

Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)

Interim guidance

19 July 2021

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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Abbreviations and acronyms

AEFI	Adverse event following immunization
aHIT	Autoimmune heparin-induced thrombocytopenia
Ad26.COVID-19 vaccine	Johnson & Johnson (J&J) Janssen COVID-19 Ad26.COVID-19 vaccine
APTT	Activated partial thromboplastin time
BC	Brighton Collaboration
ChAdOx-1 vaccine	AstraZeneca COVID-19 ChAdOx-1 vaccine
CT scan	Computerized tomography scan
CTPA	CT pulmonary angiogram
CVST	Cerebral venous sinus thrombosis
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EtD	Evidence-to-decision-making
FEU	Fibrinogen Equivalent Units
GACVS	Global Advisory Committee on Vaccine Safety
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation (a method of assessing the certainty of evidence)
HIT	Heparin induced thrombocytopenia
ITP	Idiopathic thrombocytopenic purpura
IVB	Immunizations, Vaccines and Biologicals Department
IVIG	Intravenous immunoglobulin
LMICs	Low-and-middle income countries
MRI	Magnetic resonance imaging
MSD	Mental Health and Substance Use Department
NCD	Noncommunicable Diseases Department
NHAC	Non-heparin-based anticoagulants
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PF4	Platelet factor 4
PICO	Patient/intervention/comparator/outcome)
QNS	Quality Norms and Standards
RPQ	Regulation and Prequalification
SMR	Standardized morbidity ratio
SVT	Splanchnic vein thrombosis
TTP	Thrombotic thrombocytopenic purpura
TTS	Thrombosis thrombocytopenia syndrome
WHE	WHO Health Emergencies Programme

Key points

Background	Thrombosis with thrombocytopenia syndrome (TTS) has been reported in individuals vaccinated with COVID-19 non-replicant adenovirus vector-based vaccines (AstraZeneca COVID-19 ChAdOx-1 vaccine and Johnson & Johnson (J&J) Janssen COVID-19 Ad26.COV2-S vaccine).
Scope	The present document aims to provide interim guidance on the recognition and management of thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination.
Case definition	TTS is defined by the presence of a thrombosis/thromboembolism, generally in uncommon locations, such as cerebral venous sinus or splanchnic veins and marked thrombocytopenia ($<50 \times 10^9/L$) following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine. Cases of thrombosis/thromboembolisms (i.e., pulmonary, deep vein thrombosis, coronary arteries, cerebral arteries) in common location have also been reported following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine.
Incidence	The cumulative incidence of TTS following vaccination with a non-replicant adenovirus vector-based vaccine ranges from 0.5 to 6.8 cases per 100 000 vaccinees. Incidence rates differ depending on the vaccine, age, sex, geographical distribution and interpretation of the case definition. The observed-to-expected rate is higher following vaccination with the ChAdOx-1 vaccine, in females and in patients aged <60 years. Most TTS cases have been reported within 3 to 30 days following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine. Information from low- and middle-income countries will be fundamental for understanding the incidence of TTS better, given that the adenovirus vector-based vaccines have been used more extensively in these countries.
Risk factors	The main risk factors for TTS following vaccination with COVID-19 adenovirus vector-based vaccines are the use of non-replicant adenovirus vector-based vaccines and younger age. There is currently no evidence that traditional risk factors for thrombosis/thromboembolisms increase the risk of TTS in this context.
Pathophysiology	TTS has been associated with the presence of anti-platelet factor 4 (anti-PF4) antibodies. There are similarities with autoimmune heparin-induced thrombocytopenia (aHIT). TTS may be caused by the binding of anti-PF4 to platelets, causing platelet activation and aggregation, thrombosis, platelet consumption, and thrombocytopenia. However, the exact mechanisms are still unclear and should be further investigated.
Clinical presentation	TTS should be suspected in patients presenting with severe and unusual headache, abdominal pain with or without vomiting, sudden onset of breathing difficulty, chest pain or limb pains, particularly in those aged under 60 years, within four weeks following vaccination. Patients with suggestive clinical symptoms should promptly undergo investigations to rule out thrombotic events and presence of thrombocytopenia.
Laboratory diagnosis	Individuals who present with thrombosis within four weeks following vaccination should be evaluated for thrombocytopenia, increased D-dimer and positive anti-PF4 antibodies. An enzyme-linked immunosorbent assay (ELISA) should be used to detect anti-PF4 antibodies, as rapid immunoassays are not as sensitive. The presence of anti-PF4 antibodies in a patient with a thrombotic event and thrombocytopenia following COVID-19 vaccination is highly suggestive of TTS. Other biomarkers can be helpful in the laboratory diagnosis of TTS, including D-dimer, fibrinogen, and blood smear to confirm reduced platelets and to rule out platelet clumping. The case definition implies the absence of a better alternative explanation for the condition.

Imaging	Suitable imaging examinations should be performed in patients with suspected TTS as soon as possible, depending on anatomical location, especially in those who present with thrombocytopenia within 30 days post-vaccination.
Clinical case management	Vaccinated individuals should be advised to seek immediate medical attention if they develop symptoms including severe or persistent headache, blurred vision, shortness of breath, chest pain, leg swelling, persistent abdominal pain or unusual skin bruising and/or petechiae (tiny purple, red, or brown spots on the skin) occurring within four weeks after vaccination, although some cases have been reported later than 30 days post-vaccination. These patients should be investigated for thrombosis and thrombocytopenia. Reporting these symptoms must be made easy for the vaccine recipients, and could include helplines and hospital vaccine centre, online reporting systems.
Treatment	<p>WHO advises against the use of heparin in individuals with TTS in the context of COVID-19 vaccination (<i>conditional recommendation, very low certainty</i>).</p> <p>WHO recommends against the use of platelet infusion for individuals with TTS in the context of COVID-19 vaccination in all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe (platelets $<50\,000/\mu\text{L}$), and platelet transfusion is required to be able to proceed with emergency surgery (<i>strong, very low certainty</i>).</p> <p>WHO recommends the use of intravenous immunoglobulins (IVIG) and/or non-heparin-based anticoagulants for individuals with TTS following COVID-19 vaccination (<i>strong, very low certainty</i>).</p> <p>WHO does not provide any recommendation for steroid treatment, but notes the general use of steroids and the likelihood that steroids will usually be given in combination with other treatments.</p>

Background, scope, and rationale

Since March 2021, cases of thromboses associated with thrombocytopenia have been reported in patients vaccinated with the Oxford-AstraZeneca ChAdOx1-S and Johnson & Johnson (J&J) Janssen Ad26.COVID-19 COVID-19 vaccines. Evaluation of the cases by national and international bodies concluded that there was a plausible causal link between these two adenovirus vectored vaccines and the events (1-3).

The association was based on the temporal association with vaccination, an increased incidence when compared with expected baseline rates, for cerebral venous sinus thrombosis (CVST), the presence of simultaneous multiple thromboses in some patients, the presence of thrombocytopenia and anti-platelet factor 4 antibodies (anti-PF4), and a higher mortality rate than that reported in the literature (1-30).

The purpose of this document is to provide interim guidance on the recognition and clinical management of this rare adverse event, known as thrombosis with thrombocytopenia syndrome (TTS), following vaccination. This newly reported syndrome has received different names, including vaccine-induced immune thrombotic thrombocytopenia (VIITT), vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), and vaccine-induced thrombotic thrombocytopenia (VITT). **In the present document, the term TTS will be used in the context of COVID-19 adenovirus-vector vaccines unless otherwise specified.**

Knowledge about TTS following vaccination with a COVID-19 adenovirus vector-based vaccine is rapidly evolving. This document aims to increase awareness about TTS in the context of COVID-19 vaccination and thereby help healthcare providers in the assessment and management of potential TTS cases. Individuals and healthcare providers must be aware of the symptoms of possible TTS to enable prompt diagnosis and early treatment. Healthcare providers should be aware of the relevant diagnostic tests and know which treatments should be given and which should be avoided. This document reviews the existing information on the epidemiology, risk factors, aetiology, diagnosis and clinical management protocol for TTS with specific considerations for low-and-middle income countries (LMICs). It will be revised as new evidence emerges. Detailed data regarding the methodology used in the guideline development is available in [Annex 5: Methods for guideline development](#). TTS is a very rare adverse event following immunization (AEFI) and the benefits of COVID-19 vaccination clearly outweigh the potential risks.

Case definition

An interim case definition that could be practical to use in clinical settings has been developed with input from a representative of the Brighton Collaboration (BC) group, to ensure the harmonization with the BC definition of TTS (*version 10.16.3-May-23-2021*). The present interim case definition aims to provide an optimal balance between sensitivity and specificity while ensuring applicability across all resource settings. It is based on the existing evidence and as needed, can be updated with the publication of new cases and data (32).

It is important to note that there is a difference between the clinical management of a potential case, and the case definition. The clinical management algorithms (see below) aim to identify all possible cases with the intent of offering the most adequate treatments while continuing to confirm or rule out TTS, and avoid potentially harmful treatments. Since platelet counts can evolve over time and results for some investigations are not available instantly, the classification of cases should ideally be finalized once all available and existing data have been analysed. The investigations must be repeated if symptoms do not resolve.

The definition of TTS is based on the combined presence of a thrombosis and new onset thrombocytopenia (**Table 1**). Three levels of certainty are proposed, based on the anatomical location of the thrombosis, the severity of thrombocytopenia and the outcome of laboratory investigations (**Table 2**). The most common thromboses in the general population are limb vein thrombosis, pulmonary artery/vein thrombosis, cerebral artery thrombosis or myocardial artery thrombosis. However in the case of TTS, the thromboses have been observed mainly in cerebral and splanchnic veins. Multiple-organ thromboses have also been observed, although less commonly. In view of these observations, the term 'unusual location' thrombosis is used to describe the thromboses in TTS.

WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty (**Table 2**). It includes three mandatory criteria (A, B and C) with C defining the degree of certainty based on the combination of major and minor criteria presented in **Table 1**:

- A. Vaccination against COVID within last 30 days.
- B. No alternative explanation for the condition (i.e., no heparin exposure within the previous 100 days).
- C. Combination of thrombosis and thrombocytopenia.

Table 1: Major and minor criteria for thrombocytopenia, thrombotic events and laboratory examinations.

Classification	Major criteria	Minor criteria
Thrombosis	<p>CONFIRMED diagnosis of thrombosis by imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism in an uncommon location:</p> <ul style="list-style-type: none"> • cerebral veins OR • splanchnic veins OR • multiple organ 	<p>CONFIRMED diagnosis of thrombosis by imaging study, surgical, or pathology consistent with thrombosis/thromboembolism in a common location:</p> <ul style="list-style-type: none"> • pulmonary arteries/veins OR • limb veins OR • coronary arteries OR • cerebral arteries OR • other arteries/veins <p>OR</p> <p>SUGGESTIVE thrombosis by supporting imaging or laboratory findings suggestive but not definitive of thrombosis/thromboembolism in any location</p> <p>OR</p> <p>SUGGESTIVE thrombosis by specific clinical syndromes consistent with thrombosis or thromboembolism event in any location</p>
Thrombocytopenia	<p>Platelet count: <50 x 10⁹/L AND Confirmatory peripheral smear showing reduced platelets AND No evidence of platelet clumping</p>	<p>Platelet count: > 50 x 10⁹/L - <150 x 10⁹/L</p> <p>OR</p> <p>>50% decrease from baseline platelet count</p>
Laboratory (other than thrombocytopenia)	<p>Positive anti-platelet factor 4 antibodies (with ELISA) or platelet functional assay (i.e., serotonin release assay)</p>	<p>D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)</p>

Table 2. WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty.

Classification	Level 1 (Confirmed case)		Level 2 (Probable case)		Level 3 (Possible case)
	Major / Minor	Major	Minor	Major	Minor
Thrombosis	Major / Minor	Major	Minor	Major	Minor
Thrombocytopenia	Major / Minor	Major	Major	Minor	Minor
Laboratory (Other than thrombocytopenia)	Major	Minor	Minor	Minor	Minor / No laboratory

Cases with incomplete investigation or the presence of other possible explanations should be classified as possible cases of TTS until better evidence is available. Detailed information on these diagnostic criteria including imaging modalities, surgical and pathological findings and clinical symptoms for TTS are available in more detail below.

The clinical diagnosis of TTS is summarized in [Figure 1](#).

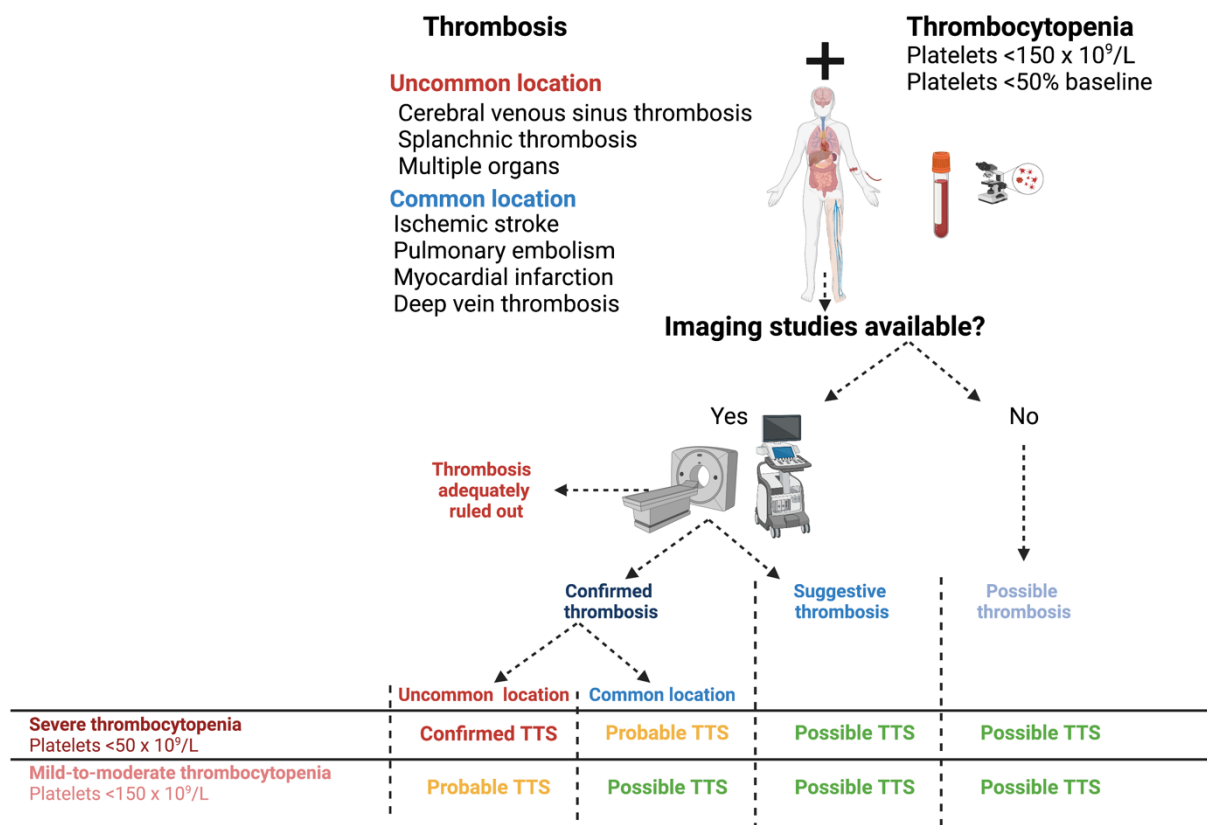


Figure 1: Algorithm for the clinical diagnosis of thrombosis thrombocytopenia syndrome

Figure created with BioRender.com

Incidence

Overview

The epidemiology of TTS is a rapidly evolving field, and its interpretation requires special considerations. The incidence may be influenced by the patient profile in each country and the specific vaccines used. The risk may depend on age, sex or other factors. Public awareness may also influence the clinical outcome as patients who present earlier could receive treatment sooner, resulting in lower morbidity/mortality. In most studies and official reports, the observed case rates are from spontaneous notifications and therefore these are the notification rates rather than with the real case rates, which may be under-estimated due to underreporting. In addition, the epidemiology of uncommon thrombotic events, such as splanchnic thrombosis, is not well established in the general population, so increased risk may be difficult to estimate. In addition, a precise denominator is needed, i.e., the numbers of those vaccinated in different age groups and by gender. A study analysing the background rates of TTS from eight countries reported significant population-level heterogeneity in the rates, suggesting that estimates from one country or region should be interpreted with caution, due to systematic error associated with the databases used to estimate the control rates (33-35).

TTS incidence can be estimated using the crude cumulative incidence per 100 000 persons or the standardized morbidity ratio (SMR), also known as observed-to-expected analysis, that analyses the ratio between the observed number of cases in the population and the number of cases that would be expected according to baseline incidence, with a 95% confidence interval (CI) (1-3).

Incidence of CVST in the general population and in COVID-19 patients

The incidence of CVST in the general population is estimated to be between 1.2 and 2.0 cases/100 000 person/year (36). In a national study done in the United States of America from 2006 to 2016, the incidence varied by sex (more frequent in women), age (more frequent between 18-44 years) and race (more frequent in African American > Caucasian > Asian). The incidence of venous thromboembolism has been reported to be almost 70% less frequent in southeast Asian populations compared to those of European descent (36).

Thrombotic complications are frequent in patients with active or recent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (37). Thrombocytopenia (<150 000 platelets/ μ L) has been reported to occur in about 15% of COVID-19 patients with CVST. The relative risk of having CVST for patients with COVID-19, compared with those without, is estimated to be at least 14 times higher. The incidence of CVST in COVID-19 patients was analysed in a study collecting real-time data from electronic medical records between 24 March 2020, and 1 March 2021. Among the 667 551 COVID-19 patients at risk there were 42 CVST cases and among the 65 796 480 non-COVID patients there were 1022 cases (rate 0.0001 vs. 0.000002, OR: 41.0; 95% CI: 30.1-55.8), with a higher mortality rate in the COVID-19 group (11.9% vs. 2.8%, OR: 4.6; 95% CI: 1.3-13.0) (35). Thrombocytopenia may also be present in patients with COVID-19 infection, including patients with thrombotic complications, however it is generally milder than thrombocytopenia reported in patients with TTS (37). The presence of an active SARS-CoV-2 infection was ruled out in most TTS cases reported to date (1-30).

Incidence of CVST following vaccination with a COVID-19 non-replicant adenovirus-vectored vaccine

[Table 1 in Annex 4](#) summarizes the existing evidence from studies reporting the incidence of TTS after vaccination with a non-replicant adenovirus vector-based COVID 19 vaccine as of 27 May 2021 (18, 39, 41–48). A report from the European Medicines Agency (EMA), published on 8 April 2021, assessed the number of reported cases in the European Economic Area member states and the United Kingdom up to 22 March 2021, using databases from Italy (Agenzia Regionale di Sanità, ARS) and Spain (Foundation for the Promotion of Health and Biomedical Research of Valencia Region, FISABIO) as comparators, reported a global observed-to-expected rate of 7.73 (95% CI: 5.3-10.8) per 100 000 persons over 14 days (7). A population study conducted in Denmark and Norway in patients who received the first dose of ChAdOx-1 vaccine, from 9 February 2021 to 11 March 2021, reported an observed-to-expected incidence of 20.25 (95% CI: 8.14-41.73) cases within 28 days of vaccination, and an excess of 2.5 (95% CI: 0.9-5.2) CVST cases per 100 000 vaccinations over 28 days. The observed-to-expected rate for venous thromboembolic events was 1.97 (95% CI: 1.5-2.54) with 11 (95% CI: 5.6-17.0) excess events per 100 000 doses (38).

