# COVID-19 Vaccine-Induced Thrombotic Thrombocytopenia Leading to Stroke: An Extremely Rare but Possible Condition

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**Abstract**

Coronavirus disease 2019 (COVID-19) vaccines remain the safest and most effective strategy against the COVID-19 pandemic. However, clinicians must be aware of any adverse events that might arise as a peculiar side effect in certain individuals. One of such extremely rare side effect that needs to be routinely integrated into the clinical decision-making arise from vector based COVID-19 vaccines that result in vaccine-induced thrombotic thrombocytopenia (VITT) and consequently stroke. Understanding any evolving information that relates with COVID-19 is critical to its successful containment and control. As such, unraveling the mechanism of VITT leading to stroke as well as its relevant clinical information is essential towards its successful integration into clinical guidelines. This short communication was therefore aimed at focusing on proposed mechanism through which stroke evolved from vaccine-induced thrombotic thrombocytopenia and its relevant clinical information for clinical practice. This study stresses the importance of being vigilant to the development of vaccine-induced thrombotic thrombocytopenia and stroke especially from the viewpoint of clinicians and other health care personnel. The phenomenon of VITT leading to stroke was also recommended for inclusion as a standard operation procedure in the standard clinical guidelines for the management of acute ischemic stroke.

**Keywords:** Coronavirus Disease 2019, Vaccine-Induced Thrombotic Thrombocytopenia, Stroke, COVID-19 Vaccines, Adenovirus Vector-Based Vaccine (J Thai Stroke Soc. 2024;23(1): 29-33)

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## *Introduction*

Vaccine against SARS-CoV-2 infection remains the most effective way towards COVID-19 prevention, control and elimination[1-4]. An encouraging and fascinating data from the World Health Organization (WHO) has indicated that about 11 billion COVID-19 vaccine doses have been administered to people worldwide as of the end of March 2022. COVID-19 vaccines are generally categorized into vector-based vaccines which are virtually adenovirus-vectored-DNA vaccines, and mRNA-based vaccines which are messenger RNA (mRNA) containing vaccines[5].

Events and evidences have emerged on the occurrence of blood clot (thrombosis) with concomitant low platelet levels (thrombocytopenia) as an extremely rare side effect of vector based COVID-19 vaccines[6-9]. This condition was named vaccine-induced thrombotic thrombocytopenia (VITT), but other synonymous nomenclature for VITT such as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) and thrombotic thrombocytopenia syndrome (TTS) have also been documented[8]. VITT pathophysiological manifestation mimics autoimmune heparin-induced thrombocytopenia that occurs as side effect of heparin medication[6], in which heparin binding with platelet (forming heparin-platelet factor complex) in a susceptible individual triggers the immune system to produce antibodies against the complex, thus stimulating the platelets to be more functionally activated and aggregated (hypercoagulability) as well as increasing the platelet consumption leading to thrombocytopenia.

Vaccine-induced thrombotic thrombocytopenia has far-reaching implications that prompt for deeper biological understanding, rapid identification, diagnosis, and treatment[10]. One of the clinical implications that need such deeper understanding is the occurrence of clinical cases involving different population and geographical location about stroke presentation secondary to vaccine-induced thrombotic thrombocytopenia[11-13]. Stroke secondary to COVID-19 vaccine-induced thrombotic thrombocytopenia is an extremely rare but possible condition. In a systematic review study that assessed the literature on the report of such clinical cases of stroke, only 21 and 24 isolated cases were identified among all the people that received COVID-19 vaccine globally as of 12th October 2021[14] and 3rd December 2021[15] respectively. Hence this short communication aimed to unravel from available evidence the proposed mechanism through which VITT translates into stroke presentation and its relevant clinical information for clinical practice.

## *Methods*

This short communication paper searched for published articles on COVID-19 and stroke as a result of VITT from the PubMed database, using the search terms "COVID-19" and "stroke or vaccine-induced thrombotic thrombocytopenia".

## *Result*

The information from the articles identified were used to narratively synthesize the findings of the present study.

## *Discussion*

This short communication studied the proposed mechanism through which VITT translates into stroke presentation and its relevant clinical information for clinical practice. The mechanism and the clinical information are therefore summarized as follows.

**Mechanism of vaccine-induced thrombotic thrombocytopenia leading to stroke**

Figure 1 illustrates the proposed mechanism through which COVID-19 VITT leads to stroke. The pathogenesis of VITT is not completely understood as it remains an active area of research with plethora of information still under investigation. The hallmark pathogenesis of VITT is triggering of the aberrant exaggerated titers of immunoglobulin G class antibodies that target platelet factor 4 (PF4) bound to platelets[16, 17] by the SARS-CoV-2 vaccine. PF4 is a cationic platelet chemokine, which normally opsonizes polyanionic surfaces of pathogens to facilitate the binding of anti-PF4 antibodies thus aiding subsequent activation of platelets.

