



Vaccine-induced thrombotic thrombocytopenia: the elusive link between thrombosis and adenovirus-based SARS-CoV-2 vaccines

Rossella Marcucci¹ · Marco Marietta²

Received: 16 May 2021 / Accepted: 9 June 2021 / Published online: 30 June 2021
© Società Italiana di Medicina Interna (SIMI) 2021

Abstract

The amazing effort of vaccination against COVID-19, with more than 2 billion vaccine doses administered all around the world as of 16 June 2021, has changed the history of this pandemic, drastically reducing the number of severe cases or deaths in countries where mass vaccination campaigns have been carried out. However, the people's rising enthusiasm has been blunted in late February 2021 by the report of several cases of unusual thrombotic events in combination with thrombocytopenia after vaccination with ChAdOx1 nCov-19 (Vaxzevria), and a few months later also after Ad26.COV2.S vaccines. Of note, both products used an Adenovirus-based (AdV) platform to deliver the mRNA molecule - coding for the spike protein of SARS-CoV-2. A clinical entity characterized by cerebral and/or splanchnic vein thrombosis, often associated with multiple thromboses, with thrombocytopenia and bleeding, and sometimes disseminated intravascular coagulation (DIC), was soon recognized as a new syndrome, named vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS). VITT was mainly observed in females under 55 years of age, between 4 and 16 days after receiving only Adenovirus-based vaccine and displayed a seriously high fatality rate. This prompted the Medicine Regulatory Agencies of various countries to enforce the pharmacovigilance programs, and to provide some advices to restrict the use of AdV-based vaccines to some age groups. This point-of view is aimed at providing a comprehensive review of epidemiological issues, pathogenetic hypothesis and treatment strategies of this rare but compelling syndrome, thus helping physicians to offer an up-to dated and evidence-based counseling to their often alarmed patients.

Keywords COVID-19 · Vaxzevria · Vaccine-Induced Thrombotic Thrombocytopenia · Heparin-Induced Thrombocytopenia · COVID-19 Vaccine Janssen

Background

The still ongoing history of vaccination against COVID-19 looked like a roller coaster ride for people's expectations.

The unprecedented fast development of vaccines has kindled hope of having finally found the way out of pandemic. The rising enthusiasm has been blunted in late February 2021 by the report of several cases of unusual thrombotic events in combination with thrombocytopenia after vaccination with ChAdOx1 nCov-19 (Vaxzevria).

Following that report, in mid-March, several European countries paused distribution of the COVID-19 vaccine made by the University of Oxford and the pharmaceutical firm AstraZeneca.

The review of data analyses from European system of pharmacovigilance EudraVigilance (EUDRA) pointed to signals of atypical thromboembolism (i.e., cerebral vein sinus [CVT] and/or splanchnic vein thrombosis [SVT] and arterial thrombosis [AT]), with or without thrombocytopenia, mainly occurring in women below 60 years old, with a typical time-to-onset within 2 weeks following vaccination.

On 7 April 2021, European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that a causal relationship between vaccination with Vaxzevria and adverse events of thrombosis in combination with thrombocytopenia (TTS) was at least a reasonable possibility but confirmed that the overall benefits of Vaxzevria in the prevention of COVID-19 outweighed the

✉ Marco Marietta
marco.marietta@unimore.it

¹ Department of Experimental and Clinical Medicine, "Careggi" University Hospital, University of Florence, Florence, Italy

² Hematology Unit, Azienda Ospedaliero-Universitaria, via del Pozzo 71, 41124 Modena, Italy

risks from adverse events including thrombosis in combination with thrombocytopenia [1].

The European countries then resumed vaccinations, although Germany, Spain and Italy restricted the use of Vaxzevria to people over 60 years, UK to those over 30 and France to subjects more than 55 years old.