The incidence of CVST after vaccination with a non-replicant adenovirus vector-based COVID 19 vaccine is also proportionally higher in women (although this may have been due to vaccination of priority groups that may have included more women) and patients aged <60 years (1, 2). The incidence of cerebrovascular events per 100 000 person-years after ChAdOx1-S vaccination was higher in women (29.4; 95% CI: 19.8-42.0) compared with men (6.2; 95% CI: 1.3-18.0) within one month in a German study (18). The median age was 40 years, with few cases occurring in patients aged >60 years. This study reported a CVST rate of 20.52 (95% CI: 5.59-52.5) per 100 000 person-years in females aged >60 years, but not in males aged >60 years (18). The EMA signal assessment report published on 8 April 2021, reported an increased SMR for CVST over 14 days, in patients vaccinated with the ChAdOx1-S COVID-19 vaccine, compared with the background rate, particularly in patients aged 18-60, in patients with and without thrombocytopenia. The association with disseminated intravascular coagulation (DIC) or other embolic and thrombotic events was inconclusive at that time.

Most cases of TTS have been reported after the first dose of ChAdOx-1, but there are still insufficient data to establish whether the risk of TTS differs between the first and second dose because substantially fewer second doses of the ChAdOx-1 vaccine have been given. The Ad26.COVS-2 vaccine is administered as a single dose. Data about Ad26.COVS-2 was initially reported in the United States of America. The Center for Disease Control and Prevention reported 28 confirmed TTS cases among 8 739 657 people vaccinated, as of 12 May 2021, which appears less frequent than for ChAdOx1-S, with the highest rate reported being 12.4 cases per million doses for women aged 30-39 years (39). At the time of publication of this interim guidance, no TTS cases have been reported following vaccination with other adenovirus vector-based COVID-19 vaccines or mRNA COVID-19 vaccines (40). It is also important to acknowledge that although TTS events have been reported following vaccination with the two adenovirus vector-based vaccines, other vaccines using adenovirus as a vector, should also be under careful surveillance since the absence of TTS cases may be due to underreporting, given the absence of well-established pharmacovigilance systems in some countries. Country-level active surveillance could be considered in addition to passive surveillance systems.

Risk factors

The main risk factors for TTS are age (41-48) and the type of non-replicant adenovirus vector-based COVID-19 vaccine, with a higher risk associated with ChAdOx1-s than with Ad26.COV2-S (1-30). To date, there is no evidence that supports an increased risk of vaccine-related TTS or a more severe clinical presentation in patients with pre-existing thrombotic risk factors. The frequency of thrombotic risk factors in TTS (approximately 30%) does not appear to differ from the reported frequency of thrombotic risk factors (37-84%) in patients with thrombotic events unrelated to vaccination (49-58). However, the presence of additional causes for the thromboses must be evaluated according to the local standard of care, to ensure that patients are treated appropriately, whenever necessary, particularly in common location thromboses, such as deep vein thrombosis (DVT) or pulmonary embolism (PE). The list of thrombosis risk factors is available in [Annex 1](#).

Pathophysiology

The aetiology of TTS is thought to be immune-mediated (59). The presence of anti-PF4 antibodies, the temporal association with immunization, the clinical onset of symptoms and the presence of multiple thromboses supports this hypothesis. Since there are several similarities with autoimmune heparin-induced thrombocytopenia (aHIT), it is thought that the pathophysiology of TTS is similar to that of aHIT's. Hence, like for aHIT, TTS may be caused by the binding of PF4 antibodies to an unknown (or yet to be described) polyanion, which then leads to a conformational change in the PF4 antibodies which reveals a new antigen, resulting in IgG antibodies being developed against this neo complex of polyanion-PF4 antibodies (4-6, 10, 59-64). The PF4-polyanion bound to the anti-PF4 antibodies subsequently binds to the Fc-gamma receptors of platelets, thereby crosslinking the platelets which results in platelet activation and aggregation. This leads to platelet consumption and thrombocytopenia as well as microparticle production and thrombin generation that contributes to development of thrombosis (59-69). There are clinical and laboratory similarities between TTS and aHIT, however, the explanation for unusual intracranial or splanchnic vein locations is currently unknown. Some of the cases reported had normal platelet counts but positive anti-PF4 antibodies/abnormal platelet function test or a highly suggestive clinical presentation but were negative for anti-PF4 antibodies (1-30). It is still unclear whether cases without thrombocytopenia are variations of the same syndrome or due to a different cause. The technique and the timing of laboratory tests may partially explain the negative results. (69-74)

Clinical presentation

The most specific elements of TTS are the **delayed onset** after vaccination and **greater severity** (1-30). Most adverse events and symptoms following immunization occur within the first 72 hours and tend to resolve spontaneously, while vaccine-related TTS typically presents after these have resolved. The median time from vaccination to symptom onset is 8 to -9 days with a range of 1 to 37 days. As of 27May 2021 only one of the 21 case series reported cases that occurred within the first 72 hours (18). Onset within the first 72 hours was described for 4 of the 62 cases who had all received the ChAdOx-1 vaccine in that study (18), while the remaining 165 cases reported so far, all occurred within 3 to 25 days, based on the available data, with one case occurring after day 30, reported on day 37 (1-30). Cases could be expected to occur within 30 days, the estimated elimination time of antibodies. Therefore, any case of concurrent thrombosis and thrombocytopenia within 30 days after vaccination with an adenovirus vector-based vaccine must be managed as a potential TTS case, with platelet count monitoring. However, cases occurring between 30-100 days should also be carefully monitored.

TTS is associated with a more severe thrombosis profile, with greater extension of thrombi and a higher frequency of concomitant intracranial haemorrhage in the case of CVST. Mortality rates (20-25%) are two-to-three times higher compared with non-vaccine related thrombotic events, however, there may be a significant reporting bias and the reasons for these findings are still yet to be clarified. In addition, the use of heparin-based anticoagulants could have influenced the clinical outcome of the initial cases that have been reported. Importantly, the clinical symptoms of thromboses in TTS **may be similar** to those of thrombotic events in the general population (75-82).

[Table 2 in Annex 4](#) summarizes the clinical presentation of the most common locations of thrombosis in TTS. Possible symptoms and signs must be recognized, however the clinical evaluation is not sensitive or specific, so a high index of suspicion applies to in patients at risk for TTS. As the clinical symptoms for TTS are non-specific and can be associated with other conditions, physicians should be aware of the possibility of TTS in patients who have received a COVID-19 vaccine.

1. Cerebral venous sinus thrombosis

The most frequently reported vaccine-related TTS location is CVST. The most frequent symptom of CVST is headache (50%), mostly severe, which typically presents with other symptoms or signs ([Table 2 in Annex 4](#), [Figure 2](#)). Vaccine-related CVST presents with an increased rate of intracranial haemorrhage (approximately 40% of patients) and a higher mortality rate, compared with non-vaccine related CVST. The mortality rate of CVST in patients with COVID-19 is similar to that in patients with vaccine-related TTS, however, thrombocytopenia is less frequent in COVID-19-related CVST and when present, tends to be less marked (between 100 000 and 150 000 platelets per μL).

2. Splanchnic vein thrombosis

The second most common TTS involves splanchnic vein thrombosis (SVT), including portal, superior mesenteric and/or splenic veins, reported in approximately 30% of cases. The symptoms of SVT are expected to be similar in vaccine-related TTS and TTS related to another aetiology, with the most frequent symptom being abdominal pain.

3. Deep vein thrombosis and pulmonary embolism

DVT and PE have been described in the reported cases of patients with TTS following vaccination with an adenovirus vector-based COVID-19 vaccine. The clinical symptoms of the DVT and PE are non-specific, and these symptoms are as likely to be due to DVT or PE as other alternate diagnoses. Consequently, clinical prediction tools, such as the Wells score for PE and DVT, which takes into consideration the symptoms and signs of DVT/PE, risk factors, and the possibility of an alternate diagnosis, have been derived and validated. Patients who are determined to be 'likely' based on such prediction scores should undergo further investigation with appropriate imaging to confirm or exclude DVT or PE.

4. Multiple organ thromboses

Approximately 20-25% of patients with vaccine-related TTS have multiple-organ thromboses, which requires thorough clinical examination and appropriate investigations, as necessary.

Laboratory diagnosis

1. Platelet count

Haemogram (complete blood count) must be done for all patients. Thrombocytopenia is defined as a platelet count $<150\,000/\mu\text{L}$ or a 50% decrease from a recent previous platelet count, if available. In most of the reported cases, the platelet nadir was $<50\,000$ platelets/ μL , with a median value around 25 000 platelets/ μL (83-88).

A few of the reported cases had a normal platelet count but they were positive for anti-PF4 antibodies which was not explained by another cause of thrombosis. If the platelet count is normal, follow-up haemograms must be repeated daily as the patient might be in the early stages of TTS. In inconclusive cases, an increased D-dimer values may be equally suggestive and additional laboratory parameters may be helpful (1-30).

2. Blood smear/film

A peripheral blood smear should be done to rule out a pseudo thrombocytopenia, caused by platelet clumping. The presence of schistocytes (fragmented red blood cells) was reported in one case of TTS (6).

3. D-dimer

A D-dimer value of four times the upper limit of the normal range (i.e., usually $>4000\ \mu\text{g/L}$ FEU (fibrinogen equivalent units)) is also highly suggestive, and a value of between 2000 and 4000 $\mu\text{g/L}$ FEU may be suggestive (3-6).

4. Anti-platelet factor 4 antibodies

The presence of anti-PF4 antibodies, in the absence of heparin therapy, is highly specific for TTS (4-6). However, the sensitivity of the assay is influenced by the type of technique used (ideally based on ELISA,

since rapid immunoassays are neither sensitive nor specific and should not be used, if possible) and the timing of the analysis. The anti-PF4 ELISA must be done on a sample taken prior to the administration of intravenous immunoglobulin (IVIG) treatment, as IVIG can interfere with the results.

