Pulmonary embolism after anti-SARS-CoV-2 vaccines in two female patients

Katarzyna Korzeniowska[1], Artur Cieślewicz[1], Katarzyna Grabańska-Martyńska[2], Anna Flotyńska[1], Anna Jabłecka[1]

[1]Department of Clinical Pharmacology, Poznan University of Medical Sciences, Poznań, Poland
[2]Department of Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland

Address for correspondence:
Katarzyna Korzeniowska
Department of Clinical Pharmacology
Poznan University of Medical Sciences
św. Marii Magdaleny 14
61–861 Poznań, Poland
e-mail: kkorzeniowska@ump.edu.pl

Hematology in Clinical Practice
2023, vol. 14, 18–23
DOI: 10.5603/HCP.2023.0004

ISSN: 2720–1015
e-ISSN: 2720–2690

Received: November 18, 2022
Accepted: April 5, 2023

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic. To protect people from severe COVID-19 course, vaccines have been recently developed. Vaccines' safety was confirmed during clinical trials; however, massive vaccination action resulted in rare cases of adverse effects emerging, such as thromboses associated with thrombocytopenia. We present two cases of pulmonary embolism after anti-SARS-CoV-2 vaccines in two female patients, with negative history of SARS-CoV-2 infections. In both patients additional risk factors for thrombotic events (hormonal contraception, varicose veins) were present. Pulmonary embolism occurs when a blood vessel in the lungs becomes blocked by a blood clot. It is a very rare adverse effect associated with COVID-19 vaccines and is often accompanied by thrombocytopenia. However, recent studies have found that he incidence of pulmonary embolism after COVID-19 vaccines was not increased compared to the general population. Moreover, the risk of PE after vaccination is significantly lower than the incidence of thrombotic events during COVID-19.

Key words: pulmonary embolism, anti-SARS-CoV-2 vaccines, thromboembolism, thrombosis with thrombocytopenia syndrome, TTS

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic. The infection is mediated via the coupling of viral spike protein with angiotensin-converting enzyme 2 (ACE2). As ACE2 can be found in the heart, infection with SARS-CoV-2 may result in cardiovascular complications, including thromboembolism [1]. According to the actual state of knowledge, the prothrombotic mechanism associated with COVID-19 may be direct (micro vasculitis due to viral damage), indirect (downregulation of ACE2 receptor, hypoxia, and disseminated intravascular coagulation), and behavioral (bed restriction due to prolonged mechanical ventilation and decreased deambulation due to social isolation) [1–3]. Factors that increase the risk of venous thromboembolism in hospitalized COVID-19 patients include prolonged immobilization during illness, dehydration, an acute inflammatory state, presence of other cardiovascular risk or cardiovascular disease, previous history of venous thromboembolism and classical genetic thrombophilia, such as heterozygous factor V Leiden mutation [4]. The D-dimer elevation is a significant indicator for detecting and assessing the severity of thromboembolism in COVID-19 patients [4].

To protect people from severe COVID-19 course, vaccines have been recently developed. As of now, seven such preparations have been approved by European Medicines Agency (EMA): Comirnaty (Pfizer), Spikevax (Moderna), Vaxzevria (AstraZeneca), Jcovden (Janssen), Nuvaxovid (Novavax), COVID-19 Vaccine Valneva (Valneva Austria) and VidPrevtyn Beta (Sanofi Pasteur) [5]. Vaccines' safety was confirmed during clinical trials; however, massive vaccination action resulted in rare adverse effects, such as thromboses with thrombocytopenia syndrome (TTS) in patients who received Vaxzevria or Jcovden [6–8].

