AGENZIA ITALIANA DEL FARMACO

Thromboembolic complications after anti-COVID-19 vaccination with Vaxzevria (ChAdOx1 nCov-19, AstraZeneca) or with COVID-19 Vaccine Janssen (Ad.26. COV2.S, Johnson & Johnson)

1. Background

There have been several reports of thrombotic events at atypical sites (thrombosis of the cerebral venous sinuses and/or splanchnic district), associated with thrombocytopenia and with particularly serious clinical courses, in subjects recently vaccinated against SARS-CoV-2 with the viral vector vaccines Vaxzevria (ChAdOx1 nCov-19 of the company Astra Zeneca) and with COVID-19 Vaccine Janssen (Ad.26.COV2.S of the company Johnson & Johnson).

The competent authorities (Pharmacovigilance Risk Assessment Committee - PRAC of the European Medicines Agency and the Italian Medicines Agency) have intensified their pharmacovigilance activities, activating at the same time working groups to investigate the biological plausibility of the events, possible risk minimisation strategies, and the most appropriate methods for the clinical management of these rare events.

The following document (structured in questions and answers) represents the conclusions of the Haemostasis and Thrombosis Working Group of experts in coagulation pathologies appointed to support the AIFA Technical Scientific Committee CTS and is aimed at providing non-specialist physicians and healthcare professionals with the information currently available to identify this rare adverse event early and appropriately manage it.

2. What thromboembolic complications have been observed in subjects vaccinated with Vaxzevria and COVID-19 Vaccine Janssen?

In general, venous thromboembolic events occurring in subjects vaccinated with Vaxzevria and Janssen vaccine were not more frequent than those expected in the unvaccinated population [1,2].

However, rare cases of very peculiar events, characterised by cerebral venous sinus thrombosis (CVST) and/or splanchnic vein thrombosis, often associated with the presence of thrombi in multiple sites and thrombocytopenia, with severe bleeding and sometimes signs of disseminated intravascular coagulation (DIC), have been reported. These events have been observed almost exclusively within about three weeks after vaccination in healthy individuals under 60 years of age, predominantly women.

What is their frequency?

For the Vaxzevria vaccine, as of 4 April 2021, 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis, often associated with thrombocytopenia, have been reported by EudraVigilance[1], out of a total of about 34 million doses of Vaxzevria vaccine administered in the European Economic Area (EEA) and the United Kingdom (UK) [3], equal to 6.5 cases per million subjects who received at least one dose, referring at the date of analysis essentially to the first dose of vaccine.

From the preliminary EMA report, in the context of the ongoing European re-evaluation procedure of the Vaxzevria vaccine[2], it can be seen that for events of venous thrombosis at atypical sites associated with thrombocytopenia, a rate of about one case per 100,000 vaccinated individuals has been estimated.

The cases reported in the UK pharmacovigilance systems in the latest report published on 20 May[3] are also in line with this figure (309 cases for 23.9 million first doses with Vaxzevria vaccine).

In Italy, 34 cases of venous thrombosis in atypical sites were reported as of 26 April, 18 of which were associated with thrombocytopenia[4]. Compared to Vaxzevria administrations, 0.45 cases per 100,000 vaccinees were observed, a figure that could be affected by the lower representativeness of the Italian sample compared to European and Anglo-Saxon data.

As regards the events observed after the administration of the Janssen vaccine, the US surveillance system "Morbidity and mortality weekly report"[5] as of 30 April 2021 reports 17 cases of thrombosis in atypical sites associated with thrombocytopenia (events very similar to those observed with the Vaxzevria vaccine) out of 7.98 million doses of this vaccine administered in North America.

3. What might be the pathophysiological mechanisms underlying the most severe thromboembolic manifestations (cerebral venous sinus and/or splanchnic district thrombosis associated with thrombocytopenia)?

Cerebral venous sinus thrombosis (CVST) is a rare manifestation, with an annual incidence ranging between 0.2 and 1.5 cases per 100,000 inhabitants per year and a prevalence in women. It is typically associated with congenital or acquired prothrombotic conditions, some of which are characteristic of women, such as use of the pill or pregnancy and puerperium. However, it is rarely associated with thrombocytopenia.