By April 12, 2021, 6 cases of CVST with thrombocytopenia were identified among the recipients of approximately 7 million Ad26.COVID-19 S vaccine doses in the US, resulting in a temporary pause in vaccination with this product on April 13, 2021 in US and Europe [2]

Following a thorough safety review, the U.S. Food and Drug Administration (FDA), the U.S. Centers for Disease Control and Prevention (CDC) and the PRAC determined that the use of the Ad26.COVID-19 S vaccine should resume.

As a precautionary measure, the Italian Medicine Agency (AIFA) recommended the preferential use also of this vaccine in people more than 60 years old.

What are we talking about?

A recent paper from Denmark showed that, altogether, the cases of venous thromboembolisms reported in relation to the Vaxzevria vaccine did not exceed the expected incidence rate [3].

However, very rare cases of a peculiar syndrome, characterized by cerebral and/or splanchnic vein thrombosis, often associated with multiple thromboses, with thrombocytopenia and bleeding, and sometimes disseminated intravascular coagulation (DIC), occurring in otherwise healthy subjects have been reported [4–8].

This syndrome, named vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS), was mainly observed in females under 55 years of age, between 4 and 16 days after receiving the Vaxzevria and in a few more cases after Ad26.COVID-19 S vaccine [9] and displayed a seriously high fatality rate.

But the true question is: how actually rare is this rare syndrome, very intriguing for researchers, but very troubling for common people?

COVID-19 vaccines have been tested in clinical trials with thousands of participants before governments authorized their widespread use. However, even the largest clinical trials are not sized to detect extremely rare side effects, which might occur in fewer numbers than one case per 100,000 vaccinations. Now, more than a billion of people have been vaccinated against COVID-19, and it is not surprising that even very rare adverse events, such as VITT, can appear in safety reports.

Table 1 summarizes the cases of major thromboembolic events reported by the involved Regulatory Agencies.

These data deserve some further comments.

First, the incidence of VITT reported in Table 1 refers to the entire population of vaccinated subjects. A higher incidence rate following the first dose of Vaxzevria has been reported in the younger adult age groups (18–49 years) compared to the older ones (over 50 years): 18.0 vs. 10.2 per million doses, respectively. Moreover, there is evidence that the incidence rate is higher in females compared to men, although this is not seen across all age groups and the difference remains small.

On the other hand, in balancing risks and benefits, it should be also considered that COVID-19 seems per se

Table 1 Cases of VITT reported by Regulatory Agencies

	MHRA Cases as of May, 26	EUDRA Cases as of April, 21	VAERS Cases as of May, 7
	VAXZEVRIA	VAXZEVRIA	Ad26.COVID-19 S
Cerebral venous sinus thrombosis with thrombocytopenia	128 cases (average age 46 years)		28 cases (median age 40 years; range 18–59 years)
Other major thromboembolic events with thrombocytopenia	220 (average age 54.5 years)	142 cases	–
Estimated Case incidence	13.6 per million doses (348/24.3 million doses ^a)	5.68 per million doses (142/25 million doses ^b)	3.2 per million doses (28/8.7 million doses ^c)

MHRA UH Government Medicines & Healthcare products Regulatory Agency; EUDRA European system of pharmacovigilance EudraVigilance; VAERS U.S. Vaccine Adverse Event Reporting System

^a18 cases reported per 13.4 million second doses (estimated case incidence: 1.3 per million doses). <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>

^bData as of May, 1. https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf

^c<https://www.cdc.gov/vaccines/acip/meetings/slides-2021-05-12.html>

to increase the risk of atypical venous thromboembolism. Indeed, an incidence of first-diagnosed CVT in COVID-19 patients of 35.3 per million (95% CI 22.6–55.2) has been found, significantly higher than that observed in a matched cohort of patients with influenza (RR = 3.83, 95% CI 1.56–9.41, $P < 0.001$) or people who received an mRNA vaccine (RR = 6.67, 95% CI 1.98–22.43, $P < 0.001$) [4]. In the same study, the incidence of first-diagnosed Portal Vein Thrombosis (PVT) in COVID-19 patients was 175.0 per million (95% CI 143.0–214.1), significantly higher than that reported in a matched cohort of patients with influenza (RR = 1.39, 95% CI 1.06–1.83, $P = 0.02$) and people who received an mRNA vaccine (RR = 7.40, 95% CI 4.87–11.24, $P < 0.001$) [10].