5. Fibrinogen

Fibrinogen concentrations tend to increase in TTS, but when the blood fibrinogen concentrations decrease or remain low (<1.5 g/L), this should be considered a sign of worsening TTS.

6. Other coagulation parameters: prothrombin time, activated partial thromboplastin time

Prothrombin time (PT) and activated partial thromboplastin time (APTT) should be evaluated whenever possible, as part of a differential diagnosis for other coagulation disorders, such as DIC.

7. SARS-CoV-2 tests

SARS-CoV-2 real-time polymerase chain reaction (PCR) test on a oropharyngeal swab sample should be done for all patients with a suspected TTS and the result provided at the time of the notification. Serum antibody testing should also be considered to evaluate potential past exposure to SARS-CoV-2.

[Table 3 in Annex 4](#) summarizes the laboratory differential diagnosis between TTS, immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP) and DIC. Patients with isolated thrombocytopenia and continued absence of thrombosis may have post-vaccination ITP and not TTS. Other entities that should be included in the differential diagnosis of thrombosis/disseminated thrombosis and thrombocytopenia are listed in [Table 4 in Annex 4](#).

Imaging diagnosis

Imaging and clinical workup for thrombosis should be based on the symptoms and location. [Table 5](#) in Annex 4 summarizes the specific diagnostic modalities consistent with a confirmed diagnosis of thrombosis or thromboembolism and the diagnostics modalities that may be supportive but not definitive (89-98).

[Table 6](#) in Annex 4 summarizes the typical and specific radiological signs and the optimal and/or alternative imaging modalities that may be useful for TTS diagnosis. The concept of optimal is based on sensitivity, specificity and availability. In case of suspected CVST, imaging studies should be done promptly, not only for confirming/supporting the diagnosis, but also to rule out the presence of intracranial findings that might increase the risk of complications or may need urgent neurosurgical treatment. This should be considered in patients with altered fundoscopy, decreased level of consciousness, seizures or focal neurological symptoms/signs.

Clinical case management

Patients with suspected TTS within 30 days post-vaccination must be referred urgently to a hospital emergency room/urgent care for evaluation. Management of patients with suspected TTS may benefit from multidisciplinary evaluation, whenever available, including haematology, neurology, neurosurgery, radiology, intensive care, internal medicine and emergency department clinicians. Patients must be hospitalized and whenever possible, transferred to a tertiary-care hospital equipped with all the facilities listed above (83, 84, 99–102).

Clinical evaluation of patients must include the presence of symptoms and signs of thrombosis. CVST may present with headache, visual disturbances, seizures, altered mental status, decreased level of consciousness, focal neurological symptoms and/or vomiting; splanchnic thrombosis may present with abdominal pain, nausea, diarrhoea/constipation, fever, anorexia, back pain or gastrointestinal bleeding; deep vein thrombosis manifesting as limb swelling, pain or tenderness, redness and vein distension; pulmonary embolism may present as dyspnea, chest pain, difficulty to perform physical exercise, haemoptysis, syncope or palpitations; myocardial infarction may present with chest or left arm pain, shortness of breath or cyanosis; and ischemic stroke may present as sudden onset focal neurological symptoms (for further information, please see [Table 2](#) in Annex 4). In settings of high COVID-19 incidence and transmission, patients should be tested for COVID-19, and, whenever possible, fundoscopy carried out to assess for papilledema. Imaging studies should be requested based on the clinical index of suspicion and should not be delayed while waiting for the PCR result or the fundoscopy. The different diagnostic options, including the optimal and alternative tests are described in [Table 6](#) in Annex 4. Patients must be monitored closely, since new-onset thrombosis might occur, and multiple thromboses have been reported in 20-25% of patients.

If a venous or arterial thrombosis is diagnosed or suspected and has a temporal relationship with vaccination with an adenovirus vector-based COVID-19 vaccine, laboratory workup should be requested as outlined above, with at least a **haemogram** (full blood count), and, whenever possible, a D-dimer test. If the index of suspicion for TTS remains high in a patient who presents with a normal platelet count, then **the platelet count must be rechecked at least daily**. Additional laboratory tests that can be done include peripheral blood smear, D-dimer test, fibrinogen concentration, additional coagulation parameters and anti-PF4 antibodies. The differential diagnosis of thrombosis, based on the laboratory results is described in [Table 3](#) in Annex 4.

It is important to consider that patients with high D-dimer and persistently low platelet count, or organ specific laboratory abnormalities (such as increased liver enzymes) may have subtle or paucisymptomatic thrombosis.

Reporting these symptoms must be made easy for the vaccine recipients, and could include helplines and hospital vaccine centre and online reporting systems.

Figures 2 and 3 summarize the clinical workup for patients.

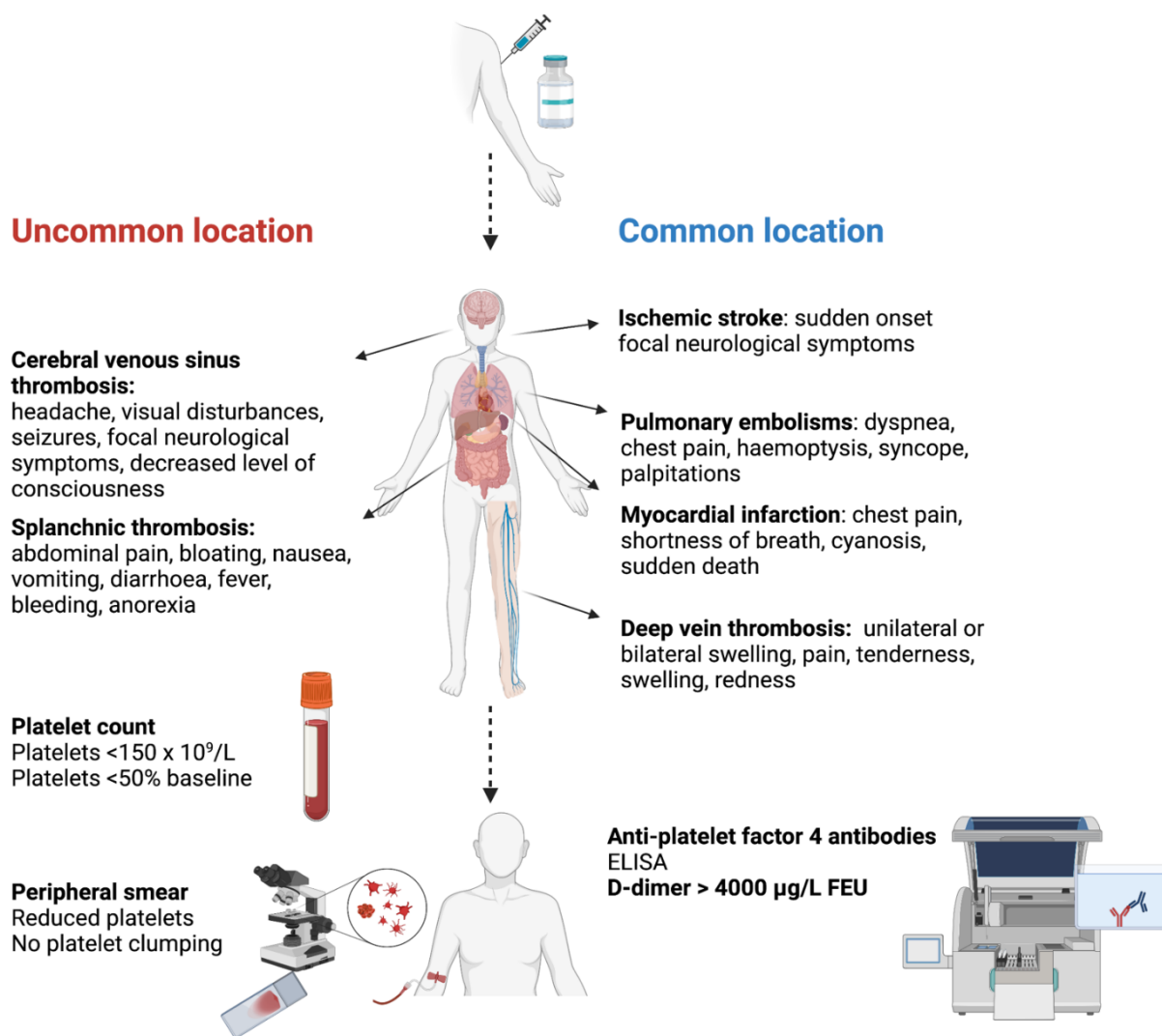


Figure 2: Clinical workup in patients with clinical symptoms and signs suggestive of thrombosis with 30 days of vaccination with a COVID-19 adenovirus vector-based vaccine

