



# Possibility of the blood clot, thrombotic thrombocytopenia following injection of COVID-19-vaccine AstraZeneca; a systematic review

Mahnaz Momenzadeh<sup>1</sup>, Ebrahim Moayedi<sup>2</sup>, Seyedeh Leila Dehghani<sup>3</sup>, Shahrzad Shadabi<sup>4</sup>, Mohammad Moein Derakhshan Barjoei<sup>5</sup>, Masoumeh Sadat Mousavi<sup>2,6\*</sup>, Samira Pourrezaei<sup>7</sup>

<sup>1</sup>Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>2</sup>Department of Epidemiology and Biostatistics, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>3</sup>Department of Public Health Behbahan Faculty of Medical Sciences, Behbahan, Iran

<sup>4</sup>Graduated in Medical Virology University of Kerman, Kerman, Iran

<sup>5</sup>Student Research Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

<sup>6</sup>Modeling in Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>7</sup>Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

## Correspondence to:

Masoumeh Sadat Mousavi,  
Email: mousavi68.ma@yahoo.com, ma@skums.ac.ir

Received: 27 Oct. 2022

Accepted: 26 July 2023

ePublished: 5 Aug. 2023

**Keywords:** Coronavirus, COVID-19, ChAdOx1 nCoV-19 vaccine (AstraZeneca), Blood-clot, Thrombocytopenia, Systematic review

## Abstract

**Introduction:** Recently, it has been reported that the injection of vaccines such as the ChAdOx1 nCoV-19 (AstraZeneca) involves some rare cases of thrombocytopenia and blood clots, although the vaccines created immunity in people. Estimates of this phenomenon are not the same in different countries, probably due to age distribution and number.

**Objectives:** This study attempted to study AstraZeneca's rare side effects in people injected with this vaccine.

**Methods:** This systematic study was conducted using articles published in 2021 under the title of blood clot and thrombocytopenia by AstraZeneca injection. The references and data were gathered through national and international sites such as Magiran, Google Scholar, PubMed, Web of Science, and Scopus. They were also gathered and examined using report cases and the available data on COVID-19 vaccine immunization in various countries. The keywords used mainly are COVID-19 vaccine, ChAdOx1 nCoV-19 vaccine, blood clots, thrombus, thrombotic, and thrombocytopenia. Eventually, 25 articles were searched and examined, of which 15 related ones were selected after reviewing and re-studying. While investigating the summary and method in those 15, they were filtered more accurately; finally, ten articles were chosen. Inclusion criteria consisted of all related articles and exclusion criteria contained articles that were less related to our research subject after purification or were redundant and not of high quality.

**Results:** This study found that rare blood clot cases and thrombocytopenia were seen despite mild side effects after AstraZeneca injection. After assessing its benefits, adverse effects, and age distribution, the countries using AstraZeneca decided to continue using it. The main difference in reported statistics in these countries is due to the variety in the age and number of people receiving the vaccine.

**Conclusion:** Blood clots and thrombocytopenia are among the rare side effects of the AstraZeneca vaccine. In different countries, the vaccine side effects vary depending on the age and number of participants. Anyway, according to the investigations conducted in this area, the highest records of these side effects are observed in Norway, which is still low. Overall, through studying this study and other similar ones, politicians, managers, and even ordinary people can be informed about the pros and cons of this vaccine.



**Citation:** Momenzadeh M, Moayedi E, Dehghani SL, Shadabi S, Derakhshan Barjoei MM, Mousavi MS, Pourrezaei S. Possibility of the blood clot, thrombotic thrombocytopenia following injection of COVID-19-vaccine AstraZeneca; a systematic review. J Prev Epidemiol. 2023;8(2):e34192. doi: 10.34172/jpe.2023.34192.

## Introduction

The vaccine produced by AstraZeneca Company has been recently placed in the COVAX Basket. The Oxford-AstraZeneca vaccine is a replication-deficient adenoviral vector that expresses the SARS-CoV-2 spike protein gene, which forces the host cells to produce the S-antigen protein related to SARS-CoV-2. As a result, the host's body generates an immune response to the virus and keeps that information in memory

immune cells (1).

AstraZeneca/Oxford does not require storing in extremely cold conditions, unlike Pfizer and Moderna; it can be stored in a refrigerator at 2 to 8 °C (2). This feature makes this vaccine a great choice in mass vaccination programs and facilitates its delivery to developing countries. However, rare cases of blood clots and thrombocytopenia were reported after the vaccination against COVID-19 by Astra

**Key point**

With the global onset of the COVID-19 pandemic, we need world-approved vaccines to prevent this virus. This systematic review explores the effects of the ChAdOx1 nCoV-19 vaccine (AstraZeneca).

