Life Cycle | The best science From birth To senescence

eISSN: 2799-8894
Life Cycle 2023;3:e16
https://doi.org/10.54724/lc.2023.e16

State-of-the-Art Reviews

SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia: A comprehensive review, release 1 (epidemiologic perspective)

Kalthoum Tizaoui[1*], Ines Zidi[2], Masoud Rahmati[3,4], Ai Koyanagi[5], Andreas Kronbichler[6,7], Michael Eisenhut[8], Jae Il Shin[9*], Lee Smith[10]

[1]Laboratory of Biomedical Genomics and Oncogenetics, Institut Pasteur de Tunis, University Tunis El Manar, Tunis, Tunisia
[2]Laboratory Microorganismes and Active Biomolecules, Sciences Faculty of Tunis, University Tunis El Manar, Tunis, Tunisia
[3]Department of Physical Education and Sport Sciences, Faculty of Literature and Human Sciences, Lorestan University, Khoramabad, Iran
[4]Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, Vali-E-Asr University of Rafsanjan, Rafsanjan, Iran
[5]Research and Development Unit, Parc Sanitari Sant Joan de Deu, Barcelona, Spain
[6]Department of Medicine, University of Cambridge, Cambridge, United Kingdom
[7]Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria
[8]Luton & Dunstable University Hospital, NHS Foundation Trust, Luton, UK
[9]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[10]Centre for Health, Performance, and Wellbeing, Anglia Ruskin University, Cambridge, UK

Abstract

More than eight billion vaccine doses have been delivered to battle the COVID-19 pandemic. SARS-CoV-2 vaccines have been carefully developed and proven efficacious as evidenced by clinical assays and studies in real-world settings. However, rare but severe side effects raise important safety concerns. Particularly, severe complication after vaccination with adenoviral vector vaccines, vaccine-induced immune thrombotic thrombocytopenia (VITT), has attracted worldwide attention. It is characterized by thrombosis at unusual sites, including cerebral or abdominal thrombosis, thrombocytopenia, and the presence of antibodies against platelet factor 4. Although rare, VITT progresses rapidly with a high mortality rate, and new severe symptoms continue to appear with increased VITT vigilance, and a growing body of evidence. The COVID-19 pandemic is still ongoing with continuously emerging variants. It is therefore important to vaccinate a large population and work to overcome current vaccine limitations. The scientific community needs to be aware of specific side effects and understand their exact mechanisms in order to overcome vaccine hesitation.

Keywords: COVID-19, SARS-CoV-2, Vaccine, vaccine-induced immune thrombotic thrombocytopenia, public health; virology

Received: date: Aug 2, 2023.
Revised date: Sep 14, 2023.
Accepted date: Oct 12, 2023.
Published date: Oct 29, 2023.

***Correspondence**:
Jae Il Shin
E-mail: shinji@yuhs.ac
Kalthoum Tizaoui
E-mail: kalthoum.tizaoui@pasteur.utm.tn

ORCID
Jae Il Shin
https://orcid.org/0000-0003-2326-1820
Kalthoum Tizaoui
https://orcid.org/0000-0001-8524-6058

1. Introduction

Scientists have expedited vaccine development to combat COVID-19, and several types of vaccines have been developed: mRNA vaccines, non-replicative vector vaccines, inactivated and subunit vaccines.[1] Globally, as of June 1, 2021, more than 1.93 billion doses of COVID-19 vaccine have been administered.[1] From December 2020 through March 2021, based on randomized, blinded and controlled trials, the European Medicines Agency (EMA) approved four vaccines: two messenger RNA–based vaccines that encode the spike protein antigen of SARS-CoV-2, encapsulated in lipid nanoparticles: BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna); the two other vaccines encode the SARS-CoV-2 spike glycoprotein: ChA-

Copyright © 2023 Life Cycle.
This is an Open-Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited (CC-BY-NC).

dOx1 nCov-19 (AstraZeneca) which is a recombinant chimpanzee adenoviral vector and Ad26.COV2.S vaccine (Johnson & Johnson/Janssen) which is a recombinant adenovirus type 26 vector. Similarly, the United States Food and Drug Administration (FDA) authorized the use of the following vaccines: mRNA vaccines, BNT162b2 and mRNA-1273, and the adenovirus-vectored vaccine, Ad26. COV2.S.[2]

After that, many other countries have implemented their own vaccination programs to combat the COVID-19 pandemic. Analyses of clinical trials have demonstrated the efficacy and safety of COVID-19 vaccines and preliminary studies have shown that COVID-19 vaccines are effective in the prevention of SARS-CoV-2 infection in real-world settings.