CASE REPORT

We present two cases of pulmonary embolism (PE) after anti-SARS-CoV-2 vaccines in two female patients with no previous SARS-CoV-2 infections. Both patients were admit-

Table 1. Cases of pulmonary embolism (PE) after anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines

Variable	Patient 1	Patient 2
Age [years]	26	65
Sex	F	F
Body mass [kg]	65	74
Height [cm]	175	170
BMI [kg/m^2]	21.22	25.61
Vaccine	Pfizer (Comirnaty)	Vaxzevria (AstraZeneca)
Hospitalization		
Begin	January 26, 2021	April 17, 2021
End	February 1, 2021	April 26, 2021
Diagnosis	Low-risk PE after anti-SARS-CoV-2 vaccination; arterial hypertension	Intermediate-high-risk PE after anti-SARS-CoV-2 vaccination; arterial hypertension
PE risk factors	Contraception (ethinylestradiol 0.03 mg + + drospirenone 3 mg) for 2 years	Varicose veins of the lower extremities in the history
Laboratory examinations [reference range]		
D-dimer [0–0.50 µg/mL]	3.660 µg/mL (1st day of hospitalization)	4.617 µg/mL (1st day of hospitalization)
CRP [< 0.5 mg/dL]	22.6 mg/dL (1st day of hospitalization) 23.2 mg/dl (2nd day of hospitalization) 15.3 mg/dl (4th day of hospitalization)	18.4 mg/dL (1st day of hospitalization)
NT-proBNP [< 226 pg/mL]	–	6.193 pg/mL (1st day of hospitalization)
hs-troponin T [< 6 ng/L]	–	42 ng/L (1st day of hospitalization)
Lower extremity veins diagnostics	No blood clots or inflammatory changes	No blood clots or inflammatory changes
Anticoagulant treatment		
Hospital	Enoxaparin	Unfractionated heparin Dabigatran
Recommendations after hospitalization	Rivaroxaban 15 mg bd for 2 weeks; then 20 mg qd;	Dabigatran: 150 mg bd

bd (*bis in die*) — two times a day; BMI — body mass index; CRP — C-reactive protein; hs — high-sensitive; F — female; NT-proBNP — N-terminal pro-B-type natriuretic peptide; qd (*quaque die*) — once a day

ted to the hospital due to pulmonary symptoms. Patients' characteristics and results of laboratory examinations are presented in Table 1.

Case 1

A 26-year-old woman was hospitalized due to low-risk PE (46 points in Pulmonary Embolism Severity Index — PESI [9]). She was administered the second dose of the Comirnaty vaccine five days before hospitalization. It resulted in the following adverse effects: fever up to 38°C, dry cough, and chest pain in the lower quadrant of the right lung. Moreover, the patient observed a decrease in SpO_2 (oxygen saturation) during home measurements. On admission, the patient was respiratorily and hemodynamically stable. She reported severe pleural pain in the right half of the chest. The patient was on regular oral hormonal contraception (ethinylestradiol 0.03 mg + drospirenone 3 mg for two years), which did not yield any adverse effects. In auscultation, correct vesicular breathing with symmetrical breath sounds. SpO_2 was 98% without oxygen supplementation. The heart rate was 118/min. The blood pressure was elevated (150/85 mm Hg). Echocardiography did not reveal any significant abnormalities. Computed tomography (CT) of the chest revealed the presence of thromboses in the branches to the 8, 9, and 10 segments of the lower right lung filling them quite tightly with atelectasis changes in this area. The image showed embolic material and compaction of parenchymal-interstitial inflammation or secondary to embolism. Thromboses in the lower lobe segments of the left lung with less severity and no pulmonary component were found. Ultrasound examination of the lower limbs excluded the presence of blood clots and inflammatory changes. Laboratory examination resulted in increased C-reactive protein (CRP) and D-dimer.

Due to the diagnosis of low-risk PE after anti-SARS-CoV-2 vaccination, the treatment with enoxaparin was started. After six days of hospitalization, the patient was discharged home with the recommendation to use rivaroxaban 15 mg *bis in die* (bd; twice daily) for two weeks, then 20 mg *quaque die* (qd; once a day), and was directed to a coagulation disorder clinic for further consultation. Regular blood pressure measurements and internal medicine control were also recommended. Due to a history of PE, the patient discontinued oral contraception for six months. After this time, hormonal contraception was restarted under the supervision of a gynecologist. The patient was also informed that it was essential to cease smoking.