Zeneca in some countries (3).

After a short time, it was found that clotting conditions can be seen in all venous and arterial parts (1,4). Then, some cases with antibody-platelet factor 4 were reported (5). It is of note that these side effects were mostly seen in patients younger than 55 years old vaccinated by AstraZeneca, while a small number were older (1,5,6). Hence, some countries considered the age limit regarding vaccination by AstraZeneca against COVID-19, and others stopped using this vaccine. Decision-making about continuing vaccination through AstraZeneca requires observing its benefits and risks among various age groups.

The highest death rate caused by COVID-19 has been reported among patients over 50 years compared to the limited number of side effects related to the vaccine among young recipients. Meanwhile, there are disagreements about whether the risks of AstraZeneca outweigh its benefits among different countries considering the age of people. For instance, in the US, the AstraZeneca shot is just recommended for those over 30, in Australia over 50, in France 55, and in Germany and Spain over 60 years old (6-8). Accordingly, it is so important to provide an accurate estimation considering blood clot. European Pharmacists' Association recorded the incidence rate as 1 out of every 290 000 and later changed it to 1 out of every 153 000 (7-8). This study provides different records of countries considering the number of persons vaccinated, their age, and vaccination time. Our hypothesis states that the incidence of clotting syndrome related to the AstraZeneca vaccine differs among age groups. Overall, AstraZeneca's side effects are rare, and its benefits outweigh the risks (6-9).

**Objectives**

The study aimed to review the reported studies on common and rare effects of the AstraZeneca vaccine on vaccinated individuals and to report to the authorities and the general public.

**Methods**

A literature search was conducted using electronic databases, including PubMed, Google Scholar and, Medline, Magiran, Science Direct, SID. We used the terms "COVID-19 Vaccine", "AstraZeneca ChAd.Ox1-S/nCoV-19", "Blood Clots", "Thrombus", "Thrombotic", and "thrombocytopenia" to identify reports.

The inclusion criteria were All case reports, cross-sectional, case-control, cohort, and review studies were included in the study.

Studies and articles on blood clots and thrombocytopenia after the AstraZeneca shot were used for the present systematic study. We gathered the data through Google Scholar, Scopus, Medlin, and PubMed (Table 1). Likewise, we applied case reports, available data during the vaccine's immunization period, thrombocytopenia, and a blood clot in various countries. The present systematic study was conducted using the word processing MESH program. Then, the data related to blood clots and thrombocytopenia were analyzed. The data were gathered and evaluated since April 2021 from countries with accurate records of blood clots and thrombocytopenia cases. Meanwhile, we excluded some data and studies (e.g., those from the U.S. and Sweden) as these countries did not record their cases. Some others, such as Israel and New Zealand, provided ambiguous records. Australia and Fenland did not report their records at all. All available articles, scientific media, and magazines were examined. For example, in England, approximately 20 000 000 were vaccinated by AstraZeneca, among which 79 blood clot and 19 deaths were announced. This is rare, which means one death for every one million persons being vaccinated.

**Table 1.** Summary of articles submitted to the systematic review

Author Name	Location	Population	Type of study	Result
Douxflis (10)	European and United	34 million people	Descriptive study-case report	However, the EMA pharmacovigilance risk assessment concluded that unusual thromboses with low blood platelets should be listed as infrequent side effects of Vaxzevria.
Greinacher (11)	Germany and Austria	11 patients	Analytical studies.	Vaccination with ChAdOx1 nCov-19 can cause rare immune thrombotic thrombocytopenia due to platelet-activating antibodies against PF4.
Tobaigy (12)	European countries	17 million people	A retrospective descriptive study.	The vaccine is safe, effective, and the benefits outweigh the risks. Conducting further analyses based on more detailed reporting of thrombotic adverse events, including patient characteristics and comorbidities, may allow the assessment of causality with higher specificity.
Cari (13)	European (ECDC)	86919	Analytical studies	The immune response promoted by the ChA vaccine may lead not only to thrombocytopenia and cerebral/splanchnic venous thrombosis, but also to other thrombotic and thromboembolic SAEs.
Pai (14)	United Kingdom, European Union, and Scandinavian countries	1 million people	Case report study	VIPIT is a rare side effect following AstraZeneca's COVID-19 vaccine.