[1] https://www.aifa.gov.it/documents/20142/1289823/2021.04.07_COVID-19%20AstraZeneca_IT.pdf
[2] https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf
[3] https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting
[4] https://www.aifa.gov.it/documents/20142/1315190/Rapporto_sorveglianza_vaccini_COVID-19_4.pdf
[5] https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e2.htm?s_cid=mm7018e2_w

The cases of CVST and/or splanchnic district that have been observed after administration of Vazxevria and the Janssen vaccine have shown as common features an onset between 5 and 21 days after vaccination, the concomitant presence of thrombocytopenia of varying severity and a rapidly progressive course, often with thrombosis in several other vascular districts, especially venous but also arterial, and in some cases coagulative alterations compatible with consumption coagulopathy (disseminated intravascular coagulation) in the days following hospitalisation.

This type of presentation, that is the association between thrombocytopenia and often multiple thrombotic complications with a rapidly worsening clinical course, is known to occur in certain thrombotic forms with an autoimmune basis, such as 'catastrophic' antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, or heparin-induced thrombocytopenia associated with thrombosis.

Indeed, some German and later Norwegian researchers found in 16 post-vaccination CVST cases a positivity for antibodies to the complex between platelet factor 4 and heparin, suggesting that the mechanism that triggers this complication in subjects not previously exposed to heparin may be what is defined as "heparin-induced autoimmune thrombocytopenia", perhaps triggered by the formation of complexes between polyanionic groups induced by the viral vector and platelet factor 4 or by the production of antibodies generated by the inflammatory reaction to the vaccine capable of cross-reacting with platelets and platelet factor 4 (PF4). However, there is still no evidence that this is the only pathophysiological mechanism that triggers this thrombotic syndrome and at least some of the cases described so far have not tested positive for antibodies to PF4/heparin complexes. It also remains to be defined why this adverse reaction develops only in some rare cases.

Alternative mechanisms, previously described with SARS-CoV and MERS vaccines, called 'antibody-induced disease escalation' (ADE) and triggered by the activation of specific inflammatory cell receptors by immune complexes generated after vaccination, cannot be excluded.

4. Have any factors been detected that can identify individuals at increased risk of developing these thromboembolic events?

At present, the lack of definition of a unitary pathophysiological mechanism underlying the rare cases of cerebral venous sinus and/or splanchnic district thrombosis associated with Vaxzevria vaccination makes it impossible to identify risk factors to look for in the general population.

This is particularly true when looking for the most common inherited thrombophilic conditions (e.g. Factor V Leiden mutation or Factor II G20210A heterozygosity, natural coagulation inhibitor deficiency), which can be estimated to be present in 5-6% of the European general population [6]. It is therefore to be expected that approximately 5,000-6,000 people per 100,000 subjects vaccinated with Vaxzevria are carriers of these coagulation anomalies, which clearly contrasts with

the extreme rarity of the most serious thrombotic complications observed (thrombosis of the cerebral venous sinuses and/or the splanchnic district).

The same interpretation can also be given in the case of risk factors, such as taking oestrogen, which in Italy is used by about 2,300,000 women.

It has long been known that these medicines increase the risk of VTE by about 4 times in all women, with some differences depending on the various types of compounds [7]. This means that the absolute annual risk of having a VTE episode for a woman aged <40 years, heterozygous for the FV Leiden mutation and taking an oestrogen preparation, is in the order of 0.4%. [8].

In light of this absolute risk of VTE, which is very low even in subjects with the most common conditions of hereditary thrombophilia, it has been determined that generalised thrombophilic screening prior to the use of oestrogen-progestagen compounds offers no advantage and is therefore not recommended for any woman [9].

These considerations apply all the more to extremely rare clinical conditions, in the order of a few cases per million people, such as venous thrombosis in atypical sites reported in subjects vaccinated with Vaxzevria or the Janssen vaccine.

Therefore, a hypothetical scenario in which vaccination acts as a trigger on a condition of congenital predisposition to lead to these atypical thrombotic events would concern approximately 1 thrombophilic subject out of 10,000 vaccinated.

All these data show that the most common thrombophilic conditions present in the population cannot be the determinant of these cases, and that therefore their systematic research before vaccination is in no way recommended.

5. Are there any medicines that can prevent these thromboembolic events?

The use of the most commonly available antithrombotic medicines – namely acetylsalicylic acid (ASA), unfractionated heparin (UFH) and low molecular weight heparins (LMWH) - is associated with a modest, but not negligible, increased risk of bleeding.

