

## Short Communication

# Vaccine-Induced Thrombotic Thrombocytopenia (VITT) Associated with AstraZeneca Vaccine: A Comprehensive Review

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### Abstract

Several vaccines have been approved to be used during the COVID-19 pandemic. However, serious concerns have been raised due to vaccine-induced thrombotic thrombocytopenia (VITT) reported with the AstraZeneca vaccine. This study is done to assess the vaccine's safety and summarize the background, evaluation, and management of a patient with VITT. Employing a meticulous literature search on PubMed and Google Scholar using keywords such as "AstraZeneca," "COVID-19 vaccine," "Clot," "Clots," "Thrombosis," and "Thrombus formation" in various combinations, 34 resources were identified, with 11 containing primary data on 28 documented VITT cases. The analysis revealed a gender distribution of 28.6% male and 71.4% female, spanning ages 22 to 74 years (median: 36 years). VITT symptoms manifested within 1 to 17 days post-vaccination. The predominant thrombotic sites were Central Venous Thrombosis, Splenic Vein Thrombosis, and Pulmonary Embolism. Notably, 46.4% of cases showed improvement, while 53.6% resulted in fatalities. This research underscores the rare but serious risk of vaccine-induced thrombotic thrombocytopenia associated with AstraZeneca vaccination, highlighting the importance of continued vigilance and monitoring in the ongoing global vaccination campaigns.

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### Introduction

The global emergence of Coronavirus Disease 2019 (COVID-19) in Wuhan, China, in December 2019 led to an unprecedented health crisis, with over 770 million confirmed cases and 6 million deaths reported worldwide as of September 24, 2023.<sup>1</sup> Efforts to combat the virus initially relied on lockdowns and various drugs, but the pivotal role of a safe and effective vaccine became evident as the most effective strategy. The Food and

Drug Administration (FDA) authorized three vaccines—Pfizer-BioNTech, Moderna, and Janssen COVID-19 Vaccine—while the European Union approved four, including the AstraZeneca vaccine developed by Oxford University. The swift adoption of vaccines globally presented a breakthrough in pandemic control, with varying vaccination rates across countries.<sup>2</sup> With widespread vaccine usage, monitoring safety and efficacy became imperative.

AstraZeneca's ChAdOx1 nCoV-19 vaccine, developed at Oxford University, utilizes a modified chimpanzee adenovirus to code for the SARS CoV-2 spike protein, activating the immune system. Interim analysis from randomized clinical trials in the UK, Brazil, and South



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Africa indicated a 62% efficacy with two standard doses and 90% with a low dose followed by a standard dose, resulting in an overall effectiveness of 70.4% in preventing symptomatic COVID-19.<sup>3</sup>

Despite the effectiveness of COVID-19 vaccines in reducing mortality and morbidity, reported side effects, particularly with AstraZeneca, include mild reactions such as fatigue, pain at the injection site, and myalgia. Severe reactions, though extremely rare, involve anaphylaxis, blood clots, angioedema, and Guillain-Barré syndrome.<sup>3,4</sup>

Notably, concerns have arisen regarding AstraZeneca's association with abnormal clot formation, specifically cerebral thrombosis and low platelet count leading to vaccine-induced thrombotic thrombocytopenia (VITT) or thrombotic thrombocytopenia syndrome (TTS). European countries temporarily suspended AstraZeneca's use in March 2021 due to thrombosis concerns, but subsequently, vaccine distribution resumed with assurances from the World Health Organization (WHO) and European Medicine Agency (EMA) that the benefits outweigh the risks.<sup>5</sup> Reports indicated rare instances of cerebral venous thrombosis (CVT) and other thrombosis cases in the European Union and the United Kingdom.

The mechanism of VITT remains unknown, but molecular mimicry is proposed, with antibodies against spike proteins potentially cross-reacting against platelet antigens, leading to platelet activation and aggregation, resulting in thrombocytopenia and thrombus formation. This phenomenon parallels heparin-induced thrombocytopenia and is supported by the detection of anti-platelet antibodies in VITT patients.<sup>6,7</sup> VITT typically manifests 4 to 30 days post-vaccination with symptoms like severe headache, abdominal pain, and shortness of breath. Prompt medical evaluation, including CBC, imaging for thrombosis, and assessing anti-PF4, fibrinogen, and D-dimer levels, is crucial when VITT is suspected.<sup>8,9</sup>

Considering that clinical trials primarily assess vaccine efficacy, post-marketing surveillance and pharmacovigilance are vital to identifying rare side effects. This study aims to comprehensively review thrombotic reactions associated with the AstraZeneca vaccine, providing insights for understanding and managing this syndrome based on current knowledge.