Case 2

A 65-years old woman suffering from arterial hypertension and varicose veins of the lower extremities for several years was admitted to the ward for symptoms of breathlessness for several days. Before a hospitalization, no exacerbation of chronic disease symptoms was noted. She was

administered the first dose of the Vaxzevria vaccine seven days before hospitalization. It resulted in the following adverse effects: fever up to 38°C, dry cough, and breathlessness. CT of the chest, made on the day of admission, revealed the loss of contrast in the main lobar arteries to the upper and lower lobe of the left lung and the segmental arteries to the upper lobe of the left lung. Contrast loss/embolism was observed in the right lower and middle lobe arteries and in segmental arteries. The heart had a predominance of the right ventricle. Discreetly mottled areas of ground-glass opacity were visualized in the right (segments 1, 3, 7) and left lung (segments 3, 6, 4, 8). Besides fibrosis at the left lung base, the pulmonary parenchyma was without focal lesions and of airborne characteristics. Pleural cavities were free of fluid. Laboratory examination resulted in increased D-dimer, N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitive (hs) troponin T, and CRP. The pharmacotherapy was started with unfractionated heparin (APTT, activated partial thromboplastin time-controlled dose), and after five days was changed to dabigatran 150 mg bd. Echocardiography of the heart confirmed the presence of signs of acute PE (enlarged right ventricle and right ventricle free wall hypokinesia). Ultrasound examination of the lower limbs excluded the presence of blood clots and inflammatory changes. After ten days of hospitalization, the patient was discharged home with the recommendation to use dabigatran 150 mg bd. Due to the combination of the transient and persistent presence of PE risk factors (vaccination and the history of varicose veins), the patient was recommended to undergo periodic cardiological check-ups. Three months after the onset of the embolism, the treatment with dabigatran was discontinued. Within 12 months of the onset of the embolism, the patient returned every three months for follow-up visits to the cardiologist. During subsequent visits, a gradual improvement in exercise tolerance and a reduction in dyspnea were observed.

DISCUSSION

PE occurs when a blood vessel in the lungs becomes blocked by a blood clot (usually developed elsewhere and moved to the lung artery). The symptoms include dyspnea, chest pain, cough, hemoptysis, concurrent symptoms of deep venous thrombosis, tachypnea, tachycardia, and hypoxia [10]. It constitutes the third most common cause of cardiovascular death worldwide [11]. The most important risk factors for PE are male sex, Afro-American descent, age > 50 years, recent surgery, extreme immobility, prior venous thromboembolism, venous stasis/varicose veins, solid cancers, hematologic cancers, hormonal contraception, prolonged bed rest, thrombophilias, indwelling catheters, > 6 hours in a continuous seated position, smoking-related lung disease, congestive heart failure, stroke, obesity, metabolic syndrome, pregnancy, and post-partum state, noninfectious inflammatory conditions [11, 12].

