



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Thrombocytopenia after COVID-19 vaccination

Kristian Kragholm^{a,b,*}, Maurizio Sessa^c, Thomas Mulvad^d, Mikkel Porsborg Andersen^e, Helle Collatz-Christensen^{f,g}, Stig Nikolaj Blomberg^f, Freddy Lippert^f, Soren Mikkelsen^h, Peter Leutscherⁱ, Dorte Melgaardⁱ, Christian Torp-Pedersen^e, Soren Risom Kristensen^j, Torben Bjerregaard Larsen^k, Peter Sogaard^{a,l}

^a Department of Cardiology, Aalborg University Hospital, Denmark

^b Unit of Clinical Biostatistics and Epidemiology, Aalborg University Hospital, Denmark

^c Faculty of Health Sciences, Department of Drug Design and Pharmacology, Metabolism and Inflammation Research Cluster, Pharmacovigilance Research Center, Copenhagen University, Denmark

^d Department of Business Intelligence and Analysis, North Denmark Region, Denmark

^e Department of Cardiology, Nordsjaellands Hospital, Denmark

^f Emergency Medical Services, Capital Region of Denmark, Copenhagen, Denmark

^g Danish Clinical Quality Program, National Clinical Registries, Denmark

^h The Prehospital Research Unit, Department of Regional Health Research, University of Southern Denmark, Denmark

ⁱ Centre for Clinical Research, North Denmark Regional Hospital, Denmark

^j Department of Clinical Biochemistry, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Denmark

^k Aalborg Thrombosis Research Unit, Aalborg University, Denmark

^l Department of Clinical Medicine, Aalborg University, Denmark

Recent data suggests a link between the Oxford-AstraZeneca adenoviral (ChAdOx1) vector-based COVID-19 vaccine (AZD1222) and immune-mediated thrombotic thrombocytopenia resembling heparin-induced thrombotic thrombocytopenia (HITT) and therefore called VITT (vaccine-induced immune thrombotic thrombocytopenia) [1–3]. However, a case series of 20 patients hospitalized due to thrombocytopenia occurring 1–23 days (median 5 days) after vaccination with the PfizerBioNTech BNT162b2 mRNA Covid-19 vaccine or the Moderna mRNA-1273 SARS-CoV-2 vaccine, including a fatal intracranial hemorrhage, has also been reported [4]. Finally, emerging data has suggested that thrombocytopenia events may likely occur unevenly across the three COVID-19 vaccines, with higher events among individuals vaccinated with the Oxford-AstraZeneca vaccine relative to the PfizerBioNTech vaccine, but further data is needed [5].

Using data from the North Denmark Region (capture population ≈ 600,000 inhabitants), we reviewed cases with thrombocytopenia and associated clinical events among healthcare personnel ≤ 65 years of age vaccinated with the PfizerBioNTech/Moderna (N = 11,689) or the Oxford-AstraZeneca (N = 16,509) COVID-19 vaccine. Due to the very rare but severe clinical entity of VITT, the use of the AstraZeneca vaccine in Denmark was put on hold on March 11, 2021, and later suspended. Therefore, individuals who were vaccinated with this vaccine in our study only had one injection. Of 2130 individuals with post-

vaccination platelet measurements available, 50 (40 women and 10 men) had thrombocytopenia (platelet count < 145 × 10⁹/L in men and < 165 × 10⁹/L in women). Among 1873 women, 24/813 (3.0 %) vaccinated with the Oxford-AstraZeneca COVID-19 vaccine versus 16/1060 (1.5 %) vaccinated with PfizerBioNTech/Moderna COVID-19 vaccines had thrombocytopenia, odds ratio [95 % confidence interval] for thrombocytopenia of 1.99 [1.05–3.76] for Oxford-AstraZeneca versus PfizerBioNTech/Moderna. Among 257 men, the corresponding odds ratio [95 % confidence interval] was 0.49 [0.14–1.79].

Severe thrombocytopenia (platelet count < 50 × 10⁹/L) was seen in three patients vaccinated with Oxford-AstraZeneca (all women between 50 and 60 years of age) versus none among the PfizerBioNTech/Moderna vaccines. One fatal event occurred following adrenal gland bleeding seven days after vaccination, thrombocytopenia (lowest platelet count of 5 × 10⁹/L), massively elevated D-dimer (> 100 mcg/mL), and ischemic stroke nine days after vaccination [6]. This patient was strongly positive for platelet factor 4 (PF-4) reactive antibodies, imitating what is seen in HITT. The two other cases were evaluated in the emergency department on day 20 and 35 post-vaccination without subsequent hospitalization but referral to outpatient diagnostic work-up. PF4-antibodies were not proven in one of the remaining two cases with severe thrombocytopenia and not tested in the other. None of the three cases had previously received heparin.

* Corresponding author. Department of Cardiology, Aalborg University Hospital, Denmark.

E-mail address: kdk@rn.dk (K. Kragholm).

<https://doi.org/10.1016/j.jaut.2021.102712>

Received 5 July 2021; Received in revised form 20 July 2021; Accepted 24 July 2021

Available online 27 July 2021

0896-8411/© 2021 Published by Elsevier Ltd.