However, several reports raised serious concerns regarding the risk of vaccine-related thrombosis named as vaccine-induced thrombosis and thrombocytopenia (VITT).[3] VITT or thrombosis with thrombocytopenia syndrome is a new, rare and potentially life-threatening disorder, following immunization with adenovirus vector COVID-19 vaccines ChAdOx1 nCOV-19 (AZD1222; AstraZeneca) and Ad26.COV2·S (Johnson & Johnson/Janssen).[4] As of June 1, 2021, the estimated incidence rate of VITT, based on the total number of first-dose vaccinations, was approximately 0.00086%, 0.000127%, 0.00028%, and 0.000087% in the UK, Canada, Australia, and central Europe, respectively.[4] More and more VITT cases have been reported across the UK, Europe, Canada, and Australia, but VITT remains a rare syndrome.[5] The United States Centers for Disease Control and Prevention has confirmed 28 cases among more than 8 million recipients of the Ad26.COV2.S vaccine.[4] VITT syndrome, that generally occurs 5 to 30 days after vaccine administration, is characterized by moderate to severe thrombocytopenia, thrombosis, including cerebral venous sinus thrombosis (CSVT)/splanchnic thrombosis, positive platelet factor 4 (PF4)-heparin enzyme-linked immunosorbent assay (ELISA) and platelet activation assays. Thrombosis occurs at unusual sites, particularly at the cerebral venous sinuses and splanchnic veins.[4, 6]

Thus, we aimed to review the up-to-date published literature to further understand and provide updated information on COVID-19 vaccine-related thrombosis and thrombocytopenia. Understanding VITT mechanisms and pathogenesis should provide a platform to orient future research and to optimize management of VITT.

2. Epidemiology of VITT

2.1 General clinical picture of VITT

By late December 2020, mass vaccination campaigns have started around the world, but thromboembolic events have been reported after SARS-CoV-2 vaccines, in particular after ChAdOx1 n COV-19 vaccine and the Ad26.COV2.S.[7] In these cases, VITT has been described as severe characterized by thrombosis, particularly at unusual sites including cerebral/splanchnic thrombosis, mild to severe thrombocytopenia and positive PF4-heparin ELISA and platelet activation assays.[4] Available literature indicated that most of the investigated cases are associated with a clinical picture of moderate-to-severe thrombocytopenia and thrombotic complications beginning 10–15 days after vaccination, resembling severe heparin-induced

thrombocytopenia (HIT).[6, 7] VITT symptoms include severe headache, blurred vision, seizure, severe and persistent abdominal pain, painful swelling of the lower leg, and chest pain or dyspnoea.[6, 7] Although a marked elevation of D-dimer levels is highly suggestive of thrombocytopenia and thrombotic syndrome (TTS), the PF4 antibody assay remains a confirmatory test. VITT is diagnosed in the first 30 days of vaccination and described as acute thrombosis and thrombocytopenia with elevated D-dimer, with the use of a D-dimer threshold of <2000 μg/L, which makes VITT unlikely, and >4000 μg/L for VITT, which would underpin a suspected VITT.[8] Scully and colleagues reported that 22 (96%) of 23 patients with VITT had antibodies against PF4. Such definition was approved by the scientific community since similar observations were made in other reports worldwide.[8]

2.2 VITT associated with ChAdOx1 nCoV-19 or Ad26.COV2.S vaccines

VITT was described after vaccination with ChAdOx1 nCoV-19 or Ad26.COV2.S vaccines in patients not receiving heparin, and few of these individuals had risk factors for thrombosis, and cases were generally younger than 55 years and mostly females, and up to one-half of the reported patients died (Table 1).[3] The clinical picture of VITT was moderate to severe thrombocytopaenia associated with arterial and/or venous thrombosis, often in unusual locations.[4] A common denominator in all five patients was a high level of antibodies to PF4–polyanion complexes.[4] Another report showed that eight patients developed VITT after administration of ChAdOx1 nCoV-19. Autopsies showed arterial and venous thromboses in various organs and the occlusion of glomerular capillaries by hyaline thrombi. Sera from VITT patients contain high-titres of antibodies against PF4.[4] PF4 antibodies in patients with VITT induced significant increase in procoagulant markers (P-selectin and phosphatidylserine externalization) compared to healthy volunteers and healthy vaccinated volunteers.[9] Clinical and laboratory features have included thrombosis at unusual sites[10]; in intracranial venous sinus[11], pulmonary, portal, hepatic, renal and mesenteric veins, and cerebral thrombosis was reported in choroid plexuses, suggesting a very aggressive form of VITT.[12] Patients with VITT-associated CSVT had more intracranial veins thrombosed and more frequently had extracranial thrombosis compared with non-VITT.[13] Pottegård et al. assessed the rate of haemostatic events in the first 28 days after vaccination with the Oxford-AstraZeneca vaccine, in which the vaccinated cohort included 281,264 people.[14] They found higher than expected rates of venous thromboembolic events among the vaccinated cohort than general population; an excess of 11 events per 100,000 vaccinations.[15]

In the UK, by early June, 40 million first doses and 29 million second doses of ChAdOx1 nCOV-19 vaccine have been administered; nonetheless, 390 thrombotic events, including 71 fatal events have been reported. Interestingly, the cases reported low platelet counts with the presence of anti-PF4 antibodies, indicating an abnormal clotting reaction.[15] Nation-wide analysis of the Paul-Ehrlich Institute in Germany represents one of the largest cohorts of laboratory confirmed patients with VITT. The adverse drug reaction database was queried for VITT/thrombosis with thrombocytopenia syndrome (TTS) cases following ChAdOx1 nCoV-19 vaccination. [15] VITT has a high mortality and can present with isolated thrombocytopenia,