In this context, a causal relationship between vaccination and these adverse events has been considered “plausible” by the PRAC of the EMA Agency [11].

This cautious approach makes sense, because the VITT only partially meets the Bradford Hill’s Criteria conventionally requested to “pass from an observed association to a verdict of causation” [12].

Among them, that of biological plausibility is probably the most intriguing one, as raises the issue of which mechanism could induce an apparently paradoxical coexistence of thrombosis and thrombocytopenia.

What could the connection be between blood clots and vaccines?

The association between thrombocytopenia and thrombosis, with a catastrophic clinical picture demonstrating both venous and arterial thromboses, raised rapidly the attention of clinicians. It was soon clear that we were facing a new disease, probably associated with a trigger linked to Adenovirus-Based SARS-CoV-2 Vaccines. The fact that these clinical pictures were not observed after mRNA vaccines put adenoviruses in the dock. The subsequent reports of similar cases associated with Janssen Vaccine, reinforced this hypothesis.

The binomial constituted by thrombocytopenia and thrombosis is very rare in medicine. We can recognize it in (a) Thrombotic thrombocytopenic purpura—together with anemia and hemolysis signs; (b) Heparin-induced thrombocytopenia and autoimmune HIT; (c) Catastrophic Antiphospholipid Syndrome [13]; (d) disseminated intravascular coagulation—together with signs of clotting factors consumption. The latter, however, represents a condition which can complicate several diseases associated with clotting activation, and does not represent a ‘per se’ disease.

Quickly it emerged the HIT hypothesis as the most plausible one. The time window for symptoms onset—between

4 and 16 days—comparable to that seen in HIT corroborated the hypothesis.

HIT is a rare immune-mediated adverse drug reaction occurring after exposure to heparin [14]. It is a serious and potentially fatal condition, which may be associated with the development of arterial or venous thrombotic events. From a pathophysiologic point of view, circulating molecules of heparin bind to platelet factor 4 (PF4), a plasmatic positively charged protein released upon platelet activation. PF4 normally binds to negatively charged glycosaminoglycans on the endothelium, displacing anti-thrombin and thus activating coagulation. However, PF4 binds with greater affinity to heparin/PF4 complexes, which become “neoantigens” and induce the formation of antibodies against them. Heparin-PF4-IgG immune complexes activate platelets through their FcγRIIA receptors, causing their activation, aggregation and the additional release of PF4, thus determining a positive feedback loop of further platelet activation. Pre-test clinical probability, screening for anti-PF4/heparin antibodies and documentation of their platelet activating capacity are the cornerstones of diagnosis. Both immunoassays—to detect the presence and quantify the titer of PF4-heparin antibodies—and functional assays—to assess the ability of anti-PF4-heparin antibodies to bind and activate platelets in the presence of heparin, are needed to confirm the diagnosis.

The time window for symptoms onset, the presence of both thrombocytopenia and thrombosis, with venous and arterial localizations, are the points which are similar between HIT and VITT. In the first cases described in Europe, the lethality was very high (about 20%) differently from that we usually observe in HIT. Furthermore, in a significant proportion of patients with VITT, the disease was complicated by DIC, with the presence of very low levels of platelet count (in the majority of cases $< 20,000/\text{mmc}$). These characteristics make this clinical entity more similar to autoimmune HIT with respect to classical HIT. Autoimmune HIT [15], in fact, is often complicated by DIC and it is characterized by a very low platelet count. Autoimmune HIT is the term adopted to define form of HIT in which the previous exposure to heparin is not always present: in these cases, we can demonstrate the presence of both heparin-dependent and heparin-independent antibodies activating platelets. In autoimmune HIT, some case reports [16] document the clinical efficacy of high-dose IgG administration which, conversely, is not routinely used in classical HIT. PF4 also binds to polyanions expressed on the cell wall of a wide variety of Gram-negative and Gram-positive bacteria and plays a role in bacterial host defense. Binding of PF4 to polyanions results in its conformational change. These antibodies are associated in the general population with the presence of chronic bacterial infections such as periodontal disease [17]. There is a continuum of clinical sequelae resulting from anti-PF4/polyanion antibodies (anti-PF4/P-ABS): the