Only 25 studies were selected, which included review, systematic, meta-analysis, cross-sectional, and descriptive studies. About ten studies were excluded, and the conclusions of about 15 remaining studies were purified and separated again. Finally, five were selected (Figure 1).

### Discussion

The considerable difference in the countries' records is mainly for the variety in the age of persons injected. Some studies state that the abovementioned side effects may be created by anti-platelet factor 4, sometimes resulting from heparin injection. The hypothesis state that antibodies produced by anti-platelet factor 4 (PF4) can be due to adenovirus transparent tissue used in AstraZeneca construction. Notably, some data and studies were excluded from our article (e.g., those from America and Sweden) as they did not record their cases, Israel and New Zealand had delivered ambiguous records, and Australia and Fenland reported not at all (1,5). Overall, about 20 000 000 people in England received AstraZeneca shots, of which 19 blood clots and 19 death cases were recorded. This death rate is one for every one million persons vaccinated, which is so rare. Most people who died were below 55 years, while fewer were of higher age. Public Health of England declared that one dose of AstraZeneca shot results in 80% less risk of death from the disease, which is the most crucial advantage of this vaccine compared with its disadvantage (12,15). AstraZeneca company also announced that the vaccine's side effects, including clotting syndrome, are so rare that the European Pharmacist Association and the Medicine Regulatory Agency have decided to keep AstraZeneca in the market and announced that its advantages outweigh its disadvantage. Anyway, the vaccine's label is updated to refer to clotting as one of its rare side effects (1,4,6,15)

Moreover, after evaluating the advantages and disadvantages of AstraZeneca and considering their countries' age distribution, various countries decided to inject it. For example, countries such as Germany, Netherlands, and Spain restricted their injection for those below 60, France below 55, and Australia below 50 years old (1,12). The main difference among these countries' records is the age of the people injected and their population share. It is worth noting that these countries' policies regarding vaccinating through AstraZeneca are completely vivid and clear (9,15). The last point is that all studies done regarding AstraZeneca's side effects have shown that its advantages are so higher than its disadvantages. Vaccinating through AstraZeneca not only in Iran but also in all other countries reduced death rates considerably (1,9,12).

### Conclusion

General vaccination is the most critical solution to the coronavirus pandemic and its high death rate. AstraZeneca and similar vaccines are important in controlling the pandemic and decreasing the death rates. Considering

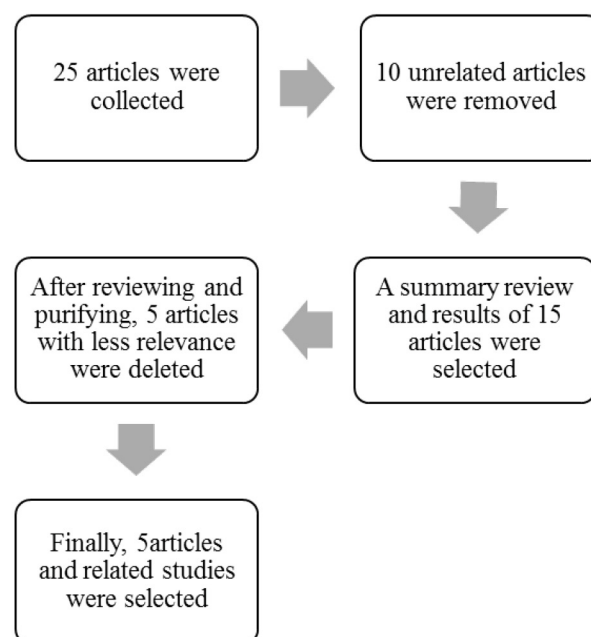


Figure 1. Summary of search strategy and paper exclusion.

AstraZeneca injection in some countries and its rare side effects (blood clotting syndrome and thrombocytopenia) and according to the conducted studies, it is clarified that its advantages outweigh its disadvantages. Therefore, it is recommended to administer AstraZeneca and similar ones for controlling the pandemic considering their dominant age constructions.

### Limitations of the study

One limitation of this review was the small number of studies included in our analysis that were relevant to our results. Also, we had rare data due to incomplete research on the very rare side effects of vaccines such as AstraZeneca.