Table 1. Characteristics of epidemiological studies reporting VITT

Author	Study design days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
Thiele 2021	Retrospective analysis 69 suspected TTS	F 37 (71%) and M 15 (29%)	46.0 (range, 31.0 to 60.3)	Germany	ChAdOx1 nCoV-19	- Cerebral venous sinus thrombosis (71%) - Multiple thromboses (37%) - Twelve patients died. Non-survivors showed lower platelet counts compared to survivors. - Four patients with thrombocytopenia but without thrombosis presented with severe headache or cerebral bleeding.
Althaus 2021	8 patients (6 to 20 days)	5 F/3M	41.5 (range, 24 to 53)		ChAdOx1 nCoV-19	- Median platelet count of 46.5×10^9 /L (range, 8-92). - Three had a fatal outcome and five were successfully treated. - Autopsies showed arterial and venous thromboses in various organs and the occlusion of glomerular capillaries by hyaline thrombi. - High-titre antibodies against PF4 - Contribution of antibody-mediated platelet activation in the pathogenesis of VITT
Reilly-Stitt 2021						- Thrombosis at unusual sites - Detection of anti-PF4 antibodies
Huynh 2021	5 patients (14–40 days)	40% female	44 (range, 35 to 72)	India	single dose of the ChAdOx1 nCoV-19 vaccine	- Antibodies against PF4
Schultz et al 2021	5 patients in a population of more than 130,000 vaccinated persons (7 to 10 days)		32 to 54		ChAdOx1 nCoV-19	- High levels of antibodies to PF 4–polyanion complexes - Rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia - Severe cerebral venous thrombosis with intracranial haemorrhage, and the outcome was fatal in three. - Unusual sites and concomitant thrombocytopenia

Table 1. Continued

Author	Study design days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
Greinacher 2021	11 patients (5 to 16 days)	9F/2M	36 (range, 22 to 49)	Germany and Austria	ChAdOx1 nCov-19	- Moderate-to-severe thrombocytopenia - Unusual thrombosis, particularly cerebral venous thrombosis and splanchnic-vein thrombosis - Disseminated intravascular coagulation in 5 of the patients on the basis of the combination of greatly elevated d-dimer levels (>10.0 mg per litre) - Pulmonary embolism - Other thromboses - Of the 6 patients with available fibrinogen levels, 4 had hypofibrinogenemia.
Holm 2021	5 patients (7 to 10 days)	32 to 54	4F/1M	Oslo	ChAdOx1 nCoV-19	- Four patients had major cerebral haemorrhage and three patients died. - Increased levels of innate immune response cytokines and markers of systemic inflammation - Extensive degranulation of neutrophils, and tissue and endothelial damage. - Activation of neutrophils - Increased levels of circulating H3Cit, dsDNA, and myeloperoxidase–DNA complex.
Sessa 2021	out of 13.6 million	≤ 50	Female	US	- At least one dose of COVID-19 mRNA vaccines	- 61 cases were reported with a total of 68 thromboembolic events (1 case per 222,951 vaccinated).
Tiede 2021	Single-centre cohort (2 weeks)	Female	- 1F (41) - 4F (61 to 67)	Hannover	ChAdOx1	- Cerebral venous sinus thrombosis - Splanchnic vein thrombosis - Arterial cerebral thromboembolism, and thrombotic microangiopathy. - Elevated D-dimer - Autoantibodies against PF4

Table 1. Continued

Author	Study design days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
	3 patients			UK	First dose of ChAdOx1 nCOV-19	- Fatal thromboembolism - Low platelet counts - Presence of anti-PF4 antibodies - Pre-existing condition of thrombocytopenia due to myelodysplasia.
Mauriello 2021	23 patients (6 to 24 days)	M	58		ChAdOx1nCoV-19 vaccine	- Severe thrombocytopenia - Low fibrinogen serum levels - Marked increase of D-dimer serum levels. - Thrombi detected in the capillaries of glomerular tufts. - In the hearth, thrombi observed in veins and capillaries. - In the liver, voluminous fibrin thrombi in the branches of the portal vein. - In the brain, microthrombi in the capillaries of the choroid plexuses. - Diffuse haemorrhagic necrosis observed in the intestinal wall - Low fibrinogen serum - Very high D-dimers levels (39.000 ug/L, reference range 0-200 ug/L).
Smadja 2021	1197 cases	F:708 (59.1%)	76 (18 to 102)		Comirnaty	- Thrombotic events
Smadja 2021	325 cases	F: 173 (53.2%)	72 (19 to 102)		Moderna	- Thrombotic events
Smadja 2021	639 cases	F: 332 (52%)	67 (19 to 99)		AZD1222	- Thrombotic events
Krzywicka 2021	213 cerebral venous sinus thrombosis cases			Europe	- ChAdOx1 nCov-19 -BNT162b2 - mRNA-1273	- Thrombocytopenia in 107/187 CVST cases - Cerebral venous sinus thrombosis - Mortality was 49%.