Figure created with BioRender.com

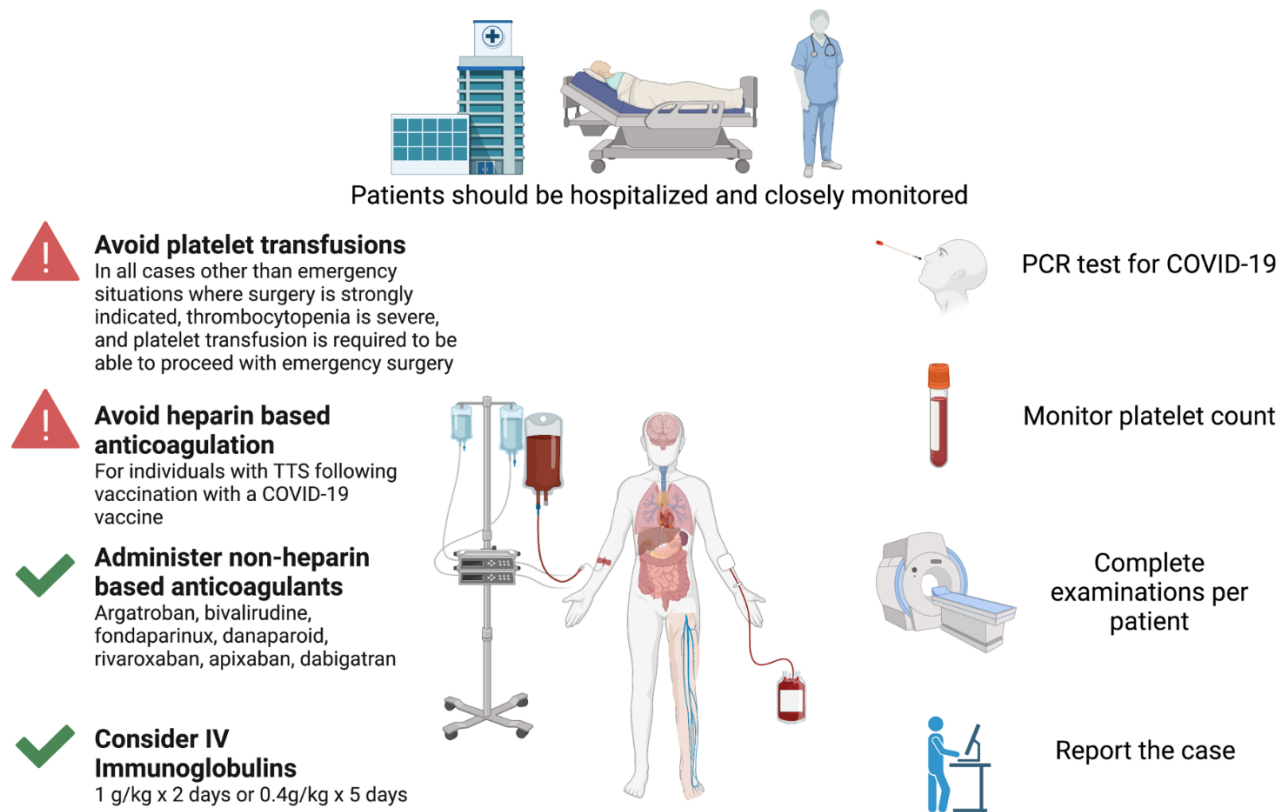


Figure 3: Clinical management of patients with confirmed, probable or possible vaccine related TTS

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Treatment recommendations

More complete details on the methods used for evidence assessment and formulation of these recommendations can be found in [Annex 2](#) and [Annex 3](#). Consult the [Summary of findings](#) and the [Evidence tables](#) for full details of the data used to formulate these recommendations.

Recommendation 1: WHO advises against the use of heparin for individuals with TTS following vaccination with a COVID-19 vaccine (*conditional recommendation, very low certainty evidence*)

Recommendation 2: WHO recommends against platelet infusion for individuals with TTS following vaccination with a COVID-19 vaccine in all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe, and platelet transfusion is required to be able to proceed with emergency surgery (*strong, very low certainty*).

WHO recommends the use of IVIG and non-heparin-based anticoagulants (NHAC) for individuals with TTS following vaccination with a COVID-19 vaccine (*strong, very low certainty*)

Full details on the evidence-to-decision process are available in [Annex 6](#).

[Table 7](#) in Annex 4 provides examples of non-heparin anticoagulants based on guidelines and national recommendations for TTS management that are available at present (103 -150). A GRADE evaluation of existing cases was carried out based on available information with these options. A GRADE evaluation of individual treatment options could not be carried out at present because of insufficient number of cases for each option. GRADE evaluation of treatment options will be possible in future versions of this guideline as global experience in TTS case management increases.

The GDG did not provide any judgment on steroid treatment, but noted the general use of steroids and the likelihood that steroids would usually be given in combination with other treatments.

Recommendations addressing vaccination, prevention and lifestyle changes in post-recovery TTS patients and the general population

No studies that provide information about post vaccine-related TTS, prophylaxis and lifestyle were identified. Important considerations include:

1. Future vaccination

Patients with TTS following non-replicant adenovirus-vector-based vaccine should not receive the second dose of this vaccine to avoid repeated exposure to the antigen that caused the syndrome.

2. Possible prophylactic medication to prevent thrombotic/thrombocytopenic events or other prophylactic measures

Although no studies have yet assessed the use of prophylactic medication in patients with post vaccine-related TTS, there are some studies on the long-term use of anti-thrombotic drugs to prevent TTS in patients recovering from COVID-19 disease. There is presently no indication or guideline for prophylactic treatment, including prophylactic anticoagulation or anti-aggregation in patients with other risk factors for thrombosis.

3. Contraindicated drugs

The use of heparin-based anticoagulants is not recommended in patients with suspected TTS. There is insufficient evidence to contraindicate other drugs that have been associated with immune thrombocytopenia syndrome.

4. Contraindication of adenovirus vector-based COVID-19 vaccines

Adenovirus vector-based COVID-19 vaccines and other adenovirus vector-based vaccines must be avoided in patients with a prior history of HIT or major venous and arterial thromboses occurring with thrombocytopenia.

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Annexes

Annex 1: Thrombosis risk factors

The main risk factors for venous thromboses in the general population include:

- inherited prothrombotic disorders (Factor V Leiden, prothrombin G2021A mutation, antithrombin deficiency, protein S deficiency, protein C deficiency);
- pregnancy/puerperium;
- hormone therapy or contraceptive treatment;
- obesity;
- cancer;
- myeloproliferative neoplasms;
- immobility;
- dehydration;
- smoking;
- infections;
- inflammatory or immune-mediated conditions (inflammatory bowel disease, Behçet's disease, thyroid disease, systemic lupus erythematosus, antiphospholipid syndrome, nephrotic syndrome, sarcoidosis, paroxysmal nocturnal haemoglobinuria);
- jugular vein catheterization;
- trauma;
- severe anaemia;
- recent neurosurgical procedure;
- post-surgical state.

Chronic liver disease is the main risk factor for splanchnic vein thrombosis, but myeloproliferative neoplasms, cancer, chemotherapy, fatty liver, diabetes and coeliac disease are also known risk factors. Patients with COVID-19 also have a significantly increased risk of thrombotic events, including CVST, however, there were no markers of an active or recent COVID-19 infection in most of the reported cases.

Annex 2: PICO 1: evidence-to-decision formulation

Results of the rapid literature review

The review identified eight studies providing valid data for the outcome of recovery [7 case series and 1 case report] in 127 patients, 45 of who were treated with heparin (5, 6, 10, 11, 14, 15, 18, 39). At the time of publication of the individual studies, 68/127 (53.5%) of patients had recovered. The recovery rate in patients treated with heparin was 7/14 (50%) based on data from 4 studies including 14 patients (5, 6, 10, 11).

Nine studies provided valid data for mortality rates [7 case series and 2 case reports] in 128 patients, 46 of who were treated with heparin (5, 6, 10, 11, 13, 14, 18, 39). The overall mortality rate was 30/128 (23.4%). The mortality rate in patients treated with heparin was 6/32 (18.7%) based on data from 5 studies including 32 patients (5, 10, 11, 14, 15).

Eight studies providing valid data for haemorrhage [6 case series and 2 case reports] including 67 patients, 34 of them treated with heparin (5, 6, 10, 11, 13-15, 39). The overall intracranial haemorrhage rate was 27/67 (40.3%). It was 7/21 (33.3%) in patients treated with heparin, based on data available in 6 studies (5, 6, 10, 11, 13, 14).

Certainty of evidence was very low for recovery, mortality, and haemorrhage.

Certainty of evidence

All studies were observational, either case series or case reports. There were nine valid studies for the mortality outcome and eight for haemorrhage and recovery. There were 127 patients for the recovery outcome, 128 for the mortality outcome and 67 for the haemorrhage outcome. The total number of treated patients was 14 for the recovery outcome, 32 for the mortality outcome and 21 for the haemorrhage outcome. The risk of bias was judged to be very serious, with possible selection bias, as fatal cases were more likely to be quickly published as case reports (within a range of between 5 and 8 days). Not all confounding factors influencing the prognosis were analysed (age, time between symptom onset and treatment, concomitant treatments, presence of multiple organ thrombosis) and follow-up was incomplete in many cases. The degree of inconsistency was judged to be serious, since the dose was not described in many studies, the duration and follow-up protocols varied within the different studies. Imprecision was judged to be very serious, since the number of patients included was less than the number of patients that would be needed for a single adequately powered trial, according to a sample size calculation. There was also a strong suspicion of publication bias.

Balance of benefits versus harms

The evidence was limited and the [Guideline Development Group](#) (GDG) agreed with the very low certainty rating. In judging the balance of benefits and harms, the GDG members also discussed that that in heparin induced thrombocytopenia (HIT), which has a similar presentation to TTS, heparin-based anticoagulants could be more harmful than beneficial and that, based on what is known about the pathophysiology of TTS, heparin may also be harmful in TTS. The GDG experts agreed on the need for more and better data, and some stated that heparin could be harmful, and that no benefit had been demonstrated for TTS.

Values and preferences

No data was available to inform how patients judge the value or benefit of heparin. Heparin is the main treatment for most thromboses and thromboembolisms. It is also the most frequently used anticoagulation treatment. Members of the GDG noted that if patients were aware of the uncertainty of the data and aware of the possible harms, some may prefer not to receive it. However, overall, the GDG agreed that there was likely to be major uncertainty and variability in how patients would value heparin for the treatment of TTS.

Resources use

The GDG discussed that not all heparin-based anticoagulants require the same resources. Non-fractionated heparin requires continuous intravenous administration and frequent laboratory monitoring in order to adjust the dose, whereas low-molecular-weight heparin does not need regular monitoring, but its administration requires specific training.

The GDG also noted that not all heparin-based anticoagulation treatments are equally cost-effective, with the cost being associated with not only to the direct cost of the product, but also with laboratory checks and monitoring visits.

Given the lack of specific data available to inform this judgement, the GDG judged that the costs for heparin treatment were likely to be variable and some GDG members reported costs would be large.