## Methods

A literature search was conducted utilizing PubMed, Google Scholar, and an internal database to accomplish these objectives to identify resources and articles. The search process was carried out on June 20, 2021, and was updated on March 25, 2023, using the following Keywords: "AstraZeneca", "COVID-19 Vaccine", "Clot", "Clots", "Thrombosis", and "Thrombus formation" in isolation as well in different combinations. The literature search was limited to the articles available in English and published in peer-reviewed journals. Papers were excluded if they were written in any language other than English, had a duplicate study population, and were not peer-reviewed. We reviewed all relevant sources and decided which sources to include by consensus.

## Results

A total of 34 resources were found in the literature search, and 11 of these contained primary data. A total of 28 cases of Vaccine-Induced Thrombotic Thrombocytopenia (VITT) were identified in these studies. Among these cases, 28.6% (n=8) were male, while 71.4% (n=20) were female. The age range of the patients spanned from 22 to 74 years, with a median age of 36 years. The onset of VITT symptoms after vaccination varied, occurring anywhere from 1 day to 17 days post-vaccination. The most prevalent thrombotic site observed in these patients were Central Venous Thrombosis, followed by Splenic Vein Thrombosis and Pulmonary Embolism. Within the scope of the included studies, 46.4% (n=13) of the cases showed signs of improvement, while 53.6% (n=15) of them resulted in fatalities.

A summary of these studies is given in Table 1.

## Discussion

The incidence of clot formation post-AstraZeneca vaccination is exceptionally rare, estimated at around 6 per 100,000 vaccinations, with 28 reported cases in Europe and the United Kingdom, involving nearly 17 million doses.<sup>10</sup> Data from Denmark and Norway, covering 280,000 vaccinated individuals, reported 11 adverse events per 100,000 vaccinations.<sup>11</sup> Case series from Norway, Germany, and Austria outlined patients developing clotting abnormalities and thrombocytopenia within 5-30 days of AstraZeneca vaccination.<sup>6,12</sup>

Compared to AstraZeneca, other vaccines like Moderna

**Table 1:** CVT, Cerebral venous thrombosis; SVT, splanchnic venous thrombosis; PE, pulmonary embolism.

Sr #	Authors	Sample size	Age	Sex	Days after vaccination	Clinical Site of Thrombosis	outcome
1	J. Helms et al	01	74	Male	1	CVT	improved
2	Bjørnstad-Tuveng et al	01	30	Female	3	CVT	Expired
3	Andreas Greinacher et al	11	Median age e36 years (range 22-49)	9=female 2= male	5-16 days	CVT=09 SVT= 03 PE=03	6 expired 5 improved
4	Nina H. Schultz et al.	05	37	F	8	CVT	Expired
			42	F	10	CVT	Expired
			32	M	7	SVT	Improved
			39	F	10	CVT	Improved
			54	F	07	CVT	Expired
5	Marc E Wolf et al.	03	22	F	04	CVT	Improved
			46	F	13	CVT	Improved
			36	F	17	CVT	Improved
6	Puja R. Mehta	02	32	M	09	CVT	Expired
			25	M	06	CVT	Expired
7	Massimo Franchini	01	50	M	07	CVT	Expired
8	Vincenzo D'Agostino	01	54	F	12	CVT	Expired
						Vein of Galen, myocardial infarction, aortic arch, portal vein, and subhepatic vein	
9	RA Blauenfeldt et al.	01	60	F	09	MCA	Expired
10	Antonios Bayas	01	55	F	10	Ophthalmic vein MCA	Improved
11	Maaïke Vierstraete et al	01	49	M	09	Aortic Right femoral	Improved

and Pfizer reported fewer cases of deep vein thrombosis, with 29 and 13 cases, respectively, from February 17 to March 12, 2021.<sup>10,13</sup> However, considering the background incidence of clot formation (56-182 per 100,000 population), establishing a clear causal link between AstraZeneca and thrombosis is challenging due to limited data, under-reporting, and confounding factors.<sup>13</sup> Larger cohort studies are needed for a comprehensive understanding.

Vaccine-Induced Thrombotic Thrombocytopenia (VITT) symptoms typically onset 1 to 17 days post-vaccination, presenting as severe or recurrent headache, vomiting, abdominal pain, shortness of breath, chest pain, limb pain or swelling, or visual changes within 4-30 days.<sup>8,9</sup> Symptoms within 24-48 hours post-vaccination, like fever or headache, are normal immune responses and not indicative of VITT.