Table 1. Continued

Author	Study design days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
Perry 2021	70 patients	F: 39 (35.71%)	47 (32 to 55)	UK	ChAdOx1 (Oxford–AstraZeneca)	- VITT - Cerebral venous thrombosis - Intracranial veins thrombosed and more frequently had extracranial thrombosis compared with non- VITT - Lowest platelet count below 150×10^9 per L - D-dimer, the highest value greater than 2,000 μg/L
Boonyawat and Angchaisuksiri	5 VITT cases	F (60%)	31	Thailand	ChAdOx1 n-CoV-19	- Severe headache - Marked thrombocytopenia, and a markedly elevated D-dimer level but no evidence of cerebral vein thrombosis
Bhuyan 2021	13 cases of TTS (14 days)		45 to 85		second dose of AZD1222	- 8 patients with pulmonary embolism, co-occurring with cerebral venous sinus thrombosis in 2 patients - 1 patient with CVST occurring alone - 1 patient with deep vein thrombosis - 1patient with thrombotic stroke - 2 patients with unspecified embolisms
Billy 2021	27 cases	60 (21 to 74)	13 F/14 M		ChAdOx1 nCov-19	- Atypical thrombosis - Of 16 patients tested, 12 were positive for anti-PF4 antibodies. - Mortality rate of 30%

Table 1. Continued

Author	Study design days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
Cari 2021	Eudravigilance	Matched	Matched		-ChAdOx1 nCoV-19 - BNT162b2	- Higher rate of thrombo-haemorrhagic events in ChAdOx1 nCoV-19 than BNT162b2 recipients. - Thrombosis and thrombocyto-penia were more frequent in young people (18–24 years) and adult females (25–60 years). - In BNT162b2 recipients, the frequency of thrombo-haemorrhagic events, was not increased compared to that in the general population.
Andrews 22	over 45 mil-lion COVID-19 vaccine eligi-ble individuals			UK	-ChAdOx1 nCoV-19 - BNT162b2	- Thrombotic episodes and thrombocytopenia in adults under 65 years of age within a month of a first dose of ChAdOx1 - Cerebral venous thromboses and venous thromboses at other sites, in those aged 15-64 years of age with the greatest elevated risk within 4- 13 days after vaccination in those aged 15-39 years. - No side effects after the BNT162b2 vaccine.
Sørvoll 2021	492 patients (11 to 35 days)			Norway	Ad26.COV2.S	- Low thrombocytopenia - Antibodies to PF4/polyanion-complexes
Tobaiqy 2021	17 million vaccinated people	F 19/M 9	57% aged over 85		ChAdOx1-S	-Thromboembolic reports was 28, of which 19 - Pulmonary embolism; one fatality to thrombosis - Immune complexes that in-cluding T cell-mediated pro-cesses

Table 1. Continued

Author	Study design days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
Pottegård et al., 2021	281,264 people (28 days)			UK	ChAdOx1 nCov-19	- Cerebral venous thrombosis - Higher rate of thrombocytopenia/coagulation
Wolf 2021	5 patients (10 days)	4F/1M	32 to 54		ChAdOx1 nCoV-19	-Thrombosis at unusual sites and thrombocytopenia - Pulmonary, abdominal, portal and intracranial thromboembolic - Mild to moderate thrombocytopenia - Intracranial venous sinus thrombosis
Hunter, 2021	6 patients				Ad26.COV2.S	- Severe thrombosis
Gras-Champel 2021	11,206 reports	13F/14M	60 (21 to 74)	France	VaxZevria®	- Coagulation disorders namely thrombocytopenia - Disseminated intravascular coagulation - Venous and/or arterial thrombosis
Pavord 2021	40 patients	F: 25	21 to 76	U.K.	- Second dose of ChAdOx1 nCoV-19 (n=5) - mRNA-1273 (n=2) - BNT162b2 (n=33).	- No symptoms after second dose - VITT after receiving their first dose of ChAdOx1 nCoV-19
Cacciola 2021	60 patients (7 days)	20 F/40M	55±10 years	Italy	ChAdOx1 nCoV-19	- Thrombocytopenia ($60±5×10^9$/L) - Longer prothrombin time (28±10 s) - Activated partial thromboplastin time (50±10 s), - Lower fibrinogen (80±20 mg/dl), higher D-dimer (550±100 mg/L).

Table 1. Continued

Author	Study design Days after vaccination	Sex (female [F] / male [M])	Age (years)	Country	Vaccine type	Adverse side effects
Lee 2022	68 patients (12 to 17 days)	F (53%)	51 (range, 30 to 69)	Canada	ChAdOx1 nCoV-19	- Three patients had thrombocytopenia and thrombosis with D-dimer levels >4.0 mg/L -- Patients with VITT were treated successfully with intravenous immunoglobulin, non-heparin anticoagulants and corticosteroids.
See 2022	57 TTS	F (69%)	44.5 (range, 18 to 70 years)	US	Ad26.COV2.S (n= 54) mRNA vaccine (n= 3)	- Venous thrombosis (98%). - Nine TTS cases (17%) had arterial thrombosis (including 8 with an accompanying venous thrombosis). - Median platelet count nadir was 32.5×10^9 cells/L - Anti-PF4 antibody ELISA test results were positive in 44 (81%), negative in 3 (6%), and not done in 7 (13%)

ELISA, enzyme-linked immunosorbent assay; PF4, platelet factor 4; HIT, heparin induced thrombocytopenia; TTS, thrombosis with thrombocytopenia syndrome; VITT, vaccine induced thrombosis with thrombocytopenia.

severe headache, and bleeding. Demonstration of platelet activating anti-PF4 immunoglobulin G (IgG) has high sensitivity for TTS and captures a wider spectrum of clinically relevant VITT, especially at low platelet counts <30,000/mL.[16] Thereafter, based on established criteria, case reports reported VITT from all over the world, cerebral venous thrombosis (CVT), CVST and TTS especially following ChAdOx1 nCoV-19 vaccine. A recent meta-analysis presented evidence suggesting the occurrence of VITT following the AstraZeneca vaccine. Clinical practice must, therefore, account for the possibility of VITT and subsequent embolic events in certain individuals' post vaccination with adenovirus-based COVID-19 vaccines.[17]