The use of ASA for primary prophylaxis of cardiovascular events, i.e. in subjects who have never had such problems, is associated with an estimated risk of major haemorrhage in the order of 23 cases/10,000 patients/year [10], equivalent to 88 cases of major haemorrhage per million patients over a 14-day period, which corresponds to that in which the majority of thrombotic adverse events reported after vaccination with Vaxzevria occurred.

Similarly, the use of NFE and LMWH for the prevention of venous thromboembolism in patients hospitalised for internal problems is associated with a risk of major bleeding in the order of 0.3% within 14 days of hospitalisation [11], equal to 3,000 cases of major bleeding per million subjects.

On the basis of these epidemiological considerations, if a generalised pharmacological prophylaxis strategy had been used, about 88 additional major bleeding associated with the use of ASA and 3,000 with the use of LMWH would have been expected per million people vaccinated with Vaxzevria.

In addition to this fundamental safety consideration, it should also be emphasised that there is no scientific evidence to support the hypothesis that ASA or LMWH are effective in reducing the risk of these very rare thrombotic events in subjects vaccinated against COVID-19 with Vaxzevria.

Therefore, in the face of a risk of serious adverse events, such as major bleeding, well quantifiable and relevant, and an unproven benefit in terms of reduction of the thromboembolic risk, however very low, the prescription of antithrombotic medicines for preventive purposes in subjects undergoing vaccination is strongly discouraged. It is clear that these medicines can be continued in patients already under treatment.

6. What are the main clinical signs or symptoms that should lead us to suspect this adverse event (thrombosis of the cerebral venous sinuses and/or of the splanchnic district)? What should be done in the face of such suspicion?

The onset of a thrombotic complication at the level of the cerebral or abdominal venous system should be suspected when some suggestive clinical manifestations appear, which are already known from the literature and clinical practice.

In about 9 out of 10 cases, cerebral venous sinus thrombosis (CVST) presents with headache of particular intensity, which patients generally report as “never experienced before”. More often the pain is worsening, progressively increasing over a couple of days, but at other times it can reach maximum intensity in a very short time. In the latter situations, nausea and vomiting, photophobia, diplopia, decreased vision or loss of consciousness are also associated [12].

Other clinical manifestations of CVST, on the other hand, may be represented by epileptic seizures, present at the onset or after the onset of the headache and neurological deficits similar to those observed after an ischaemic stroke. It should not be forgotten, in fact, that thrombosis of the cerebral venous sinuses is classified both among the rare forms of venous thrombosis and among the rare forms of stroke. They should always be suspected in the presence of neurological side deficits in young subjects, especially if preceded or associated with headache.

Even in thrombosis of the abdominal veins the most common symptom is pain, often widespread and particularly intense. It can be associated with nausea and loss of appetite. Other times it is associated with gastrointestinal bleeding, especially with the emission of faeces mixed with blood. However, this is a more subtle pathology, in which pain is reported as the first manifestation by no more than 6 out of 10 people and which is not infrequently diagnosed (up to 1 in 3 cases) without

having first been clinically suspected. For this reason, in the presence of thrombosis in other sites and thrombocytopenia after administration of the vaccine it is advisable to also study the abdominal venous circulation [12].

In the presence of one or more of the above-mentioned symptoms occurring in the days following vaccine administration, and in particular if around day 7-21, especially when the pain is of particular intensity and/or is associated with other symptoms or signs, it is advisable to rapidly submit the patient to diagnostic investigations. If the presentation is significant, it is essential to send the patient immediately to the emergency room, informing of the recent vaccination. If the clinical picture is doubtful because of the presence of mild symptoms or symptoms already experienced prior to vaccination, careful monitoring of the clinical course is recommended.

7. What instrumental and laboratory tests are indicated for the initial diagnosis of thrombosis of the cerebral venous sinuses and/or of the abdominal area with thrombocytopenia?

In the evaluation of these patients, it is important to immediately perform: CBC, PT, aPTT, fibrinogen, D-dimer, liver function tests (transaminase, bilirubin, alkaline phosphatase, gamma-GT) and creatinine.

In the case of suspected thrombosis of the cerebral venous sinuses, the first-choice exam today is cerebral CT angiography, indicating the clinical suspicion to the neuroradiologist so that the venous districts can be correctly studied with the contrast medium. In case of doubt or as an alternative, MRI angiography can be used. D-dimer has shown good sensitivity if performed within 14 days of the onset of symptoms to decide, if negative, not to submit patients to radiological examinations. The determination of D-dimer in recently vaccinated patients, however, is only recommended within specialist diagnostic procedures [13,14].