A recently published study based on data from the US-based Vaccine Adverse Event Reporting System (VAERS) reported 15 cases of thrombocytopenia among 18,841,309 doses of Pfizer-BioNTech COVID-19 vaccine and 13 cases among 16,260,102 doses of Moderna COVID-19 vaccine, suggesting no safety concern attributable to the use of mRNA COVID-19 vaccines [7]. Also reassuringly, another VAERS-based study of the two mRNA vaccines found that thromboembolic events in younger women, when compared to hormonal contraceptive use, were not disproportionately reported [8]. In continuation, VITT has been suggested to have an incidence risk of 1 in 100,000–600,000 treated cases [9]. In comparison, it is important to emphasize the extremely low incidence of more severe events in the interpretation of our results.

In conclusion, thrombocytopenia appears to be significantly more frequent among women vaccinated with Oxford-AstraZeneca COVID-19 when compared to counterparts vaccinated with the PfizerBioNTech/Moderna COVID-19 vaccines. Of \approx 30,000 vaccinated cases, three events of severe thrombocytopenia were seen only among women vaccinated with the Oxford-AstraZeneca COVID-19 vaccine.

Author statement

Kristian Kragholm: Conceptualization, Methodology, Software, Data Curation, Formal analysis, Writing - Original Draft. **Maurizio Sessa:** Conceptualization, Writing - Review & Editing. **Thomas Mulvad:** Data Curation, Software. **Mikkel Porsborg Andersen:** Writing - Review & Editing. **Helle Collatz-Christensen:** Writing - Review & Editing. **Stig Nikolaj Blomberg:** Writing - Review & Editing. **Freddy Lippert:** Writing - Review & Editing. **Soren Mikkelsen:** Writing - Review & Editing. **Peter Leutscher:** Data Curation, Writing - Review & Editing. **Dorte Melgaard:** Data Curation, Writing - Review & Editing. **Christian Torp-Pedersen:** Supervision, Writing - Review & Editing. **Soren Risom Kristensen:** Conceptualization, Methodology, Supervision, Writing - Review & Editing. **Torben Bjerregaard Larsen:** Conceptualization, Methodology, Supervision, Writing - Review & Editing. **Peter Sogaard:** Conceptualization, Methodology, Supervision, Writing - Review & Editing.

Funding sources

No external funding was used for the study conduct.

References

- [1] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination, *N. Engl. J. Med.* (2021 Apr 9), <https://doi.org/10.1056/NEJMoa2104840>. Epub ahead of print. PMID: 33835769.
- [2] N.H. Schultz, I.H. Sørvoll, A.E. Michelsen, L.A. Munthe, F. Lund-Johansen, M. T. Ahlen, M. Wiedmann, A.H. Aamodt, T.H. Skattør, G.E. Tjønnfjord, P.A. Holme, Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination, *N. Engl. J. Med.* (2021 Apr 9), <https://doi.org/10.1056/NEJMoa2104882>. Epub ahead of print. PMID: 33835768.
- [3] N. Scully, D. Singh, R. Lown, A. Poles, T. Solomon, M. Levi, D. Goldblatt, P. Kotoucek, W. Thomas, W. Lester, Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination, *N. Engl. J. Med.* (2021 Apr 16), <https://doi.org/10.1056/NEJMoa2105385>. Epub ahead of print. PMID: 33861525.
- [4] E.J. Lee, D.B. Cines, T. Gernsheimer, C. Kessler, M. Michel, M.D. Tarantino, J. W. Semple, D.M. Arnold, B. Godeau, M.P. Lambert, J.B. Bussel, Thrombocytopenia following pfizer and Moderna SARS-CoV-2 vaccination, *Am. J. Hematol.* 96 (5) (2021 May 1) 534–537, <https://doi.org/10.1002/ajh.26132>. Epub 2021 Mar 9. PMID: 33606296; PMCID: PMC8014568.
- [5] L. Cari, P. Fiore, M. Naghavi Alhosseini, G. Sava, G. Nocentini, Blood clots and bleeding events following BNT162b2 and ChAdOx1 nCoV-19 vaccine: an analysis of European data, *J. Autoimmun.* 122 (2021 Jun 23) 102685, <https://doi.org/10.1016/j.jaut.2021.102685>. Epub ahead of print. PMID: 34174723; PMCID: PMC8220408.
- [6] R.A. Blauenfeldt, S.R. Kristensen, S.L. Ernsten, C.C.H. Kristensen, C.Z. Simonsen, A. M. Hvas, Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine, *J. Thromb. Haemostasis* 19 (7) (2021 Jul) 1771–1775, <https://doi.org/10.1111/jth.15347>. Epub 2021 May 5. PMID: 33877737; PMCID: PMC8250306.
- [7] K.J. Welsh, J. Baumblatt, W. Chege, R. Goud, N. Nair, Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS), *Vaccine* 39 (25) (2021 Jun 8) 3329–3332, <https://doi.org/10.1016/j.vaccine.2021.04.054>. Epub 2021 Apr 30. PMID: 34006408; PMCID: PMC8086806.
- [8] M. Sessa, K. Kragholm, A. Hviid, M. Andersen, Thromboembolic events in younger women exposed to Pfizer-BioNTech or Moderna COVID-19 vaccines, *Expert Opin. Drug Saf.* (2021 Jul 15), <https://doi.org/10.1080/14740338.2021.1955101>. Epub ahead of print. PMID: 34264151.
- [9] D.B. Cines, J.B. Bussel, SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia, *N. Engl. J. Med.* 384 (23) (2021 Jun 10) 2254–2256, <https://doi.org/10.1056/NEJMe2106315>. Epub 2021 Apr 16. Erratum in: *N Engl J Med.* 2021 Jun 10;384(23):e92. PMID: 33861524; PMCID: PMC8063912.