Along with ongoing research on VITT, new clinical features are appearing and new tests and treatments are proposed. Cacciola and collaborators conducted and confirmed VITT by investigating the platelet and coagulation activation using new specialized tests.[17] In addition, new clinical features are reported such as ischaemic stroke as a manifestation of VITT secondary to ChAdOx1 nCoV-19 vaccine.[18]

In comparison to US and Europe, few studies investigated VITT in Eastern, African, Latino-American and Asian populations. Only two studies described VITT cases in the Middle

East.[19] Also, few reports from Thailand described VITT after administration of the ChAdOx1 nCoV-19. Five VITT cases occurred after 15 million (10 million first doses and 5 million second doses) doses of ChAdOx1 n-CoV-19 have been administered in Thailand.[20] The incidence of VITT is estimated at 1 in 3 million. In other Asian countries, only a few cases of VITT have been reported. Current Australian data estimates that the risk of developing TTS/VITT is approximately 2–3 in 100,000 persons following the administration of an adenoviral vector vaccine.[20]

Several scientists assumed, although severe with aggressive outcomes, VITT remains a rare complication. A retrospective descriptive study, reported 54,571 adverse reactions, of which 28 were associated with thrombotic adverse reactions and many delayed reactions were classified as type III hypersensitivity reactions. The authors suggested that with 17 million people having had the ChAdOx1 nCoV-19 vaccine, these are extremely rare events. Accordingly, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee concluded that the vaccine was safe and effective and that the benefits outweigh the risks.[20] A study using nationwide population-based data from Denmark, reported that the number of VITT cases caused by the ChAdOx1 nCoV-19 vaccine did not appear to increase beyond the expected incidence rate.[21] Low prevalence of both thrombocytopenia and antibodies to PF4/polyanion-complexes were reported among four hundred and ninety-two Norwegian health care workers after vaccination with ChAdOx1 nCoV-19.[22] Major limitation of such studies was the small number of potential thrombotic adverse events, thus questioning the clinical relevance of widespread antibody testing after vaccine administration.

2.3 VITT associated with other COVID-19 vaccines

There are less reports of VITT following other approved COVID-19 vaccines. Out of 13.6 million women aged ≤ 50 years exposed to at least one dose of COVID-19 mRNA vaccines in the US, a total of 68 thromboembolic events was reported. When compared to hormonal contraceptive use, the mRNA vaccines do not show disproportional reporting of thromboembolic events in younger women.[23]

Curcio et al. reported vaccine-induced massive pulmonary embolism and thrombocytopenia following a single dose of Janssen vaccination.[23] Reported rates for TTS were 3.83 per million vaccine doses (Ad26.COV2.S). The used TTS case definition excluded cases without thrombocytopenia and included cases with negative anti-PF4 antibody.[24] VITT syndrome occurred following vaccination with Ad26.COV2.S vaccine.[24]

In late February 2021, the first report for a total of 3,263,188 injections of ChAdOx1 vaccine showed 11,206 adverse reactions in France of which 2811 were serious, unexpected, thrombotic events. There was multi-site thrombosis, associated with or without thrombocytopenia or coagulation disorders, and the study reported eight fatalities, indicating a mortality rate of 30%.[25] Five cases of prothrombotic immune thrombocytopenia have been reported after exposure to the ChAdOx1 vaccine. The spectrum of clinical manifestations included CVST, splanchnic vein thrombosis, arterial cerebral thromboembolism, and thrombotic microangiopathy.[26]

Health Security Agency (formerly Public Health England) in UK reported that none of the 40 VITT secondary to ChAdOx1 vaccine in the UK had any relapse of symptoms or severe adverse reactions after receiving the second dose of the vaccine, regardless of the vaccine received.[27] None of the 29 patients with VITT who received a second vaccination dose with an mRNA COVID-19 vaccine developed new thromboses or relevant increase in anti-PF4/heparin IgG enzyme-immunoassay optical density , regardless whether PF4-dependent platelet-activating antibodies were still present. PF4-dependent platelet-activating antibodies are transient in most patients with VITT. Those can safely receive a second COVID-19 mRNA vaccine, as part of a heterologous vaccination strategy.[27]

