnesses. Furthermore, immunological reactions triggered by viral vectors associated to cellular transport could be important in people with specific genetic backgrounds.**

***Keywords: Virus; Thrombosis; Covid-19; Vaccines***

## Introduction

After 18 months of sicknesses, fatalities, confinements, and lockdowns, the extraordinary development of numerous vaccinations against coronavirus disease-2019 (COVID-19) promised that there was now light at the end of the tunnel. The European Medicines Agency (EMA) has licenced four vaccinations that provide protection against severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) variations, albeit efficacy varies. The lipid nanoparticle (LNP)-formulated mRNA COVID-19 vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), as well as the adenovirus (Ad)-based vaccines ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen) are among the most notable [1]. Then, potentially more transmissible and pathogenic variations were discovered and demonstrated to spread rapidly in different parts of the world, such as the B.1.1.7 UK variant and the South African B.1.351 variant. According to

preliminary findings, the B.1.1.7 variant increased infection but not viral burden. Individuals who tested positive for the B.1.1.7 variation, on the other hand, had a 10-fold greater viral load than non-B.1.1.7 participants, according to a recent study. A major issue at the time was whether existing vaccines could protect against these novel variations and other variants that were likely to appear in the future. The B.1.1.7 and B.1.351 variants displayed antibody resistance in the context of the BNT162b2 vaccination [2]. Furthermore, in a clinical trial in South Africa, the ChAdOx1 nCoV-19 vaccination failed to protect against the B.1.351 strain. These discoveries prompted the development of second-generation vaccinations that could adapt to viral evolutionary variability while also demonstrating efficacy against newly discovered SARS-CoV-2 subtypes. As if that wasn't awful enough, after vaccinations with the simian adenovirus AdChOx1 nCoV-19 vaccine, rare incidences of thrombotic thrombocytopenia were recorded [3]. 11 participants in one research experienced one or more thrombotic events 5–16 days after vaccination. There were nine cases of cerebral venous thrombosis, three cases of splanchnic-vein thrombosis, three cases of pulmonary embolism, and four cases of miscellaneous thromboses. Six of the patients died, and five of them had disseminated intravascular coagulation. After immunizations with the Ad26.COV2.S vaccine, cases of thrombosis with severe thrombocytopenia have been observed. Three cases of VITT were recently discovered in females aged 44, 47, and 50 days after receiving their initial vaccination with the ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines. Thrombocytopenia has also been documented in 20 people who received RNA-based COVID-19 vaccinations, including 9 people who received BNT162b2 (Pfizer/BioNTech) and 11 people who received mRNA-1273 (Moderna) [4].

**COVID-19 Vaccine Characteristics and Thrombocytopenia**

The full-length SARS-CoV-2 S protein is expressed in all four COVID-19 vaccines discussed previously. The S protein is intended to be delivered to the immune system of vaccinated patients as an antigen after being translated within the host cells, eliciting humoral and cellular immunological responses that will protect immunised persons against SARS-CoV-2 infection. Because of the new finding of rare cases of vaccine-induced thrombotic thrombocytopenia (VITT), it's critical to examine all vaccine components that could be linked to these complications [5]. The ChAdOx1 nCoV-19 vaccine is made up of the ChAdOx1 simian Ad vector, which expresses the full-length SARS-CoV-2 structural surface spike (S) glycoprotein gene downstream of the tissue plasminogen activator (tPA) leader or signal sequence. Ad26.CoV2.S, the other Ad vector-based vaccine, has a tPA leader sequence as well as a stabilised SARS-CoV-2 S protein with a mutant furin site and two consecutive prolines (PP) in the S2 hinge region. The tPA leader sequence is absent from both the BNT162b2 and the mRNA-1273 vaccines. Thrombocytopenia has previously been documented in ischemic stroke and acute myocardial infarction patients treated with recombinant tPA, with 3.7 percent of 101,527 acute stroke patients receiving intravenous rtPA experiencing thrombocytopenia. As a result, it's been wondered if the tPA leader sequence in the SARS-CoV-2 S protein generated from the ChAdOx1 and Ad26 vectors will have a comparable effect in vaccinated people. However, in the European Economic Area, immunisation of 5 million people with the ChAdOx1 nCoV-19 vaccine resulted in 30 unusual incidences of thromboembolic events, which was no more than the number reported in the general population. Because only the rtPA leader sequence is present in the vaccination vector, thrombotic thrombocytopenia caused by the ChAdOx1 nCoV-19 and Ad26.COV2.S vaccine-derived rtPA is improbable.