Based on the data from the EudraVigilance database, the incidence of PE after the Vaxzevria vaccine is 4.37 $\times 10^{-5}$, making it four times more frequent than PE after the Pfizer–BioNTech vaccine (1.11×10^{-5}) [13, 14]. Cases of thrombotic events after vector COVID-19 vaccines started to be reported in February 2021, including cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, PE, deep vein thrombosis (DVT) and ischemic stroke [6, 15–21]. Greinacher et al. [15] reported 11 cases of patients with thrombotic events after the Vaxzevria vaccine. Three of them were PE. All cases were accompanied by thrombocytopenia [15]. Jafri et al. [16] described a 59-year-old male patient with mild thrombocytopenia, increased D-dimer, and pulmonary embolism confirmed by a CT angiogram. A study on a multinational registry of patients with venous thromboembolism (VTE), including DVT, PE, CVST, and splanchnic vein thrombosis (SVT), revealed 102 cases of thrombotic events after Vaxzevria (28 patients), Comirnaty (63 patients) and Spikevax (11 patients). Patients' records from 2018–2019 were used as a control. The authors concluded that, compared to controls, patients with VTE after vector vaccine more frequently had CVST or thrombosis at multiple sites, thrombocytopenia, and worse clinical outcome (higher 14-day mortality) [17]. Waqar et al. [18] published a meta-analysis of 62 studies on TTS after COVID-19 vector vaccines. They found that most patients were females. The most common thrombotic event was venous thrombosis. The most frequent complication was CVST. Other thrombotic events reported included SVT and PE. The mortality rate reached 36.2% and was more frequent in patients with suspected TTS, venous thrombosis, CVST, PE, intraneural complications, patients not managed with non-heparin anticoagulants or intravenous immunoglobulins, patients receiving platelet transfusions, and patients requiring intensive care unit admission, mechanical ventilation, or neurosurgery [18]. An interesting case of Hampton's hump pulmonary embolism after Vaxzevria was recently described [19]. The patient was a 58-year-old man with right-sided pleuritic chest pain, dyspnea, and fatigue observed 18 days after vaccination. He had significantly elevated D-dimer and mild thrombocytopenia. PE was confirmed by chest radiography and CT angiography. Moreover, the patient was heterozygous for the FV_{Leiden} mutation, resulting in increased blood clotting [19].

Some isolated cases of PE without thrombocytopenia were also described. Ifeanyi et al. [22] presented two cases of 61-year-old and 51-year-old male patients with unprovoked PE after receiving Vaxzevria. Both patients did not have any history of thromboembolic disorders. The first patient experienced symptoms such as shortness of breath, lethargy, and bilateral calf pain, eight days after the second dose of the vaccine. In the second case, shortness of breath and cough was observed four weeks after the first dose of the vaccine. Increased D-dimer with correct platelet count was present in both cases. Pulmonary embolism was confirmed with a CT angiogram of the chest. The authors

underlined the need for a well-planned post-discharge follow-up after an acute PE to evaluate and early detect chronic thromboembolic pulmonary hypertension (a potentially life-threatening complication of PE) [22]. Another paper presented two cases of PE without thrombocytopenia in patients who underwent kidney transplantation [23]. The first patient was a 52-year-old man who had kidney transplantation 13 years before vaccination with Spikevax. He received immunosuppressive treatment with cyclosporine, mycophenolate sodium, methylprednisolone, and sirolimus. Symptoms, such as right low-extremity swelling and claudication, appeared 23 days after vaccination. The D-dimer level was increased while the platelet count was correct. CT confirmed left pulmonary artery thrombosis. The second patient was a 57-year-old man who had kidney transplantation 8 years before vaccination. Immunosuppressive treatment included everolimus, mycophenolate mofetil, methylprednisolone, and cyclosporine. Exertional dyspnea and bilateral leg edema appeared 26 days after the third dose of Spikevax. The D-dimer level was increased while the platelet count was correct. PE was revealed by a pulmonary perfusion scan. The authors concluded that transplant patients might be at higher risk of thromboembolic events due to the combined synergistic effects of immunosuppressants and COVID vaccinations [23]. Borisoff et al. [24] described a case of a 67-year-old male patient with shortness of breath first noted two days after receiving the Comirnaty vaccine. The patient did not have any pro-thrombotic risk factors. The CT of the chest revealed a submassive saddle pulmonary embolism with right heart strain and a small hiatal hernia. Besides pharmacologic anticoagulation, the patient required thrombectomy which was successful and resulted in improvement of pulmonary artery pressure, mixed venous saturation, and dyspnea [24]. Another case was a 59-year-old man with prolonged dyspnea and cough, which started about one month after receiving the third dose of Spikevax [25]. Once again, the patient had no significant past medical history. Computed tomography pulmonary angiography confirmed pulmonary embolism of the right and left pulmonary arteries with features of possible early pulmonary hypertension [25]. Ahn et al. described a case of a 27-year-old man without any significant medical history who experienced the following symptoms: cough, hemoptysis, and epigastric pain ten days after receiving the second dose of Spikevax [26]. Similarly to previous cases, the patient had no family history of venous thromboembolism or coagulation disorder. The D-dimer level was slightly increased while the platelet count was within the reference range. CT angiography revealed pulmonary emboli involving the right lower lobe pulmonary arteries and pulmonary infarcts in the right lower lobe. Additionally, thrombosis was observed in the inferior vena cava (IVC) and right common iliac vein. IVC filter insertion and aspiration thrombectomy were necessary because no improvement was observed after one week of heparin treatment [26].