3. Comparison between COVID-19 vaccines in relation to VITT

An observational study assessed the CVT rate attributed to four COVID-19 vaccines approved in Europe, namely BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, and AD26.COV2.S. Data on thrombotic adverse events reported on Eudravigilance data base between January 1, 2021 and July 30, 2021, showed CVT occurring alongside thrombocytopenia for the four vaccines ranging from 3–5% to 31–44% for mRNA and adenoviral vaccines, respectively.[28] Another study from Eudravigilance European database up to April 16, 2021, compared severe adverse events related to thrombocytopenia in recipients of 20,869,192 ChAdOx1 nCoV-19 vaccine doses to 71,210,981 recipients of BNT162b2 vaccines. ChAdOx1 nCoV-19 administration was associated with a much higher frequency of severe adverse events as compared with that elicited by BNT162b2.[28] The highest risk following ChAdOx1 nCoV-19 vaccination was in young people and, likely, women of reproductive age.[28] The immune reaction promoted by the ChAdOx1 nCoV-19 vaccine may lead to not only thrombocytopenia and cerebral/splanchnic venous thrombosis but also other thrombotic and thromboembolic severe adverse events. These events are not induced by the BNT162b2 vaccine. The study may help in the evaluation of the benefit/risk profile of the ChAdOx1 nCoV-19 vaccine considering the epidemic curve present in a country.[28] Another comparison using data from VigiBase, which is the world's largest pharmacovigilance database developed and maintained by the Uppsala Monitoring Centre in Sweden, assessed clinical features of arterial and venous thrombosis after injection of BNT162b2 (1197), mRNA-1273(325) and AZD1222 (639) until 16 March, 2021.[29] They suggested that thrombotic events, including CVT, might occur in association with all three vaccines. In all, 213 CVST cases were identified: 187 after ChAdOx1 nCov-19 vaccination and 26 after a mRNA vaccination (25 with BNT162b2 and one with mRNA-1273).[29] Thrombocytopenia was reported in 107/187 CVST cases in the ChAdOx1 nCov-19 group, in none in the mRNA vaccine group and in 7/100 in the pre-COVID- 19 group.[30] Incidence rate of VITT in recipients of the ChAdOx1 vaccine is in excess to the general population, and that similar effects are not seen in recipients of BNT162b2,[30] although thrombocytopenia (without thrombosis) has been shown after BNT162b2.[30] These reports indicated that VITT is likely related to adenoviral vector-based DNA virus vaccines, but not mRNA/lipid-based vaccines. mRNA vaccines, mRNA-1273 and BNT162b2 are associated with thrombocytopenia, although typically with purpura and mucosal bleeding rather than thrombosis.[31]

A national cohort study in England assessed the risk after ChAdOx1 and BNT162b2 vaccines.[31] The incidence of events by dose in pre-defined post-vaccination risk periods relative to the unvaccinated cohort was estimated after adjustment for age, gender, co-morbidities, care home residency and health/social care worker status. The authors reported increased risk of thrombotic episodes and thrombocytopenia in adults under 65 years of age within a month of a first dose of ChAdOx1 vaccine but not after the BNT162b2.[31] Generally, estimates from such comparisons remain approximate since they are not matched for age, socioeconomic status and ethnic group.

4. Differences between VITT and HIT

A hallmark of patients with VITT is the presence of antibodies specific to PF4, resembling the immunological drug reaction HIT, which presents clinically as thrombocytopenia and thrombosis in patients who have previously been exposed to heparin.[32] The autoimmune element in VITT mimics autoimmune heparin-induced thrombocytopenia (aHIT), a well-known prothrombotic disorder caused by platelet-activating antibodies that recognise multimolecular complexes between cationic PF4 and anionic heparin.[33] In both VITT and HIT, IgG antibodies bind to PF4on the surface of platelets, resulting in widespread platelet activation. In HIT, monomeric IgG in high concentrations can trigger FcgR2A, thereby inhibiting platelet activation and aggregation by PF4/anti-PF4 immune complexes.[33] However, as most patients suffering from VITT/TTS were not previously exposed to heparin, the genesis of theanti-PF4 autoantibodies is still controversial.[34] To determine the binding site on PF4 of antibodies from patients with VITT, a study used alanine-scanning mutagenesis, and found differences in anti-PF4 antibodies binding sites.[34] The authors reported that the binding of anti-PF4 antibodies from patients with VITT (n = 5) was restricted to eight surface amino acids on PF4, all of which were located within the heparin-binding site, and that the binding was inhibited by heparin.[34] By contrast, antibodies from patients with HIT (n = 10) bound to amino acids corresponding to two different sites on PF4. VITT antibodies can mimic the heparin effect by binding to a similar sites on PF4; this allows PF4 tetramers to cluster and form immune complexes, which in turn causes FcγRIIa-dependent platelet activation.[34] This finding explains the VITT-antibody-induced platelet activation and the resemblance of HIT.

Other factors than heparin can trigger prothrombotic disorder that strongly resembles HIT, including certain polyanionic drugs. Also, both viral and bacterial infections can trigger prothrombotic syndrome in the absence of preceding exposure to any polyanionic medication.[35]

5. Potential causal factors favouring VITT

VITT pathogenesis is not fully understood and likely multifactorial. An important insight reported in investigations underpinned the multifactorial pathophysiology of VITT.[36] The presence of anti-PF4 antibodies was not sufficient to rouse clinically evident thrombosis. Generally, thrombocytopenia is attributed to infection, bone marrow suppression, lack of nutrition, genetic causes, or autoimmune processes. A large network using artificial intelligence by

Geronikolou and collaborators identified three nodes that corresponded to genes (AURKA, CD46 and CD19) expressed only in VITT, whilst *ADAM10*, *CDC20*, *SHC1* and *STXBP2* are silenced in VITT, but are commonly expressed in both COVID 19 and thrombocytopenia.[37] The calculated average node degree was immense, illustrating the complexity of VITT and confirming the importance of cytokines and PYCARD, NLP3 and P2RX7 as key potential therapeutic targets for VITT. The authors concluded that common nodes appear to be key players in illness prevention, progression, and treatment.[37]