Equity and human rights

The GDG discussed that equity was likely to be reduced if other non-heparin treatments were recommended, instead of heparin, as many are not widely available, and choice would therefore be limited. Heparin is available in many LMIC settings, while the other non-heparin treatment options may not be.

Acceptability and feasibility

The GDG members believed that not all non-heparin-based anticoagulants would be equally acceptable to all stakeholders and that not all non-heparin-based therapies are equivalent, and also some of them are not widely available in all settings. The GDG members noted that heparin is the most widely used parenteral anticoagulant, and that many clinicians may not be trained or aware of other non-heparin-based treatments.

Recommendation rationale

The GDG formulated a conditional recommendation *against* heparin use for patients diagnosed with TTS following COVID-19 vaccination because:

1. of the uncertainty of the currently available data on the benefits and harms of heparin in TTS patients;
2. the present recommendations are applicable exclusively for emergency interim use and can be modified or completely changed when evidence becomes available; and
3. heparin may be the only therapeutic drug available in some countries who may not have the resources for treatment with IVIG and non-heparin anticoagulants.

Full details regarding the evidence-to-decision, GRADE tables and the literature review are available in [supplementary data: methods for guideline development](#).

Annex 3: PICO 2: evidence-to-decision formulation

Results of the rapid literature review

Recovery

Six case series, including 110 patients with TTS, provided valid data for recovery rates., 77 who had been treated with NHAC. The global recovery rate was 65/110 (59.1%) (6, 11, 15, 18, 39, 103). Information about recovery in patients treated with non-heparin-based anticoagulants (NHACs) was available in 5 studies including 44 patients. The recovery rate in these patients was 28/44 (63.6%) (11, 6, 15, 39, 103).

Seven studies reported the use of IVIG [2 case reports and 5 case series] in 113 patients, 55 of them had been treated with IVIG (6, 10, 14, 15, 18, 39, 103). The global recovery rate was 64/113 (56.6%). The recovery rate in patients treated with IVIG was 6/9 (66.7%) from 4 studies including 9 patients (6, 10, 14, 103).

Five studies provided valid data about platelet transfusions, [2 case reports and 3 case series], including 48 patients, 16 of them had received platelet transfusion (8, 10, 14, 15, 39). The global recovery rate was 25/48 (52.1%). The recovery rate in patients who had received platelet transfusion was 0/6 (0%) from 3 studies including 6 patients (8, 10, 14).

Four case reports, including nine patients, reported data about steroid treatment seven of them had been treated with steroids (10, 14, 16, 103). The global recovery rate was 4/9 (44.4%). In patients treated with steroids it was 4/7 (57.1%) from four case reports including seven patients (10, 14, 16, 103).

The GDG noted that recovery data indicated some benefit, while noting that the studies were small and heterogenous and many studies were likely to have included combinations of drugs rather than single drugs. The GDG judged benefits as moderate but uncertain. The GDG noted that the data suggested there was no benefit from platelet transfusion although data were only available for 6 patients.

Mortality

Six case series provided data on mortality in 110 patients; 77 had been treated with NHAC (6, 11, 15, 18, 39, 103). The global mortality rate was 17/110 (15.4%). The mortality rate was 1/15 (6.7%) in 4 studies including 15 patients treated with NHAC (6, 11, 15, 103).

Eight studies [3 case reports and 5 case series] reported use of IVIG in 114 patients, 55 had been treated with IVIG (6, 10, 13-15, 18, 39, 103). The global mortality rate was 22/55 (40.0%). The mortality rate in patients treated with IVIG was 4/16 (25.0%) from 5 studies including 16 patients (6, 10, 14, 15, 103).

Five studies provided valid data about platelet transfusions [2 case reports and 3 case series] in 48 patients; 16 had received platelet transfusion (8, 10, 14, 15, 39). The global mortality rate was 12/48 (25.0%). The mortality rate in patients who had received platelet transfusion was 5/6 (83.3%) from three studies including six patients (8, 10, 14).

Six studies provided data about steroids [4 case reports and 2 case series] in 82 patients; 14 of had been treated with steroids (10, 14-16, 18, 103). The global mortality rate was 19/82 (23.2%). The mortality rate in patients treated with steroids was 3/7 (42.9%) from four studies including seven patients (10, 14, 16, 103).

Intracranial haemorrhage

Five case series provided valid data about intracranial haemorrhage in 49 patients; 44 had been treated with NHAC (6, 11, 15, 39, 103). The global intracranial haemorrhage rate was 20/49 (40.8%). The intracranial haemorrhage rate was 7/18 (38.9%) in 18 patients treated with NHAC from 4 studies (6, 11, 15, 103).

Seven studies [3 case reports and 4 case series] described the use of IVIG in 54 patients; 35 had been treated with IVIG (6, 10, 13-15, 39, 103). The global intracranial haemorrhage rate was 25/54 (46.3%). The intracranial haemorrhage rate in patients treated with IVIG was 5/10 (50.0%) from 5 studies including 10 patients (6, 10, 13, 14, 103).

Five studies [2 case reports and 3 case series] provided valid data about platelet transfusions in 48 patients, 16 had received platelet transfusion (8, 10, 14, 15, 39). The global intracranial haemorrhage rate was 23/48 (47.9%). The intracranial haemorrhage rate in patients who had received platelet transfusion was 4/6 (66.7%) from 3 studies including 6 patients (8, 10, 14).

Five studies [4 case reports and 1 case series] providing valid data for steroid treatment in 21 patients; 10 had been treated with steroids (10, 14-16, 103). The global intracranial haemorrhage rate was 12/21 (57.1%). The intracranial haemorrhage rate in patients treated with steroids was 3/7 (42.9%) from four studies including seven patients (10, 14, 16, 103).

The GDG noted that death was reduced in patients treated with NHAC or IVIG compared with the global rates and the intracranial haemorrhage rates were similar. Some GDG members noted that the harms were small and uncertain. The GDG noted a signal that mortality and haemorrhage were markedly increased in patients who had received platelet transfusion. The GDG noted that the events were reported for a small number of patients and acknowledged that platelet transfusion is usually only considered when there are limited alternatives to save the patient or prior to surgery which may introduce bias for the observed events. Uncertainty was also noted in these results., The GDG judged the harms of steroid treatment to be uncertain.

Certainty of evidence was very low for recovery, death and intracranial haemorrhage.

Certainty of evidence

The GDG agreed with the very low certainty rating. All studies were observational, either case series or case reports. The number of valid studies ranged from four to eight, the total number of included patients ranged from 9 to 113 for the recovery outcome, from 48 to -110 patients for the mortality outcome and from 21 to 54 patients for the intracranial haemorrhage outcome. The total number of treated patients ranged from 6 to 44 for the recovery outcome, from 6 to 16 for the mortality outcome and from 6 to 18 for the intracranial haemorrhage outcome. The risk of bias was judged to be very serious, with possible selection bias, as fatal cases were more likely to be quickly published as case reports (within a range of between 5 and 8 days). Not all confounding factors influencing the prognosis were analysed (age, time between symptom onset and treatment, concomitant treatments, presence of multiple organ thrombosis) and follow-up was incomplete in many cases. The degree of inconsistency was judged to be serious, since the dose was not described in many studies, the duration and follow-up protocols varied within the different studies. Imprecision was judged to be very serious, since the total number of patients included was less than the number of patients that would be needed for a single adequately powered trial, according to a sample size calculation. In addition, there was a strong suspicion of publication bias.

Balance of benefits versus harms

The GDG judged the benefits to be probably greater than the harms for NHAC and IVIG treatments. This was informed by the data but also by previous clinical experience and expert opinion, as well as pathophysiology mechanisms. The GDG judged the harms to be greater than the benefits for platelet transfusion. However, the GDG noted that when surgery is considered for thrombosis, there is a role for platelet transfusion. The GDG did not provide any judgment for steroid treatment, but noted the general use of steroids and the likelihood that steroids would usually be given in combination with other treatments.

Values and preferences

The GDG noted that from a patient perspective, given the lack of clear evidence of a single beneficial treatment modality, patients would probably show important variability and uncertainty in their choice of intervention to receive and the value they placed on specific outcomes.

However, some GDG members noted that there was probably no important uncertainty or variability, particularly with respect to not wanting to receive platelet transfusion. Mortality was noted to be the outcome the most highly valued by patients.

Resources use

Most members of the GDG described the current treatments, such as NHAC and IVIG, as expensive and the facilities and human resources required to administer them as costly. However, it was acknowledged that governments may be able to reduce costs of treatments, especially as vaccination is rolled out, in order to ensure appropriate treatment for TTS following COVID-19 vaccination. They noted that this may vary from setting to setting.

Equity and human rights

Equity was likely to be reduced if expensive interventions, such as for NHAC and IVIG that are not widely available, were recommended and this would therefore limit choice. However, it was noted that use of steroids would be unlikely have an impact on equity as these are widely available on the essential drug list.

The GDG noted that if platelet transfusions were not recommended, this would not have an impact on equity.

Acceptability and feasibility

The GDG members said they believed that all treatments were widely accepted by clinicians. The GDG said that despite high cost and requirements for specialist facilities, the treatments are feasible and should be considered as the rollout of adenovirus vector-based vaccines gathers speed in LMICs. Good referral systems and access will be essential (implementation considerations).

Recommendation rationale

The GDG formulated a strong recommendation *in favour of* the use of IVIG and NHAC for individuals with TTS following COVID-19 vaccination because:

1. The balance of benefit and harms was deemed to be in favour of their use despite the very low certainty of the evidence; and
2. Both IVIG and NHAC were likely to be widely acceptable to stakeholders and were feasible although costs and availability may continue to be a barrier to use in some settings.

The GDG formulated a strong recommendation *against* the use of platelet transfusion in individuals with TTS following COVID-19 vaccination because:

1. The extremely high rate of harms (death and intracranial haemorrhage) reported in the studies using platelet transfusion. Despite the very low certainty of this evidence, the life-threatening nature of the situation warranted a strong recommendation as the potential harms are considered to be catastrophic;
2. There was likely to be minimal variability in how patients value platelet transfusion, and most would not want to receive platelet transfusion, based on current evidence; and
3. The recommendation is strong, with the caveat that it is permissible where surgery is strongly indicated, and thrombocytopenia is severe.