**Spike Protein Structural and Biological Characteristics and Thrombosis Risk**

Although the ACE2 receptor is the predominant entrance receptor, the SARS-CoV-2 S protein interacts with various host cell components, facilitating viral entry and potentially contributing to the pandemic's spread. The S protein may target heparan sulphate proteoglycans (HSPGs), C-type lectin receptors (CLRs), and extracellular matrix metalloproteinase (CD147) on the host cell surface. The SARS-CoV-2 S protein could potentially cause thrombotic thrombocytopenia in both the existing Ad- and mRNA-based COVID-19 vaccines. In this context, a thrombosis-related mortality in a person who received the BNT162b2 mRNA vaccination was recently discovered [6]. Thrombocytopenia has also been documented in 20 people who received RNA-based COVID-19 vaccinations, including 9 people who received BNT162b2 (Pfizer/BioNTech) and 11 people who received mRNA-1273 (Moderna) [7].

**Potential Thrombosis Risk Groups**

The number of occurrences of VITT following the injection of both Ad- and mRNA-based COVID-19 vaccines is extremely rare, and experts agree that the advantages of immunisation outweigh the risks of severe vaccine side effects like VITT. A meta-analysis of 27 trials involving 3342 COVID-19 patients found a 16.5 percent pulmonary embolism (PE) and 14.8 percent deep vein thrombosis (DVT) incidence rate (DVT) [8]. In Denmark and Norway, however, 11 extra venous thromboembolic events per 100,000 immunizations with the ChAdOx1 nCoV-19 vaccine were found. However, there was no increase in the rate of total arterial events, but there was a minor increase in the rate of thrombocytopenia problems and bleeding. Furthermore, when compared to smoking and oral contraceptives, the VITT risk after vaccination is significantly reduced [9]. The overall combined relative risk (RRs) for venous thromboembolism (VTE) for ever smokers was 1.17 (95 percent CI 1.09–1.25), for current smokers 1.23 (95 percent CI 1.14–1.33), and for former smokers 1.10 (95 percent CI 1.03–1.17), indicating a slightly increased risk of VTE in smokers compared to never smokers. Because the usual risk of VTE, DVT, and PE in women of reproductive age is estimated to be 2–10 cases per 10,000 people each year, with odds of around 1:1700, using contraceptives can increase the risk 3 to 6-fold [10].

## Conclusion

This research sheds light on the potential processes of VITT. As previously stated, both Ad- and mRNA-based vaccines have been linked to induced thrombocytopenia; however this is a rare occurrence given the scale of COVID-19 mass immunizations. For the development of thrombocytopenia, various explanations have been proposed. Although ischemic stroke and acute myocardial infarction have been reported in patients treated with tPA, thrombocytopenia is unlikely to result from the presence of solely the tPA leader sequence in the ChAdOx1 vector. One possibility is that Ad causes thrombocytopenia, as has been previously described. It has to do with an increase in platelets caused by Ads, as well as cytokine activation caused by the Ad fibre protein. Thrombocytopenia has been identified after vaccinations with COVID-19 vaccines based on mRNA. The full-length SARS-CoV-2 S protein is used as an antigen in both Ad- and mRNA-based vaccines, and its interaction with various membrane components may cause thrombocytopenia. Alternatively, after ChAdOx1 nCoV-19

vaccination, heparin may activate anti-PF4 antibodies, leading in heparin-induced thrombocytopenia. The C-type lectin receptor DC-SIGN and the CD147 receptor are two more variables that affect thrombocytopenia. The topic of managing acute and subacute/chronic forms of CSVT with VITT has been addressed based on the pathogenic pathways outlined above. It should primarily include alternate anticoagulants to heparin or a direct oral anticoagulant for the treatment of heparin-induced thrombocytopenia with thrombosis (DOAC). It is evident that the chance of developing post-vaccination thrombocytopenia is far lower than the risk of death and morbidity from SARS-CoV-2 infections, regardless of whether vaccine is used. Vaccines are critical in controlling the COVID-19 pandemic and building herd immunity to SARS-CoV-2. As a result, it's critical to thoroughly investigate the causes of VITT, take the appropriate steps for people who have a pre-existing thrombocytopenia susceptibility, and, if necessary, re-engineer both vaccine vectors and formulations to ensure that we've only hit a snag and not reached a dead end.

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