### Authors' contribution

**Conceptualization:** Mahnaz Momenzadeh, Masoumeh Sadat Mousavi & Ebrahim Moayedi.

**Data curation:** Mahnaz Momenzadeh, Masoumeh Sadat Mousavi.

**Formal analysis:** Masoumeh Sadat Mousavi, Mohammad Moein Derakhshan Barjoei.

**Funding acquisition:** Masoumeh Sadat Mousavi, Mahnaz Momenzadeh.

**Investigation:** Ebrahim Moayedi, Masoumeh Sadat Mousavi.

**Methodology:** Masoumeh Sadat Mousavi, Seyedeh Leila Dehghani, Mohammad Moein Derakhshan Barjoei.

**Project administration:** Masoumeh Sadat Mousavi, Mahnaz Momenzadeh.

**Resources:** Mahnaz Momenzadeh, Masoumeh Sadat Mousavi.

**Supervision:** Masoumeh Sadat Mousavi, Mahnaz Momenzadeh.

**Validation:** Masoumeh Sadat Mousavi, Shahrzad Shadabi, Samira Pourrezaei.

**Visualization:** Masoumeh Sadat Mousavi, Mahnaz Momenzadeh.

**Writing—original draft:** Ebrahim Moayedi, Masoumeh Sadat Mousavi.

**Writing—review and editing:** Masoumeh Sadat Mousavi, Ebrahim Moayedi, Mahnaz Momenzadeh.

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

**Funding/Support**

None.

**References**

- Douxfile J, Favresse J, Dogné JM, Lecompte T, Susen S, Cordonnier C, et al. Hypotheses behind the very rare cases of thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination. *Thromb Res.* 2021;203:163-171. doi: 10.1016/j.thromres.2021.05.010.
- Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med.* 2021;384:1885-1898. doi: 10.1056/NEJMoa2102214.
- Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med.* 2021;384:2124-2130. doi: 10.1056/NEJMoa2104882.
- Mahase E. AstraZeneca vaccine: Blood clots are “extremely rare,” and benefits outweigh risks, regulators conclude. *BMJ.* 2021;373:n931. doi: 10.1136/bmj.n931.
- Billy E, Clarot F, Depagne C, Korsia-Meffre S, Rochoy M, Zores F. Thrombotic events after AstraZeneca vaccine: What if it was related to dysfunctional immune response? *Therapie.* 2021;76:367-369. doi: 10.1016/j.therap.2021.04.003.
- 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;21:2554-2558. doi: 10.1111/jth.15493.
- Wolf ME, Luz B, Niehaus L, Bhogal P, Bänzner H, Henkes H. Thrombocytopenia and Intracranial Venous Sinus Thrombosis after “COVID-19 Vaccine AstraZeneca” Exposure. *J Clin Med.* 2021;10:1599. doi: 10.3390/jcm10081599.
- D’Agostino V, Caranci F, Negro A, Piscitelli V, Tuccillo B, Fasano F, et al. A Rare Case of Cerebral Venous Thrombosis and Disseminated Intravascular Coagulation Temporally Associated to the COVID-19 Vaccine Administration. *J Pers Med.* 2021;11:285. doi: 10.3390/jpm11040285.
- Idenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, et al. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. *Hamostaseologie.* 2021;41:184-189. doi: 10.1055/a-1469-7481.
- Douxfile J, Favresse J, Dogné JM, Lecompte T, Susen S, Cordonnier C, et al. Hypotheses behind the very rare cases of thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination. *Thromb Res.* 2021;203:163-171. doi: 10.1016/j.thromres.
- Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med.* 2021;384:2092-2101. doi: 10.1056/NEJMoa2104840.
- Tobaiqy M, Elkout H, MacLure K. Analysis of Thrombotic Adverse Reactions of COVID-19 AstraZeneca Vaccine Reported to EudraVigilance Database. *Vaccines (Basel).* 2021;9:393. doi: 10.3390/vaccines9040393.
- Cari L, Fiore P, Naghavi Alhosseini M, Sava G, Nocentini G. Blood clots and bleeding events following BNT162b2 and ChAdOx1 nCoV-19 vaccine: An analysis of European data. *J Autoimmun.* 2021;122:102685. doi: 10.1016/j.jaut.2021.102685.
- Pai M, Grill A, Ivers N, Maltsev A, Miller K, Razak F, et al. Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) following AstraZeneca COVID-19 vaccination. Science briefs of the Ontario covid-19 science advisory table. 2021;1:10-47326. doi: 10.47326/ocsat.2021.02.17.1.0.
- Hwang J, Lee SB, Lee SW, Lee MH, Koyanagi A, Jacob L, et al. Comparison of vaccine-induced thrombotic events between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines. *J Autoimmun.* 2021;122:102681. doi: 10.1016/j.jaut.2021.102681.