The GDG did not make a specific recommendation on the use of steroids, noting that these were often used in combination with other treatments, and that use was variable and not indicated for all patients.

Full details regarding the evidence-to-decision, GRADE tables and the literature review are available in the [Supplementary data: methods for guideline development](#).

Annex 4: Tables

Table 1. Cumulative incidence of TTS following vaccination with a non-replicant adenovirus vector-based vaccine (27 May 2021)

First author/source	Date of publication	Study period	Country	Vaccine	Dose	Cumulative incidence (95% CI) [cases per 100 000 vaccinees]
Schultz (10)	9/4/21	Unknown-20/03/2021	Norway	ChAdOx-1	First	3.8 (95% CI 1.4-9.3)
Spanish Medicines Agency (41)	11/5/21	01/02/2021-25/04/2021	Spain	ChAdOx-1	First	0.5 [1.3 in patients aged 30-39]
Centers for Disease Control and Prevention (39)	12/5/21	Unknown-07/05/2021	United States of America	BNT162b2, Ad26.COV2S	First	Global: 0.32 [1.2 in female patients aged 30-39]
Schulz (18)	13/5/21	Unknown-14/04/2021	Germany	ChAdOx-1 and BNT162b2	First	6.5 (95% CI 4.4-9.2) overall; 17.9 (95% CI 11.8-26.1) for ChAdOx1
Medicines & Healthcare products Regulatory Agency (48)	27/5/21	09/12/2020-26/05/2021	United Kingdom	ChAdOx-1	First and second	1.4 first dose, 0.13 second dose
Chan (43)	Preprint	Unknown-15/04/2021	Norway, Denmark, The Netherlands, Italy, Canada, United Kingdom, Germany, Australia, France, Spain	ChAdOx-1	First	0.73 (95% CI 0.43-1.23). Age <65 years: 1.60 (95% CI 0.71-3.62), Age 55-64 years: 0.41 (95% CI 0.1-1.65)

Table 2. Clinical syndromes suggestive of thrombosis or thromboembolism

Thrombosis location	Symptoms	Signs
Cerebral venous sinus	<ul style="list-style-type: none"> • New onset/unexplained headache: <ul style="list-style-type: none"> • In some cases, may have headache-specific red flags, including resistance to symptomatic treatment and progressive worsening, sudden onset, strict unilaterality in some cases • Headache may present with or without symptoms of increased intracranial pressure, as worsening by decubitus, sudden onset, strict unilaterality, worsening with Valsalva manoeuvres. • Mild headaches immediately after vaccination are common. Headaches associated with TTS typically start or worsen 3-4 days after vaccination and progressively become very severe • Visual disturbances: blurred vision, diplopia, ophthalmodynia • Seizures • Altered mental status/encephalopathy • Decreased level of consciousness/coma • Focal neurological symptoms: weakness, sensory abnormalities, gait instability, speech disorders, dysarthria • Vomiting with or without nausea. 	<ul style="list-style-type: none"> • Meningeal irritation signs (Kernig sign, Brudzinski sign, Jolt accentuation sign); • Papilledema • Focal neurological signs (dysphasia, dysarthria, hemiparesis, hemi-hypoesthesia, hemianopia, aphasia, dysarthria, cranial nerve palsies, ophthalmoplegia, ataxia) • Cushing triad may suggest increased intracranial pressure: bradycardia, bradypnea (low respiratory rate) and arterial hypertension.
Abdominal veins (portal, superior mesenteric, splenic, hepatic)	<ul style="list-style-type: none"> • Abdominal pain • Bloating, nausea, vomiting • Diarrhoea/increased frequency of bowel movements • Constipation • Fever, anorexia • Back pain • Gastrointestinal bleeding 	<ul style="list-style-type: none"> • Portal hypertension signs • Abdominal distension/ascites • Hepatomegaly • Jaundice
Deep vein	<ul style="list-style-type: none"> • Unilateral or bilateral swelling • Painful and tenderness • Limb swelling • Redness, distended veins 	<ul style="list-style-type: none"> • Homan's sign (discomfort or pain in the calf, or behind the knee, or involuntary flexion of the knee with forced dorsiflexion of the foot) • Asymmetric limb perimeter circumference
Pulmonary veins or arteries	<ul style="list-style-type: none"> • Dyspnoea, with sudden onset, shortness of breath, cough • Chest pain, with pleuritic characteristics • Difficulty to perform any physical exercises • Haemoptysis • Syncope, palpitations 	<ul style="list-style-type: none"> • Increased respiratory rate • Tachycardia • Arterial hypotension

Thrombosis location	Symptoms	Signs
Myocardial arteries	<ul style="list-style-type: none"> • Chest pain, often crushing in nature • Left arm pain • Shortness of breath, cyanosis • Sudden death 	<ul style="list-style-type: none"> • Arrhythmias, including asystole
Ischemic stroke/cerebral arteries	<ul style="list-style-type: none"> • Sudden onset focal neurological symptoms <ul style="list-style-type: none"> • Weakness, sensory abnormalities, gait instability, speech disorders, dysarthria • Abnormal gait 	<ul style="list-style-type: none"> • Focal neurological signs (dysphasia, dysarthria, hemiparesis, hemi-hypoesthesia, hemianopia, aphasia, dysarthria, cranial nerve palsies, ophthalmoplegia, ataxia)
Thrombocytopenia	<ul style="list-style-type: none"> • Easy bruising 	<ul style="list-style-type: none"> • Petechiae (tiny purple, red, or brown spots on the skin)

Table 3. Laboratory tests for the differential diagnosis of TTS

Laboratory test	TTS	ITP	TTP	DIC
Platelet count	Usually 20–50 × 10 ⁹ /L	Variable thrombocytopenia	Variable thrombocytopenia	Moderate to severe thrombocytopenia
Haemoglobin	Normal	Reduced if there is bleeding	Normal	Reduced
Peripheral blood smear	Normal/schistocytes	Normal/large platelets	Schistocytes	Normal/Schistocytes
Microangiopathic haemolytic anaemia/haemolysis markers	No	No	Yes	Yes (depending on the cause of DIC, usually non-diagnostic)
Anti-PF4 antibodies	Yes	No	No	No
PT	Normal or slightly prolonged	Normal	Normal	Prolonged
APTT	Normal or slightly prolonged	Normal	Normal	Prolonged
Fibrinogen (Clauss method, if available)	Initially increased, then decreased	Normal	Normal	Decreased
D-dimer	Increased (>4 times ULN)	Normal	Normal to increased	Increased
Other			ADAMST13 <10%	

TTS: thrombosis with thrombocytopenia syndrome; ITP: immune thrombocytopenic purpura; TTP: thrombotic thrombocytopenic purpura; DIC: disseminated intravascular coagulation; PT: prothrombin time; APTT: activated partial thromboplastin time; ULN: upper limit of normality; ADAMST13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, also known as von Willebrand factor-cleaving protease.

Table 4. Other conditions that should be included in the differential diagnosis of thrombosis/disseminated thrombosis and thrombocytopenia

Conditions	Key elements
Autoimmune heparin-induced thrombocytopenia	Heparin use during the past 4-30 days.
Atypical haemolytic uremic syndrome	Decreased complement factor H, and decreased complement factors 3 and 4 (C3, C4)
Catastrophic phospholipid antibody syndrome	Positive antiphospholipid antibodies, including cardiolipin antibodies, beta 2-glycoprotein I antibodies or lupus anticoagulant
Haemophagocytic syndrome	Decreased fibrinogen, extremely high concentration of ferritins (>10 000 µg/L) and high concentration of lipids
Drug-induced thrombotic microangiopathy	Prior treatment with quinine , ticlopidine (currently infrequently used), clopidogrel, trimethoprim-sulfamethoxazole, alendronate, vancomycin, pentostatin, chemotherapy (mitomycin, cyclosporine, tacrolimus, gemcitabine, carmustine, cytarabine, Taxotere), illicit drugs (cocaine, ecstasy)

Table 5. Specific diagnostic methods that provide results that may be consistent or suggestive of thrombosis/thromboembolism

<p>Specific diagnostic methods consistent with confirmed thrombosis/thromboembolism</p>	<ul style="list-style-type: none"> • Ultrasound – Doppler • CT scan – contrast/angiography • Magnetic resonance venography or arteriography • Echocardiogram • Perfusion V/Q scan • Conventional angiography/digital subtraction angiography
<p>Procedures consistent with the presence of a thrombus</p>	<ul style="list-style-type: none"> • Surgery • Thrombectomy
<p>Pathologic examination that confirmed the presence of a thrombus</p>	<ul style="list-style-type: none"> • Biopsy • Autopsy
<p>Specific diagnostic modalities supportive of the presence of thrombosis/thromboembolism</p>	<ul style="list-style-type: none"> • Chest radiography • Echocardiogram • CT scan without contrast • D-dimer (elevated above upper limit of normal for age)

Table 6: Optimal and alternative investigational tests used in TTS workups and typical diagnostic findings