majority of individuals remain asymptomatic, while in HIT, anti-PF4/P-ABS activate platelets and the clotting system, resulting in life-threatening thrombotic complications when patients receive the polyanion heparin. Anti-PF4/P-ABS are also induced after major surgery without heparin treatment when mechanical compression devices are used for thrombosis prophylaxis [18]. In this case, continuous tissue compression likely acts as danger signal.

The extreme sequela is autoimmune HIT, in which individuals develop multiple vessel occlusions without any drug exposure. Typically, in these patients, PF4/P-ABS are found by enzyme-linked immunoassay (EIA) at very high titers and activate platelets in the absence of polyanions in functional assays.

On April 9, 2021, two papers were published reporting two EU case series of patients affected by this condition, named for the first-time VITT [4, 5]. In both papers, authors were able to document the presence of circulating antibodies able to activate platelets.

Two very recently published paper brought some more knowledge about the plausible sequence of events leading to VITT.

Mc Gonagle and Colleagues suggested that the local tissue micro-trauma following vaccine inoculation brings adenoviral DNA in contact with PF4, with substantially increased anti-PF4 autoantibody production in susceptible subjects [19]. The high-titer circulating autoantibodies against PF4 may lead to immuno-thrombosis in specific sites of susceptibility, such as the portal and the cerebral vein circulation, where an extensive platelet factor 4 (PF4)-viruses/microbiota interaction is already existing to ensure the normal immunity and antigen clearance.

Another postulated mechanism is based on the availability of soluble Spike protein variants in a systemic fashion as a result of alternative splice events [20]. These soluble Spike variants can bind to ACE2 expressing endothelial cells, which in turn may trigger an Antibody Dependent Cell-mediated Cytotoxicity (ADCC) or Complement-Dependent Cytotoxicity (CDC).

It can be assumed that this pathological phenomenon most probably will take place in those vessels where such soluble Spike protein variants can accumulate because of a non-unidirectional blood flow, i.e. the cerebral venous sinuses [20].

Whatever the pathogenic mechanism of VITT is, in order to document and diagnose this rare syndrome, besides clinical features (thrombocytopenia plus thrombosis with multiple localizations, mainly cerebral vein thrombosis and splanchnic thrombosis), laboratory should demonstrate the presence of antibodies anti-PF4 and, possibly, the ability of activating platelets. Unfortunately, not all immunological assays for detecting Ab anti-PF4/heparin have the same ability to detect also these VITT antibodies (6) and the

administration of i.v. IgG might mask the functional ability of activating platelets.

Which laboratory test, if any, is needed before or after vaccination?

No data are available on the possible utility of a laboratory test before vaccination. In fact, no correlation has been demonstrated between the onset of this reaction and laboratory evaluation, for example, of markers of clotting function, such as PT or aPTT. Similarly, the evaluation of platelet count has no role in this setting before or after vaccination. We know that vaccination may be associated with an aspecific reduction in platelet count, but this mechanism is absolutely different from that described in VITT. Therefore, the identification of a weak reduction in platelet number should generate unjustified alarmism and medical intervention. In classical HIT, which represents our model in this context, a high proportion of patients exposed to heparin develop antibodies anti-PF4/heparin, but only a small part of them develop antibodies able to activate platelets and to determine thrombotic manifestations.

At the time of writing this paper, we have to discourage clinicians from any kind of laboratory test before vaccination, to possibly identify patients at higher risk of developing VITT.

How to manage the Vaccine-Induced Thrombotic Thrombocytopenia?