If abdominal venous thrombosis is suspected, an echo-colour Doppler can be performed as a first step. This examination is quick and easy to perform and, if performed accurately, is useful in diagnosing portal, splenic and even supra-hepatic venous thrombosis, but loses diagnostic sensitivity in mesenteric venous thrombosis. However, it is advisable to perform an abdominal CT angiogram both to assess the extent of thrombosis and in the case of ultrasound findings and in case of negative ultrasound examination itself, especially if the clinical suspicion is high (e.g. abdominal pain in the lower quadrants, intestinal bleeding). There are no data on the usefulness of D-dimer in the diagnostic approach to abdominal venous thrombosis [15,16].

8. How should thrombosis of the cerebral venous sinuses or of the splanchnic district with thrombocytopenia be treated?

The incomplete knowledge of pathogenetic mechanisms allows us to express only suggestions, largely derived from general experience and not validated in this specific situation [17].

It is essential to personalise the antithrombotic therapeutic strategies according to the observed platelet count, also in consideration of the bleeding complications observed very often in these cases: as a general rule, an anticoagulant (or fibrinolytic) treatment should not be undertaken in the event of a platelet count below 25,000/mmc, should be administered at reduced dosages (halved) compared to the standard dosages in case of platelet count between 25,000 and 50,000/mmc, it can be performed with standard dosages and with relative safety in case of platelet count higher than 50,000/mmc. Of course, in case of current or recent bleeding, these indications should be reviewed by modulating the treatment according to the clinical situation. It should be remembered that in the case of thrombosis of the cerebral venous sinuses, a portion of perisinusal bleeding is linked to the alteration of circulation and is not a contraindication to treatment, except for the formation of large parenchymal haematomas or with clinical repercussions.

Therefore, the overall therapeutic strategy must take into account, as a matter of priority, the platelet count, and how to possibly increase it. The hypothesis of an immunological pathogenesis and the positive observation in some cases suggests in the case of thrombocytopenia (defined as platelet count <100,000/mmc) the use of intravenous immunoglobulins. (1 g/kg/day for 2 days) associated with high dose steroids (dexamethasone 40 mg/day i.v. for at least 4 days or prednisone 1 mg/kg/day for 7-14 days). This strategy should also be implemented in the case of platelet counts between 50,000 and 100,000/mmc, since a significant decrease in platelet counts cannot be excluded in the days following diagnosis.

In case of a critical platelet count (<25,000/mmc and/or major bleeding in progress), the use of platelet transfusions should be considered. Although contraindicated in principle due to possible immunological pathogenesis, they have proved effective and safe in some of the reported cases.

As for the choice of the anticoagulant, the use of unfractionated heparin or low molecular weight heparin should be excluded unless anti-PF4 antibodies are negative (possibly confirmed with HIPA test). If these tests are not feasible in a short time, it is suggested to use fondaparinux as an anticoagulant agent. If available, please note that argatroban i.v. may present aspects of better gradualness of treatment intensity in relation to platelet count (based on the aPTT values) and better safety, being able to stop treatment quickly in the event of bleeding complications. This treatment should be preferred in case of renal insufficiency, which makes management with fondaparinux more problematic.

9. **Why is Vaxzevria now preferentially indicated in subjects aged >60 years, contrary to what was initially recommended?**

Following EMA approval, AIFA authorised the Vaxzevria vaccine (formerly COVID-19 AstraZeneca) on 30 January 2021 [18], indicating, pending the acquisition of further data, its preferential use in subjects between 18 and 55 years of age. This choice was justified by the scarcity of data available in the registration studies for the population aged >55 years, although a good antibody response had already been observed in the limited sample for this subpopulation. The availability of further data (mainly from observational studies conducted in the United Kingdom and Scotland and released in February 2021) concerning good results in terms of efficacy and safety of the vaccine in older age groups [19,20] led to two subsequent circulars issued by the Ministry of Health allowing the vaccine to be used first in subjects up to 65 years of age and then also in those aged >65 years. Subsequently, however, rare serious adverse events have been reported, occurring within 14 days of administration of the Vaxzevria vaccine in subjects in most cases aged <60 years, predominantly women, characterised by thrombosis in unusual sites often associated with thrombocytopenia. These findings led the EMA, after an evaluation of all pharmacovigilance data, to subsequently update the vaccine safety information in the Summary of Product Characteristics and Patient Information Leaflet. The EMA analysis confirmed that the benefit/risk balance of the Vaxzevria vaccine remains positive overall, as the vaccine is definitely effective in reducing the risk of severe disease, hospitalisation and death related to COVID-19. This balance is considered progressively more favourable as age increases, both because of the higher risks of developing severe COVID-19, and because no increased risk of the thrombotic events described above was found in vaccinated subjects over 60 years of age. On the basis of these considerations, a circular of the Ministry of Health [21], taking into account the opinion of the Technical Scientific Committee (STC) of AIFA expressed on 7 April 2021, recommended the preferential use of Vaxzevria in people over 60 years of age. A subsequent circular of the Ministry of Health [22], having acquired the opinion of the CTS of 20 April 2021, taking into account the similarities between the two vaccines (Janssen and Vaxzevria), both with regard to the platforms used (adenoviral vector in both cases) and to the type of events (in particular with regard to the clinical picture and the age of onset), established that the same conditions of use of the Vaxzevria vaccine should be provided for the Janssen vaccine.