Based on previous studies describing vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or VITT that affects one individual in 1 million people around the world, Pai and colleagues suggested a possible presence of vaccinal antigens against the specific *ADAMTS13* gene, responsible for creating a robust immune response in VITT.[37] Antibodies against PF4 have been found in VIPIT like the heparin complexes formed in heparin-induced thrombocytopenic purpura, suggesting analogous immune mechanisms.[37] Cases of thrombotic thrombocytopenic purpura were found in the elderly population following post-pneumococcal vaccination, with antigens present in the vaccine against the *ADAMTS 13* gene.[37] Interestingly, hormonal factors could be among VITT causal factors. In younger females, thrombotic events are typically associated with ovarian hyperstimulation syndrome following reproductive treatment.[37]

Although the mechanism of VITT is still unclear, the absence of relapse suggests that this phenomenon is not related to spike protein immune responses. This conclusion is consistent with that reported by Greinacher et al. who showed that the anti-PF4 antibodies detected in patients with VITT do not interact with epitopes on the spike protein and appear to be independent of the spike antibody response. Scientists identified several other hereditary or naturally occurring thrombosis factors including pulmonary embolism, deep vein thrombosis, cancer, advanced age, trauma, smoking, inherited or acquired thrombophilic states, previous thromboembolism, and hospitalisation for congestive heart failure or acute exacerbation of chronic obstructive pulmonary disease.[38] Finally, considering the resemblance of VITT with thromboembolic events, it is also plausible that VITT may be multifactorial caused by similar triggers as thrombosis. However, given the small number of subjects with similar adverse events and the diversity of clinical outcomes, it remains difficult to draw final conclusions on associations.

6. Conclusion

We aimed to review the up-to-date published literature to further understand and provide updated information on COVID-19 vaccine-related thrombosis and thrombocytopenia. Understanding VITT mechanisms and pathogenesis should provide a platform to orient future research and to optimize management of VITT.

Capsule Summary

We aimed to review the up-to-date published literature to further understand and provide updated information on COVID-19 vaccine-related thrombosis and thrombocytopenia.

Patient and public involvement

No patients were directly involved in designing the research question or in conducting the research. No patients were asked for advice on interpretation or writing up the results. There are no plans to involve patients or the relevant patient community in dissemination at this moment.

Transparency statement

The leading authors (Dr. JIS) are an honest, accurate, and transparent account of the study being reported.

Acknowledgements

None

Author Contribution

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Funding

None

Conflicts of Interest

All authors state that they have no actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations.

Provenance and peer review

Not commissioned; externally peer reviewed.

References

1. Cha Y, Jung W, Seo M, Rahmati M. The emerging pandemic recent: SARS-CoV-2. Life Cycle. 2023;3:e2.
2. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412-23.
3. Hwang J, Park SH, Lee SW, Lee SB, Lee MH, Jeong GH, et al. Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: The FAPIC score. Eur Heart J. 2021;42(39):4053-63.
4. Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med. 2021;384(23):2254-6.
5. Othman M, Baker AT, Gupalo E, Elsebaie A, Bliss CM, Rondina MT, et al. To clot or not to clot? Ad is the question-Insights on mechanisms related to vaccine-induced thrombotic thrombocytopenia. J Thromb Haemost. 2021;19(11):2845-56.
6. Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral

venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. Brain Behav Immun. 2021;95:514-7.

7. Smith L, Shin JI, Koyanagi A. Vaccine strategy against COVID-19 with a focus on the Omicron and stealth Omicron variants: Life Cycle Committee Recommendations. Life Cycle. 2022;2:e5.
8. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021;384(23):2202-11.
9. Althaus K, Möller P, Uzun G, Singh A, Beck A, Bettag M, et al. Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia. Haematologica. 2021;106(8):2170-9.
10. Reilly-Stitt C, Kitchen S, Jennings I, Horner K, Jones R, Makris M, et al. Anti-PF4 testing for vaccine-induced immune thrombocytopenia and thrombosis and heparin induced thrombocytopenia: Results from a UK National External Quality Assessment Scheme exercise April 2021. J Thromb Haemost. 2021;19(9):2263-7.
11. Wolf ME, Luz B, Niehaus L, Bhogal P, Bäzner H, Henkes H. Thrombocytopenia and intracranial venous sinus thrombosis after "COVID-19 vaccine AstraZeneca" Exposure. J Clin Med. 2021;10(8).
12. Fanni D, Saba L, Demontis R, Gerosa C, Chighine A, Nioi M, et al. Vaccine-induced severe thrombotic thrombocytopenia following COVID-19 vaccination: a report of an autoptic case and review of the literature. Eur Rev Med Pharmacol Sci. 2021;25(15):5063-9.
13. Perry RJ, Tamborska A, Singh B, Craven B, Marigold R, Arthur-Farraj P, et al. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. Lancet. 2021;398(10306):1147-56.
14. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: Population based cohort study. Bmj. 2021;373:n1114.
15. Mauriello A, Scimeca M, Amelio I, Massoud R, Novelli A, Di Lorenzo F, et al. Thromboembolism after COVID-19 vaccine in patients with preexisting thrombocytopenia. Cell Death Dis. 2021;12(8):762.
16. Thiele T, Weisser K, Schönborn L, Funk MB, Weber G, Greinacher A, et al. Laboratory confirmed vaccine-induced immune thrombotic thrombocytopenia: Retrospective analysis of reported cases after vaccination with ChAdOx-1 nCoV-19 in Germany. Lancet Reg Health Eur. 2022;12:100270.
17. Matar RH, Than CA, Nakanishi H, Daniel RS, Smayra K, Sim BL, et al. Outcomes of patients with thromboembolic events following coronavirus disease 2019 AstraZeneca vaccination: A systematic review and meta-analysis. Blood Coagul Fibrinolysis. 2022;33(2):90-112.
18. Mancuso M, Lauretti DL, Cecconi N, Santini M, Lami V, Orlandi G, et al. Arterial intracranial thrombosis as the first manifestation of vaccine-induced immune thrombotic thrombocytopenia (VITT): A case report. Neurol Sci. 2022;43(3):2085-9.
19. Sheikh S. Thrombotic thrombocytopenia and central venous sinus thrombosis post - COVID-19 vaccination and its treatment with heparin alternatives. J Coll Physicians Surg