Faced to the severity of VITT, and to the lack of evidence about its management, many scientific societies provided guidance helping physicians to tackle such a pathophysiological entity [21–23].

Table 2 summarizes the main recommendations provided by these societies.

It must be noted that we are dealing with weak recommendations, based only on experts' consensus.

This is expected given the rareness of this disease, that foreclose to collect evidences stronger than these provided by case series studies.

Moreover, we have to be remember that because of the wide spread of vaccination procedures, also physicians not expert in thrombo-hemorrhagic disorders should have to face patients with suspected or confirmed VITT. To this end, a conceptual framework like this can be very useful to allow a more timely and standardized approach to this compelling disease.

Table 2 How to manage VITT**Suspect**

Patient presenting symptoms suggestive of atypical venous or arterial thromboembolism, such as:

Cerebral sinus vein thrombosis (CSVT):

- Persistent and severe headache
- Focal neurological symptoms
- Seizures, or blurred or double vision

Pulmonary embolism or acute coronary syndrome:

- Shortness of breath or chest pain
- Splanchnic vein thrombosis
- Abdominal pain

Deep vein thrombosis or acute limb ischemia:

- Limb swelling, redness, pallor, or coldness

And

- A platelet count $\leq 150,000/\text{mmc}$
- Within 28 days after COVID-19 vaccination

Confirm

Perform rapid assessment for the presence of thrombosis at sites other than that leading to hospitalization (e.g. by total body angio-computed tomography scan). Please note that imaging to rule out CVST includes also vascular imaging, either with a CT head/CT venogram or MR head/MR venogram. This potential diagnosis should be investigated urgently with same-day neuroimaging

Perform hemostatic screening for DIC along with a complete blood count

Assess anti-PF4 antibodies

Consult a Hemostasis and Thrombosis Expert

Treat

Admit the patient to an Intensive Care or High Dependency Unit, to achieve a more intensive observation, treatment and nursing care than that provided in a general ward

If platelet count is $< 50,000/\text{mmc}$, treat thrombocytopenia to allow starting anticoagulant therapy:

i.v. Ig (1 g/kg/day for 2 days) and dexamethasone (40 mg/day for 4 days)

Consider platelet transfusion after i.v. Ig in case of life-threatening bleeding

Consider plasmapheresis or plasma-exchange in most severe cases, unresponsive to the above measures,

Avoid heparin and low-molecular weight heparin unless positivity for anti-PF4 has been ruled out

Adjust the intensity of anticoagulant treatment according to the platelet count:

Platelet $< 20.000/\text{mmc}$:

Avoid anticoagulation

Platelet 20–50.000/mmc:

Fondaparinux 2.5/5 mg (bw $</>$ 50 kg)

Argatroban (aPTT Ratio 1.5; to be preferred is GFR < 30 ml/min or ICH)

Platelet 50–100.000/mmc:

Fondaparinux 5/7.5 mg (bw $</>$ 50 kg)

Argatroban (aPTT Ratio 1.5–2.5; to be preferred is GFR < 30 ml/min or ICH)

Platelet $> 100.000/\text{mmc}$:

Fondaparinux 5/7.5/10 mg (bw $< 50/50–100/ > 100$ kg)

Argatroban (aPTT Ratio 1.5; to be preferred is GFR < 30 ml/min or ICH)

Direct Oral anticoagulants are not advised for being off-label for this indication in some countries, for difficult dosage management and problems of administration in unconscious subjects

Consider FFP (15–20 ml/kg) if consumption coagulopathy with bleeding and PT or aPTT Ratio > 1.5

Consider Fibrinogen concentrate (2 g) if the patient is actively bleeding and plasma fibrinogen level is < 1.5 g/L despite FFP administration

bw body weight; *aPTT* activated Partial Thromboplastin Time; *GFR* Glomerular Filtration Rate; *ICH* IntraCranial Hemorrhage; *FFP* Fresh Frozen Plasma

Conclusion and future perspectives

This time of pandemic has been a hard one, and an often-confusing information has certainly contributed to make it even harder.