The emergence of thrombotic events resulted in suspending the use of Vaxzevria by some European countries [27]. Following the recommendation of the European Pharmacovigilance Risk Assessment Committee, which concluded that there was a causal association between vaccination with Vaxzevria and sporadic cases of thrombosis, the medicinal product characteristic was updated [21, 28]. On the other hand, it was found that the incidence of pulmonary embolism in patients vaccinated with Vaxzevria was not increased compared to the general population [29]. Similarly, no increase in PE incidence was observed for the Pfizer–BioNTech vaccine [30]. It is worth emphasizing that the risk of PE after vaccination is significantly lower than the incidence of thrombotic events during COVID-19 [31].

Contraception with exogenous estrogen was found to increase the risk of PE by two to threefold, with the highest risk of venous thromboembolism in the first few months after starting the contraception [12]. Using hormone patches and rings results in a far more significant increase in VTE than pills, as the hormones are absorbed continuously. Moreover, progestin-only contraceptive pills do not increase the risk and are a safe method of birth control for women with venous thromboembolism [32]. A French study on almost 5 million women using oral contraceptives revealed that the absolute risk of thromboembolism was 33 per 100,000 women years of oral contraceptive use. Moreover, a statistically significantly higher relative risk was observed for desogestrel and gestodene than for levonorgestrel after adjusting risk factors and estrogen dose [33]. A recent study on drospirenone's efficacy, tolerability, and safety revealed no cases of deep vein thrombosis or PE [34].

Varicose veins (varicoses) result from superficial veins becoming enlarged and twisted. The study by Mäkivaara et al. [35] on a group of 6,874 people found that the presence of varicose veins was followed by the increased subsequent incidence of arterial disease (angina pectoris, myocardial infarction, peripheral occlusive arterial disease or cerebrovascular disease). Müller-Bühl et al. [36] observed a strong association between varicose veins and deep venous thrombosis after analyzing more than 80,000 cases from the German CONTENT primary care register. This association was confirmed by a retrospective study of almost 426,000 Taiwanese adults [37]. Thrombosis and PE could also follow varicose vein surgery [38].

CONCLUSION

Both cases describe patients who developed PE shortly after receiving a COVID-19 vaccine (mRNA or vector vaccine). It confirms a possible association between COVID-19 vaccines and the development of PE, described broadly in the literature. It is important to remember that PE can occur due to various factors. In our cases, risk factors for thrombotic events were present (such as hormonal contraception or varicose veins) and could significantly contribute to the development of PE after vaccination.

Article information

Conflict of interest: The authors declare no conflict of interest.

Funding: None.