Pak. 2021;31(7):149.
20. Pang E, Ghosh S, Chemmanam T, Grove C, Phillips T. Cerebral arterial and venous thrombosis due to COVID-19 vaccine-induced immune thrombotic thrombocytopenia. BMJ Case Rep. 2022;15(1).
21. Østergaard SD, Schmidt M, Horváth-Puhó E, Thomsen RW, Sørensen HT. Thromboembolism and the Oxford-AstraZeneca COVID-19 vaccine: side-effect or coincidence? Lancet. 2021;397(10283):1441-3.
22. Sørvoll IH, Horvei KD, Ernstsen SL, Laegreid IJ, Lund S, Grønli RH, et al. An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination. J Thromb Haemost. 2021;19(7):1813-8.
23. Sessa M, Kragholm K, Hviid A, Andersen M. Thromboembolic events in younger women exposed to Pfizer-BioNTech or Moderna COVID-19 vaccines. Expert Opin Drug Saf. 2021;20(11):1451-3.
24. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. Jama. 2021;325(24):2448-56.
25. Gras-Champel V, Liabeuf S, Baud M, Albucher JF, Benkebil M, Boulay C, et al. Atypical thrombosis associated with VaxZevria® (AstraZeneca) vaccine: Data from the French Network of Regional Pharmacovigilance Centres. Therapie. 2021;76(4):369-73.
26. d'Almeida S, Markovic S, Hermann P, Bracht H, Peifer J, Ettrich TJ, et al. Thromboembolism after Astra Zeneca COVID-19 vaccine: Not always PF4- antibody mediated. Hum Vaccin Immunother. 2023;19(2):2252239.
27. Lacy J, Pavord S, Brown KE. VITT and second doses of Covid-19 vaccine. N Engl J Med. 2022;386(1):95.
28. Abbattista M, Martinelli I, Peyvandi F. Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: Thrombosis at unusual sites. J Thromb Haemost. 2021;19(10):2554-8.
29. Smadja DM, Yue QY, Chocron R, Sanchez O, Lillo-Le Louet A. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. Eur Respir J. 2021;58(1).
30. Krzywicka K, Heldner MR, Sánchez van Kammen M, van Haaps T, Hiltunen S, Silvis SM, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: An analysis of cases notified to the European Medicines Agency. Eur J Neurol. 2021;28(11):3656-62.
31. Malayala SV, Mohan G, Vasireddy D, Atluri P. Purpuric rash and thrombocytopenia after the mRNA-1273 (Moderna) COVID-19 vaccine. Cureus. 2021;13(3):e14099.
32. Hwang SR, Wang Y, Weil EL, Padmanabhan A, Warkentin TE, Pruthi RK. Cerebral venous sinus thrombosis associated with spontaneous heparin-induced thrombocytopenia syndrome after total knee arthroplasty. Platelets. 2021;32(7):936-40.
33. Warkentin TE. High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: A review. Expert Rev Hematol. 2019;12(8):685-98.
34. Huynh A, Arnold DM, Kelton JG, Smith JW, Horsewood P, Clare R, et al. Characterization of platelet factor 4 amino acids that bind pathogenic antibodies in heparin-induced thrombocytopenia. J Thromb Haemost. 2019;17(2):389-99.

35. Warkentin TE, Makris M, Jay RM, Kelton JG. A spontaneous prothrombotic disorder resembling heparin-induced thrombocytopenia. Am J Med. 2008;121(7):632-6.
36. Terpos E, Politou M, Ntanasis-Stathopoulos I, Karalis V, Merkouri E, Fotiou D, et al. High Prevalence of Anti-PF4 Antibodies Following ChAdOx1 nCov-19 (AZD1222) Vaccination Even in the Absence of Thrombotic Events. Vaccines (Basel). 2021;9(7).
37. Mendes-de-Almeida DP, Mouta Nunes de Oliveira P, Bertollo Gomes Porto V, Saraiva Pedro R, Takey PRG, Lignani LK, et al. Vaccine-induced immune thrombotic thrombocytopenia post COVID-19 booster vaccination in Brazil: A case series. Res Pract Thromb Haemost. 2023;7(8):102243.
38. Greinacher A, Selleng K, Mayerle J, Palankar R, Wesche J, Reiche S, et al. Anti-platelet factor 4 antibodies causing VITT do not cross-react with SARS-CoV-2 spike protein. Blood. 2021;138(14):1269-77.