Now, one of the main physicians' responsibilities is to provide patients with a scientifically sound, evidence-based and fair counseling to cope in the best way with their questions and concerns about the issue of vaccination.

The undeniable basis is that the expected benefits of the vaccines in preventing COVID-19 and serious complications associated with it far outweigh any currently known side effects, as very effectively displayed by EMA on its institutional site [24].

Indeed, it should not be forgotten that COVID-19 is very serious disease, which per se promotes a hypercoagulable state leading to a substantial risk of thromboembolic events and death in affected patients [25].

Therefore, physicians must strongly endorse the practice of vaccination in all patient, trusting the reliability of Regulatory Agencies to assess the safety of any drugs, including those very speedily developed, such as the COVID-19 vaccines. Indeed, Pharmacovigilance Systems have displayed an extraordinary responsiveness in noticing even small signals of rare serious events related to COVID-19 vaccines.

Although EMA's safety committee (Pharmacovigilance Risk Assessment Committee, PRAC) concluded on April 14 that a causal relationship between vaccination with Vaxzevria and very rare cases of VITT is plausible, several questions about this issue still remain unanswered, first of all that about the safety of the second dose of Vaxzevria or Ad26.COV2. S.

Indeed, an increased risk of VITT with the second dose could be possible due to boosting of potential anti-PF4 antibodies that were elicited (subclinical) following the first dose.

On the other hand, persons who have not developed this complication following the first dose may also be less likely to develop it after the second dose, because of the well-known phenomenon of depletion of susceptibles.

As reported in Table 1, the overall incidence after second doses was about 1.3 per million doses. Currently, no cases following a second dose have been reported in patients aged 18–49 years with an estimated 2.7 million in this age group having received both doses, although the time for follow-up and identification of cases in this cohort is more limited as compared to that of subjects having received the first one.

Moreover, a very recent paper reported a very low prevalence of 1.2% (95% CI: 0.4–2.2) of antibodies to PF4/polyanion complexes among Norwegian health care workers after vaccination with the first dose of Vaxzevria (6 positive individuals among 492 health care workers tested 10–35 days

post vaccination, all with platelet count > 150,000/mm³). In the same cohort, 8 subjects had reduced platelet counts, all above 100,000/mm³. No subjects had severe thrombocytopenia [26].

Although this data sounds quite reassuring, the Regulatory Agencies continue a strict monitoring of the vaccine's safety, collecting more information about serious adverse events following vaccine administration.

By this huge effort, it will be possible to further improve the already excellent safety profile of vaccines, not only by a population point of view, but also by a more individualized approach, whenever specific risk factors could be reliably assessed.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights Not applicable.

Informed consent Not applicable.

References

- EMA news. Available at: <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>. Accessed on May, 1st, 2021.
- <https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough>
- Østergaard SD, Schmidt M, Horváth-Puhó E et al (2021) Thromboembolism and the Oxford–AstraZeneca COVID-19 vaccine: side-effect or coincidence? *Lancet*. [https://doi.org/10.1016/S0140-6736\(21\)00762-5](https://doi.org/10.1016/S0140-6736(21)00762-5)
- Greinacher A, Thiele T, Warkentin TE et al (2021) Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2104840>
- Schultz NH, Sørvoll IH, Michelsen AE et al (2021) Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2104882>
- Scully M, Singh D, Lown R et al (2021) Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2105385>
- Tiede A, Sachs UJ, Czwalińska A et al (2021) Prothrombotic immune thrombocytopenia after COVID-19 vaccine. *Blood*. <https://doi.org/10.1182/blood.2021011958>
- Turi MC, Spitaleri F, Gori AM, Parruti G, Rogolino AA, Albani A, Giusti B, Agostinone L, Cesari F, Ranalli P, Pulini S, Di Gioacchino G, Paganelli R, Marcucci R (2021) A case of vaccine-induced immune thrombotic thrombocytopenia (VITT) with massive artero-venous thrombosis. *Blood Transfus*. <https://doi.org/10.2450/2021.0131-21>
- See I, Su JR, Lale A, Woo EJ et al (2021) US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. *JAMA*. <https://doi.org/10.1001/jama.2021.7517>