REFERENCES

1. Bellotti Azevedo R, Gopp Botelho B, Gonçalves de Hollanda JV, et al. COVID-19 and the cardiovascular system: a comprehensive review. J Hum Hypertens. 2021; 35(1): 4–11, doi: 10.1038/s41371-020-0387-4.
2. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020; 191: 145–147, doi: 10.1016/j.thromres.2020.04.013.
3. Bikdeli B, Madhavan MV, Jimenez D, et al. Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 75(23): 2950–2973, doi: 10.1016/j.jacc.2020.04.031, indexed in Pubmed: 32311448.
4. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020; 95(7): 834–847, doi: 10.1002/ajh.25829, indexed in Pubmed: 32282949.
5. COVID-19 vaccines. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines (March 20, 2022).
6. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19). https://www.who.int/publications/i/item/9789240061989 (April 20, 2023).
7. VAXZEVRIA/COVID-19 Vaccine AstraZeneca: risk of thrombosis in combination with thrombocytopenia — updated information. https://www.ema.europa.eu/documents/dhpc/direct-healthcare-professional-communication-dhpc-vaxzevria/covid-19-vaccine-astrazeneca-risk-thrombosis-combination-thrombocytopenia-updated-information_en.pdf (March 20, 2022).
8. COVID-19 Vaccine Janssen: risk for immune thrombocytopenia (ITP) and venous thromboembolism (VTE). https://www.ema.europa.eu/documents/dhpc/direct-healthcare-professional-communication-dhpc-covid-19-vaccine-janssen-risk-immune_en.pdf (March 20, 2022).
9. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005; 172(8): 1041–1046, doi: 10.1164/rccm.200506-862OC, indexed in Pubmed: 16020800.
10. Doherty S. Pulmonary embolism An update. Aust Fam Physician. 2017; 46(11): 816–820, indexed in Pubmed: 29101916.
11. Essien EO, Rali P, Mathai SC. Pulmonary embolism. Med Clin North Am. 2019; 103(3): 549–564, doi: 10.1016/j.mcna.2018.12.013, indexed in Pubmed: 30955521.
12. Kline JA. Diagnosis and exclusion of pulmonary embolism. Thromb Res. 2018; 163: 207–220, doi: 10.1016/j.thromres.2017.06.002, indexed in Pubmed: 28683951.
13. EudraVigilance — European database of suspected adverse drug reaction reports. https://www.adrreports.eu/en/search_subst.html# (March 20, 2022).
14. European Centre for Disease Prevention and Control. COVID-19 vaccine tracker. https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab (March 30, 2022).
15. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021; 384(22): 2092–2101, doi: 10.1056/NEJMoa2104840, indexed in Pubmed: 33835769.
16. Jafri A, Prieto A, Gashau H, et al. Thrombotic thrombocytopenia following ChAdOx1 nCov-19 vaccination. Acute Med. 2021; 20(3): 223–226, indexed in Pubmed: 34679140.
17. Bikdeli B, Jiménez D, Demelo-Rodriguez P, et al. Venous thrombosis within 30 days after vaccination against SARS-CoV-2 in a Multinational Venous Thromboembolism Registry. Viruses. 2022; 14(2), doi: 10.3390/v14020178, indexed in Pubmed: 35215771.
18. Waqar U, Ahmed S, Gardezi SM, et al. Thrombosis with thrombocytopenia syndrome after administration of AZD1222 or Ad26.COV2.S vaccine for COVID-19: a systematic review. Clin Appl Thromb Hemost. 2021; 27: 10760296211068487, doi: 10.1177/10760296211068487, indexed in Pubmed: 34907794.
19. Konstantinides SV. Thrombotic complications of vaccination against SARS--CoV-2: what pharmacovigilance reports tell us — and what they don't. Eur Respir J. 2021; 58(1), doi: 10.1183/13993003.01111-2021, indexed in Pubmed: 33888525.
20. Kriegshäuser G, Braunsteiner A. Temporal association between Hampton's hump pulmonary embolism and first-dose ChAdOx1 nCov-19 vaccine in a patient with activated protein C resistance. Vaccines (Basel). 2022; 10(10), doi: 10.3390/vaccines10101659, indexed in Pubmed: 36298523.