10. Is there a rationale for deciding what to do with the second dose for subjects <60 years who have already taken the first dose of Vaxzevria?

This issue only concerns the Vaxzevria vaccine, as the Janssen vaccine requires a single administration.

As we have seen, the cases of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) reported after the first dose were few per million vaccinees, predominantly female, and concentrated in the 25-60 age group.

The lack of a definition of the etiopathogenetic mechanism underlying the cases of venous thrombosis in atypical sites accompanied by thrombocytopenia makes it difficult to predict whether, and to what extent, these complications may occur after the second dose in subjects who are in the age group in which most cases of VITT have occurred.

One pathogenetic hypothesis is that Vaxzevria, and in particular the adenoviral vector it uses, may activate the coagulation cascade with yet undefined mechanisms and that this may lead, in subjects with unidentified predispositions, to the rare thrombotic phenomenon in atypical sites.

In this case, it is reasonable to expect that with the first administration of the vaccine, the so-called 'depletion of susceptibles' [23] has already occurred, i.e. a sort of selection of subjects who, for unknown reasons, are more exposed to the action of these hypothetical pro-thrombotic mechanisms, and that any adverse events would therefore be even rarer following the second dose.

An alternative hypothesis suggests that the thrombotic manifestations may be based on an auto-immune mechanism, with the production of auto-antibodies capable of activating coagulation. This hypothesis has been suggested by Greinacher's German group and recently published in the New England Journal of Medicine [24] and suggests that Vaxzevria induces the production of auto-antibodies that, through an interaction with Platelet Factor 4, are able to activate platelets and coagulation in general, causing a pro-thrombotic picture similar to that observed in the course of heparin thrombocytopenia (HIT).

Similar observations of the presence of anti-PF4 antibodies in subjects with VITT have also been reported by other groups [25,26], and also in association with another vaccine with an adenoviral vector [27].

In this hypothesis, re-exposure to the vaccine could lead to important clinical manifestations in some subjects who had already activated an abnormal immune response at the first dose, even if not clinically evident.

Although in the "classic" HIT there is no evidence that re-exposure to heparin more than 3 months after the first episode is associated with a reappearance of the phenomenon [28], in the particular setting of vaccination with Vaxzevria it cannot be exclude that a subject who has not developed the rare reaction involving platelets with the first dose, cannot do so with the second.

As of 12 May, the UK Medicines & Healthcare products Regulatory Agency (MHRA) reported 15 cases of atypical thrombosis with thrombocytopenia out of approximately 9 million second doses of Vaxzevria administered [3], which would seem to correspond at the moment to a weaker signal than that found for the first doses and in any case definable as very rare.

Although this data seems to support the hypothesis of the "depletion of the susceptible", and to reassure about the administration of the second doses, it should be noted that no information is currently available on the age and sex of these latter cases. Therefore, the safety of the

administration of Vaxzevria in subjects under the age of 60 remains an open issue, and there is some uncertainty about this.

In spite of these uncertainties, the Haemostasis and Thrombosis Working Group believes that the completion of the vaccine schedule represents the strategy to counter the spread of the SARS-Cov-2 virus that guarantees the best level of protection.

At the same time, the careful pharmacovigilance activity already in place will allow the collection of up-to-date data and establish whether further recommendations are needed to optimise, where appropriate, the benefit/risk profile in the individual patient.