Nevertheless, under VITT, exaggerated and misdirected anti-PF4 antibody response ensues, resulting in marked platelet activation via the Fc receptor and consequent stimulation of the coagulation system resulting in thrombosis with concomitant increase in platelet consumption leading to thrombocytopenia manifestation. The activation of the platelet coagulation cascade result in thrombosis, and this activation occurs majorly as a result of PF4/vaccine complexes binding with the FcγIIa receptor on the platelet surface, or to some certain extent via activation of the endothelium to express adhesion molecules (E-selectin, P-selectin, von Willebrand factor) by the PF4/vaccine complexes. Thrombosis in VITT has a distinctive feature of presentation often at unusual sites such as cerebral sinus veins or splanchnic veins[18]. Thrombo-embolism syndrome or arterial thrombosis in the cerebral circulation often leads to stroke[19].

**Relevance of COVID-19 VITT leading to stroke with clinical practice**

Figure 2 shows a diagrammatic illustration adopted from Kolahchi[20] showing the relevance of COVID-19 VITT leading to stroke with clinical practice. Accordingly, the clinicians should have high index of suspicion of such case only if an individual suspected of acute stroke presents with history COVID-19 vaccination within one month of the incident. Once this history is affirmative, the laboratory test for VITT such as testing for PF-4 antibodies is warranted, concurrent to which if positive imaging test to confirm the presence large vessel occlusion is indicated. If large vessel occlusion is present, the standard method of eligibility for recombinant tissue plasminogen activator (rTPA) or mechanical thrombectomy is indicated. On the contrary, if large vessel occlusion is absent, the occurrence of stroke secondary to VITT is confirmed. The acute treatment of stroke secondary to VITT should follow standard eligibility criteria for rTPA. Moreover, other recommended treatments include appropriate utilization of non-heparin anticoagulants, intravenous immunoglobulin (IVIG) or plasma exchange, as well as other measures illustrated in Figure 2 should be properly instituted.

***Conclusion***

VITT has an extremely rare incidence, estimated between 1 in 125, 000 to 1 in 1,000000 people. Therefore, the crucial benefits of COVID-19 vaccine far outweigh its risk of development and consequent manifestation of stroke complication. However, studies into this phenomenon underscore the importance of being vigilant to the development of this adverse event. The phenomenon was also recommended for inclusion as a standard operation procedure in the standard clinical guidelines for the management of stroke.

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***Figure 1.*** *Illustration showing the proposed mechanism through which COVID-19 VITT leads to stroke.*

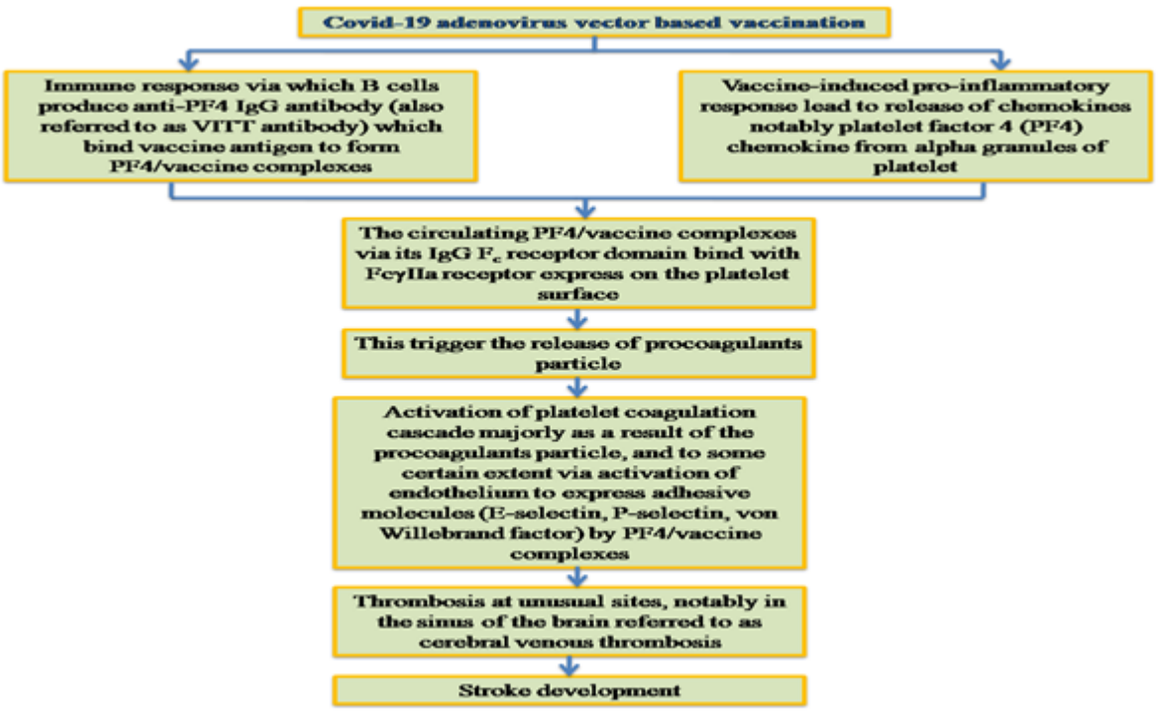


***Figure 2.*** *Illustration adopted from Kolahchi[20] showing the relevance of COVID-19 VITT leading to stroke with clinical practice.*