21. Brazete C, Aguiar A, Furtado I, et al. Thrombotic events and COVID-19 vaccines. Int J Tuberc Lung Dis. 2021; 25(9): 701–707, doi: 10.5588/ijtld.21.0298, indexed in Pubmed: 34802491.
22. Ifeanyi N, Chinenye N, Oladiran O, et al. Isolated pulmonary embolism following COVID vaccination: 2 case reports and a review of post-acute pulmonary embolism complications and follow-up. J Community Hosp Intern Med Perspect. 2021; 11(6): 877–879, doi: 10.1080/20009666.2021.1990825, indexed in Pubmed: 34804412.
23. Chan WN, Chen CS, Ho DR, et al. Pulmonary embolism after Moderna vaccination in kidney transplant patients: two case reports and literature review. Vaccines (Basel). 2022; 10(6), doi: 10.3390/vaccines10060868, indexed in Pubmed: 35746476.
24. Borisoff BD, Bohn KD, Sager J, et al. Unprovoked submassive saddle pulmonary embolism in an adult male after Pfizer COVID-19 vaccination. Cureus. 2022; 14(8): e27717, doi: 10.7759/cureus.27717, indexed in Pubmed: 35949450.
25. Ogunkoya JO, Ogunmola MI, Ogunlade AF, et al. COVID-19 vaccination associated bilateral pulmonary embolism: cause or coincidence. Case Rep Pulmonol. 2022; 2022: 9596285, doi: 10.1155/2022/9596285, indexed in Pubmed: 36212801.
26. Ahn EY, Choi H, Sim YSu, et al. Pulmonary embolism and inferior vena cava thrombosis pin a young male atient after mRNA-1273 (Moderna) immunization: a case report. Tuberc Respir Dis (Seoul). 2022; 85(4): 361–363, doi: 10.4046/trd.2022.0050, indexed in Pubmed: 35822319.
27. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. BMJ. 2021; 372: n699, doi: 10.1136/bmj.n699, indexed in Pubmed: 33707182.
28. Vaxveria. Summary of product characteristics. https://www.ema.europa.eu/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf (March 20, 2022).
29. Østergaard SD, Schmidt M, Horváth-Puhó E, et al. Thromboembolism and the Oxford-AstraZeneca COVID-19 vaccine: side-effect or coincidence? Lancet. 2021; 397(10283): 1441–1443, doi: 10.1016/S0140-6736(21)00762-5, indexed in Pubmed: 33798498.
30. Botton J, Jabagi MJ, Bertrand M, et al. Myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA COVID-19 vaccine in people aged 75 years or older. JAMA. 2022; 327(1): 80–82, doi: 10.1001/jama.2021.21699, indexed in Pubmed: 34807248.
31. Gong X, Yuan B, Yuan Y. Incidence and prognostic value of pulmonary embolism in COVID-19: A systematic review and meta-analysis. PLoS One. 2022; 17(3): e0263580, doi: 10.1371/journal.pone.0263580, indexed in Pubmed: 35286316.
32. James AH. Pregnancy, contraception and venous thromboembolism (deep vein thrombosis and pulmonary embolism). Vasc Med. 2017; 22(2): 166–169, doi: 10.1177/1358863X17690601, indexed in Pubmed: 28429662.
33. Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ. 2016; 353: i2002, doi: 10.1136/bmj.i2002, indexed in Pubmed: 27164970.
34. Palacios S, Colli E, Regidor PA. Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone-only pill. Acta Obstet Gynecol Scand. 2019; 98(12): 1549–1557, doi: 10.1111/aogs.13688, indexed in Pubmed: 31321765.
35. Mäkivaara LA, Ahti TM, Luukkaala T, et al. Persons with varicose veins have a high subsequent incidence of arterial disease: a popula-

tion-based study in Tampere, Finland. Angiology. 2007; 58(6): 704–709, doi: 10.1177/0003319707299202, indexed in Pubmed: 18216380.
36. Müller-Bühl U, Leutgeb R, Engeser P, et al. Varicose veins are a risk factor for deep venous thrombosis in general practice patients. Vasa. 2012; 41(5): 360–365, doi: 10.1024/0301-1526/a000222, indexed in Pubmed: 22915533.
37. Chang SL, Huang YL, Lee MC, et al. Association of varicose veins with incident venous thromboembolism and peripheral artery disease. JAMA. 2018; 319(8): 807–817, doi: 10.1001/jama.2018.0246, indexed in Pubmed: 29486040.
38. Oesch A. Thrombosis and pulmonary embolism risk in patients undergoing varicose vein surgery. Phlebolymphology. 2013; 20(2): 96–100.