References

1. https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots
2. Østergaard SD, Schmidt M, Horváth-Puhó E, Thomsen RW, Sørensen HT. Thromboembolism and the Oxford-AstraZeneca COVID-19 vaccine: side-effect or coincidence? Lancet. 2021 Mar 30:S0140-6736(21)00762.
3. Medicines & Healthcare products Regulatory Agency. Disponibile al sito: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Consultato: 6.5.2021.
4. EMA/CHMP/214855/2021 Committee for Medicinal Products for Human Use (CHMP). Assessment report. 23 april 2021. Disponibile al sito: https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf. Consultato: 6.5.2021.
5. European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. Disponibile al sito: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab.Consultato: 6.5.2021
6. Mannucci PM, Franchini M. Classic thrombophilic gene variants. Thromb Haemost. 2015 Nov;114(5):885-9. doi: 10.1160/TH15-02-0141.
7. Wu O, Robertson L, Langhorne P, Twaddle S, Lowe GD, Clark P et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis:Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thromb Haemost 2005;94:17-25. doi: 10.1160/TH04-11-0759
8. Middeldorp S. Is thrombophilia testing useful? Hematology Am Soc Hematol Educ Program. 2011;2011:150-5. doi: 10.1182/asheducation-2011.1.150.
9. ISS-SNLG. Prevenzione delle complicanze trombotiche associate all'uso di estro-progestinici in età riproduttiva. CONFERENZA NAZIONALE DI CONSENSO. Roma, 18-19 settembre 2008. Disponibile al sito: https://www.researchgate.net/publication/336746477_Consensus_Conference_Prevenzione_delle_complicanze_trombotiche_associate_all'uso_di_estroprogestinici_in_eta_riproduttiva. Consultato: 8 aprile 2021
10. Zheng SL et al. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. JAMA. 2019 Jan 22;321(3):277-287. doi: 10.1001/jama.2018.20578;
11. Rosenberg DJ et al. External validation of the IMPROVE Bleeding Risk Assessment Model in medical patients. Thromb Haemost. 2016 Aug 30;116(3):530-6. doi: 10.1160/TH16-01-0003.
12. Riva N, Ageno W. Clinical manifestations and imaging tools in the diagnosis of splanchnic and cerebral vein thromboses. Thromb Res. 2018;163:252-259.
13. Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, di Minno M, Maino A, Martinelli I, Masuhr F, Aguiar de Sousa D, Stam J; European Stroke Organization. **European Stroke** Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10):1203-1213

14. Silvis SM, de Sousa DA, Ferro JM, Coutinho JM. Cerebral venous thrombosis. Nat Rev Neurol. 2017;13(9):555-565.
15. European Association for the Study of the Liver. ASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016;64(1):179-202.
16. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, Lisman T, Valla DC. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;73(1):366-413
17. Gresele P, Marietta M, Ageno W, Marcucci R, Contino L, Donadini MP, Russo L, Tiscia GL, Palareti G, Tripodi A, Mannucci PM, De Stefano V. 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 (SISET). Blood Transfus 2021; DOI 10.2450/2021.0117-21
18. https://www.aifa.gov.it/en/astrazeneca
19. Vasileiou E, Simpson C R, Robertson C, Shi T, PhD, Kerr et Al Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. Pre print https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264
20. Lopez Bernal J, Andrews N, Gower C, Stowe G, Robertson C,Tessier E et Al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1.full.pdf+html
21. Ministero della Salute. https://www.aifa.gov.it/documents/20142/0/79629_1.pdf
22. Ministero della Salute. ministero salute - circolare 16722-21.04.2021.pdf
23. Lipsitch M, Goldstein E, Ray GT, Fireman B. Depletion-of-susceptibles bias in influenza vaccine waning studies: how to ensure robust results. Epidemiol Infect. 2019 Nov 27;147:e306
24. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021 Apr 9. doi: 10.1056/NEJMoa2104840.
25. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021; doi: 10.1056/NEJMoa2104882.
26. Scully M, Singh D, Lown R et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021; doi 10.1056/NEJMoa2105385.
27. See I, Su JR, Lale A, Woo EJ et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021 Apr 30. doi: 10.1001/jama.2021.7517. Online ahead of print.
28. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med. 2001;344(17):1286-1292.

This document was drawn up by the Haemostasis and Thrombosis Working Group (Walter Ageno, Valerio De Stefano -coordinator-, Paolo Gresele, Pier Mannuccio Mannucci, Marco Marietta, Gualtiero Palareti) and reviewed and approved by the AIFA Technical Scientific Committee.