In cases of suspected VITT, urgent medical evaluation is crucial, involving a complete blood count (CBC),

peripheral smear, and imaging for thrombosis. VITT patients exhibit thrombocytopenia, high anti-PF4 levels, decreased fibrinogen, and elevated D-dimers. Imaging depends on specific symptoms, with CT or MR venography for headaches or visual changes and contrast-enhanced abdominal CT for abdominal complaints.<sup>8,14</sup> The proposed mechanism involves molecular mimicry, where spike protein antibodies cross-react with platelet antigens, aligning with the observed timing of VITT occurrence and associations with other autoimmune diseases linked to COVID-19.<sup>6</sup>

While resembling Heparin-Induced Thrombocytopenia (HIT) in platelet activation and consumption, VITT presents unique features. No prior heparin exposure is noted, and thrombotic events occur at unusual sites. Research is warranted to identify risk factors and understand genetic predisposition in VITT pathogenesis.<sup>6,15</sup>

Treatment recommendations for VITT, extrapolated from HIT, include avoiding heparin, platelet transfusion,

anticoagulation, and intravenous immunoglobulin (IVIG). Non-heparin anticoagulants like fondaparinux, argatroban, and apixaban are options. Treatment initiation based on pending anti-PF4 results is acceptable if suggestive clinical presentation, CBC, and imaging are present, but confirmatory testing before IVIG is essential. No data supports corticosteroid administration; plasma exchange may be considered if no improvement is seen despite anticoagulation and IVIG. Outcomes for described patients were generally favorable.<sup>8,9,14</sup>

Acknowledging limitations, including a limited number of documented events, under-reporting, and confounders, this review provides valuable insights into AstraZeneca vaccine-related thrombosis. We conclude that, weighing benefits and risks, AstraZeneca COVID-19 vaccine administration should continue due to its overall benefits outweighing risks. Careful consideration for patients with thrombotic history is advised. Prompt symptom recognition, urgent evaluation, and collaboration with experts are crucial. Enhanced adverse effects reporting and further research are needed to refine our understanding of this rare phenomenon.

## Conclusion

AstraZeneca COVID-19 vaccine developed by Oxford is a very safe and effective vaccine against COVID-19. Most of the side effects are mild and do not require any treatment. Therefore, it is being used on a very large scale. However, concerns have been raised against the development of vaccine-induced thrombotic thrombocytopenia. This side effect is very serious but extremely rare and presents with thrombosis at unusual sites, and low platelets count.

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## References

1. COVID-19 Weekly Epidemiological Update (Edition 159 published 29 September 2023) - World | ReliefWeb [Internet]. [cited 2024 Jan 9]. Available from: <https://reliefweb.int/report/world/covid-19-weekly-epidemiological-update-edition-159-published-29-september-2023>
2. Government of Pakistan [Internet]. 2023 [cited 2023 Mar 25]. Vaccine statistics. Available from: <https://covid.gov.pk/vaccine-details>
3. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*. 2021;397(10269):99–111.
4. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *The Lancet*. 2020;396(10267):1979–93.
5. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. *BMJ*. 2021;372(2):n699.
6. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *New England Journal of Medicine*. 2021;384(22):2092–101.
7. 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. *New England Journal of Medicine* [Internet]. 2021; 384(23):2202–11. Available from: <https://doi.org/10.1056/NEJMoa2105385>
8. international society on thrombosis and haemostasis (ISTH) [Internet]. [cited 2021 Apr 20]. ISTH Interim Guidance for the Diagnosis and Treatment on Vaccine Induced Immune Thrombotic Thrombocytopenia (Updated 20 April, 2021). Available from: [https://cdn.ymaws.com/www.isth.org/resource/resmgr/ISTH\\_VITT\\_Guidance\\_2.pdf](https://cdn.ymaws.com/www.isth.org/resource/resmgr/ISTH_VITT_Guidance_2.pdf)
9. Guidance produced by the Expert Haematology Panel (EHP) focussed on Vaccine induced Thrombosis and Thrombocytopenia (VITT) [Internet]. 2021 [cited 2021 Jun 13]. Available from: <https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt>
10. Tobaiqy M, Elkout H, MacLure K. Analysis of Thrombotic Adverse Reactions of COVID-19 AstraZeneca Vaccine Reported to EudraVigilance Database. Vol. 9, *Vaccines*. 2021.
11. 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.
12. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA,



- Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *New England Journal of Medicine* [Internet]. 2021 Apr 9;384(22):2124–30. Available from: <https://doi.org/10.1056/NEJMoa2104882>
13. European medicine agency [Internet]. [cited 2021 Jun 12]. European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use. Available from: [https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-access-eudravigilance-data-medicinal-products-human-use-revision-4\\_en.pdf](https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-access-eudravigilance-data-medicinal-products-human-use-revision-4_en.pdf)
  14. James B. Bussel, Jean M. Connors, Douglas B. Cines, Cynthia E. Dunbar, Laura C. Michaelis, Lisa Baumann Kreziger, Agnes Y. Y. Lee, and Ingrid Pabinger-Fasching. Vaccine-induced Immune Thrombotic Thrombocytopenia [Internet]. Available from: <https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia>
  15. 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. *Therapies*. 2021;76(4):369–73.
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