10. Torjesen I (2021) Covid-19: Risk of cerebral blood clots from disease is 10 times that from vaccination, study finds. *BMJ* 16(373):n1005. <https://doi.org/10.1136/bmj.n1005>
11. European Medicines Agency. COVID-19 vaccine safety update. VAXZEVRIA AstraZeneca AB. 2021 April, 14th. Available at: https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-14-april-2021_en.pdf. Accessed on May, 9, 2021.
12. Hill AB (1965) The environment and disease: association or causation? *Proc R Soc Med* 58:295–300
13. Pontara E, Cheng C, Cattini MG, Bison E, Pelloso M, Denas G, Pengo V (2019) An in vitro model to mimic the thrombotic occlusion of small vessels in catastrophic antiphospholipid syndrome (CAPS). *Lupus* 28:1663–1668. <https://doi.org/10.1177/0961203319886915>
14. Marcucci R, Berteotti M, Gori AM et al (2021) Heparin induced thrombocytopenia: position paper from the Italian Society on Thrombosis and Haemostasis (SISIT). *Blood Transfus* 19(1):14–23
15. Greinacher A, Selleng K, Warkentin TE (2017) Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost* 15:2099–2114
16. Gonzales M, Pipalia A, Weil A (2019) Refractory heparin-induced thrombocytopenia with cerebral venous sinus thrombosis treated with IVIg, steroids, and a combination of anticoagulants: a case report. *J Investig Med High Impact Case Rep* 7:2324709619832324
17. Greinacher A, Holtfreter B, Krauel K et al (2011) Association of natural anti-platelet factor 4/heparin antibodies with periodontal disease. *Blood* 118(5):1395–1401
18. Bito S, Miyata S, Migita K et al (2016) Mechanical prophylaxis is a heparin-independent risk for anti-platelet factor 4/heparin antibody formation after orthopedic surgery. *Blood* 127(8):1036–1043
19. McGonagle D, De Marco G, Bridgewood C (2021) Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection. *J Autoimmun* 19(121):102662. <https://doi.org/10.1016/j.jaut.2021.102662>
20. Kowarz E, Krutzke L, Reis J, Bracharz S, Kochanek S, Marschalek R (2021) “Vaccine-induced Covid-19 mimicry” syndrome: splice reactions within the SARS-CoV-2 Spike open reading frame result in Spike protein variants that may cause thromboembolic events in patients immunized with vector-based vaccines. *Res Square*. <https://doi.org/10.21203/rs.3.rs-558954/v1>
21. British Society for Haematology. Expert Haematology Panel (EHP) Guidance on Vaccine induced Thrombosis and Thrombocytopenia (VITT). Available at: <https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focus-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt>. Accessed on May 2nd, 2021.
22. Gresele P, Marietta M, Ageno W et al (2021) Management of cerebral and splanchnic vein thrombosis associated with thrombocytopenia in subjects previously vaccinated with Vaxzevria (AstraZeneca): a position statement from the Italian Society for the Study of Haemostasis and Thrombosis (SISIT). *Blood Transfus*. <https://doi.org/10.2450/2021.0117-21>
23. American Society of Hematology. Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia). Available on line at: <https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia>. Accessed on May 2nd, 2021.
24. European Medicines Agency. AstraZeneca’s COVID-19 vaccine: benefits and risks in context. Available online at: <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context>. Accessed on May, 7th, 2021.
25. Marietta M, Coluccio V, Luppi M (2020) COVID-19, coagulopathy and venous thromboembolism: more questions than answers. *Intern Emerg Med* 15(8):1375–1387. <https://doi.org/10.1007/s11739-020-02432-x>
26. Sørvoll IH, Horvei KD, Ernsten SL et al (2021) 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*. <https://doi.org/10.1111/jth.15352>

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.