Suspected thrombosis	Optimal tests	Alternative tests	Investigational findings
Cerebral venous sinus thrombosis	Contrast brain CT with CT venogram MRI brain with MR with contrast/MR venogram	Non-contrast CT Brain MRI with T1, T2, SWI, GRE, time-of-flight venogram for those who cannot receive MR gadolinium contrast Fundoscopy	<ul style="list-style-type: none"> ● CT/MR venogram: Filling defect in sinus (empty delta sign) ● Non-contrast CT: <ul style="list-style-type: none"> ○ Hyperdense vein or sinus (cord sign) ○ Venous infarcts: Parenchymal hypodensity in a non-arterial territory, typically in a parasagittal distribution ○ Brain oedema signs: compression, obliteration of the basal cisterns, effacement of cerebral sulci, midline shift, optic nerve tortuosity, flattening of the posterior sclera, intraocular protrusion of the optic nerve head ○ Intracranial haemorrhage with early oedema in parasagittal locations ● Fundoscopy: papilledema
Splanchnic thrombosis	CT angiography	Doppler ultrasound	<ul style="list-style-type: none"> ● Doppler ultrasound: intraluminal echogenic material, absent signal on colour doppler consistent with thrombosis ● Ultrasound: Hepatic enlargement, hepatic hypo echogenicity ● Contrast-CT: filling defects ● Non-contrast CT: Non-enhanced hypo-attenuation suggesting infarct
Deep vein thrombosis	Doppler ultrasound	MRI	<ul style="list-style-type: none"> ● Doppler ultrasound: intraluminal echogenic material, absent signal on colour doppler consistent with thrombosis. Increased flow in superficial veins ● Ultrasound: increased venous diameter, non-compressible venous segment with intraluminal material, loss of phasic flow on Valsalva manoeuvre or with calf squeeze.
Pulmonary thrombosis	CTPA	Echocardiogram Plain chest radiograph ECG V/Q scan	<ul style="list-style-type: none"> ● CTPA: filling defects, thrombus surrounding by rim of contrast ● Echocardiogram: signs of right ventricular dysfunction, thrombus-in-transit, flattening or dyskinesis of the interventricular septum ● Chest radiography: Enlarged pulmonary artery, peripheral wedge of airspace opacity, regional oligemia, pleural effusions, enlarged right pulmonary artery, dilated right descending pulmonary artery with sudden cut-off ● ECG: Tachycardia, S1Q3T3 pattern ● V/Q scan: even distribution of radionuclide through both lungs (normal ventilation) with perfusion defects
Myocardial infarction	ECG, Echocardiogram, Coronary artery angiography		<ul style="list-style-type: none"> ● ECG: ST segment elevation or depression, abnormal Q wave, T wave abnormalities ● Echocardiogram: left ventricle ejection fraction, wall motion abnormalities
Ischemic stroke	Non-contrast head CT	MRI, perfusion CT, angio-CT, doppler ultrasound	<ul style="list-style-type: none"> ● CT: loss of grey-white matter differentiation, hypoattenuation of deep nuclei, cortical hypodensity, gyral effacement

CT: computerized tomography; CTPA: computerized tomography pulmonary angiography; GRE: gradient echo sequences; MR: magnetic resonance; MRI: magnetic resonance imaging; SWI: susceptibility-weighted imaging; V/Q scan: ventilation–perfusion scan.

Table 7: Examples of non-heparin anticoagulant treatments for TTS

(based on available guidelines, indirect evidence from autoimmune heparin-induced thrombocytopenia and the first case series that have been published so far (103-150)).

Drug	Dose and mode of administration	Monitoring	Treatment duration
Argatroban IV	0.5-2 µg/kg/min (continuous IV infusion)	APTT monitoring (therapeutic range: 1.5-3) Argatroban should ideally be monitored by a direct thrombin inhibitor assay, if available, e.g., HEMOCLOT™ as APTT correlates poorly with the Argatroban effect due to the high concentrations of factor VIII	≤14 days
Bivalirudin IV	0.75 mg/kg bolus and continuous IV infusion 1.75 mg/kg/h	APTT monitoring (therapeutic range: 1.5-3)	Up to 3 months or until switch to oral anticoagulation
Fondaparinux SC	5mg/24h (<50kg) 7.5mg/24h (51-99kg) 10 mg/24 h (SC) >100kg	50% dose in case of platelet count <30 000/µL Reduce dosing with severe renal impairment	Up to 3 months or until switch to oral anticoagulation
Danaparoid SC or IV	500 IU/kg /12h 1x2 (<50 kg) or 750 IU/kg / 12h (SC) IV bolus < 60 kg 1500IU 60-75 kg 2250 IU 75-90 kg 3000 IU >90 kg 3750 IU. Infuse: 400 IU/h for 4h->300 IU/h for 4h-maintenance dose 200 IU/h, if GFR (<50ml/min) 150 IU/h and anti-FXa activity target (0.3-0.5 IU/ml, or trough with SC dosing), SC: 750-1250 IU/8-12 h Prophylactic dose: 750 IU / 12h (SC)	Measure anti-FXa activity, if available.	Up to 3 months or until switch to oral anticoagulation
Rivaroxaban PO	15 mg/12 h	To be considered in less severe patients, with no active bleeding and platelet count >50 000/µL	From day 22: 20 mg/24 h once daily Adjust the dose in case of renal impairment
Apixaban PO	10 mg/12 h	To be considered in less severe patients, with no active bleeding and platelet count >50 000/µL	From day 8: 5 mg/12 h Adjust the dose in case of renal impairment
Dabigatran PO	110 mg/12 h or 150 mg/12 h	CSV T or DVT or PE	According to GFR and patient's weight

APTT: activated partial thromboplastin time; GFR: glomerulus filtration rate; IV: intravenous; PO: per os (oral); SC: subcutaneous

Annex 5: Methods for guideline development

Summary

The present guideline has been developed by a group of multidisciplinary experts and members of the WHO secretariat representing different departments. The scientific approach has been based on PICO questions and the existing literature has been systematically searched, reviewed and summarized. The treatment recommendations have been derived through GRADE methodology.

Methodology

On 13 April 2021 the COVID-19 subcommittee of the Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO) recommended the creation of an expert group for advice and guidance on the clinical diagnosis and case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine. A Guideline Development group (GDG) comprising 18 expert specialists in internal medicine, epidemiology, haematology, immunology, neurology, neurosurgery and pharmacology, was established, ensuring gender, age and geographic balance, and LMIC representation. Experts and a subject matter expert contracted by WHO had to sign a confidentiality agreement as well as undergo conflict of interest assessment. Experts with conflicts were excluded from the GDG. The WHO secretariat included staff from different departments: Immunizations, Vaccines and Biologicals (IVB), Quality Norms and Standards (QNS), Regulation and Prequalification (RPQ), Mental Health and Substance use (MSD), Noncommunicable Diseases (NCDs) and WHO Health Emergencies Programme (WHE). Key questions were formulated, a literature search was performed and identified studies were reviewed, and distributed to the GDG members, to provide comments and feedback. These were collated in a zero draft by the subject matter expert. The work of the group was coordinated by the Vice Chairperson of the GACVS. The treatment guidelines section was overseen by a Guideline Methodologist. The guideline was developed between Tuesday 27 April and Friday 4 June 2021.

Guideline development

Based on the expertise of members, four subgroups (coordinated by a secretariat focal person) were established to develop four main sections of the document that were merged and handed over to the subject matter expert (SME) (David Garcia Azorin –Hospital Clínico Universitario de Valladolid, Valladolid, Spain) for harmonization of the different sections and presented to the GDG as a single document. The subgroups were:

- Subgroup 1: Epidemiology, risk factors and pathophysiology (Kim Mulholland (GDG), Huyun Tran (GDG), David Garcia Azorin (SME), Adwoa Bentsi-Enchill (Secretariat focal point))
- Subgroup 2: Manifestation of TTS after COVID19 vaccination (Georgy Genov (GDG), Prasanna Kumar (GDG), Viola Macolic Sarinic (GDG), Huyun Tran (GDG), Nicoline Schiess, (Secretariat focal point))
- Subgroup 3: Case definition, clinical features and laboratory diagnosis. (Dale Nordenberg (GDG), Doris Oberle (GDG), Prasanna Kumar (GDG), Riitta Lissala (GDG), Tom Solomon (GDG), Kameshwar Prasad (GDG), Annick Janin (Secretariat focal point))
- Subgroup 4: Clinical case management, including review of drug treatment and other therapeutics (Kameshwar Prasad (GDG), D.S Akram (GDG), Imo J. Akpan (GDG), Kiran Thakur (GDG), Ayesha Kamal (GDG), Ushma Mehta (GDG), Julio Resendiz (GDG), NK Arora (GDG), Claudia Patricia Vaca Gonzalez (GDG), Madhava Rao Balakrishnan (Secretariat focal point))

Full affiliations of all members are provided in the [Acknowledgements](#) section.

A timeline for the work and the process were discussed and developed as described below. Then each subsection was developed independently by the respective subgroups, coordinated by a secretariat focal person, and then merged. The merged document was harmonized by the subject matter expert (SME) before being posted on a dedicated SharePoint for review by all the GDG members.

Stage	Milestone
Week 0	Identification of experts, contact and clearance
Week 0	Subgroups defined
Week 1	<p>Literature review to identify published studies by WHO Rapid Review Group Team Members* from WHO's COVID-19 database, PubMed and Global Index Medicus (GIM) (search terms and the flowchart of the identified, screened and included studies are available in Search strategies for bibliographic databases: PubMed, WHO COVID-19 Database and Global Index Medicus).</p> <p>The selected studies were categorized as</p> <p>A. Studies on patients vaccinated with a COVID-19 vaccine (40 citations)</p> <ul style="list-style-type: none"> • studies describing clinical characteristics; • studies describing health services; • studies describing physiopathology of TTS; • studies describing other aspects of TTS, e.g., diagnosis, prognosis; • studies describing epidemiology of TTS. <p>B. Studies on patients with COVID-19 without vaccination (107 citations)</p>
Week 2	Research questions developed and focus areas clearly defined by each subgroup
Week 3	First zero draft for each of the four subsections developed
Week 4	<p>Updated literature review by the WHO Rapid Review Group Team Members using a new search strategy based on the comments/ and recommendations from the clinical experts</p> <p>Only studies that included patients having received ≥ 1 dose of a COVID-19 vaccine and that met the eligibility criteria were included.</p> <ul style="list-style-type: none"> • studies describing clinical characteristics (12 records) • studies describing treatment (3 records) • studies describing diagnosis of TTS (4 records) • studies describing epidemiology of TTS (5 records) • studies describing prognosis of patients with TTS (2 records) • studies describing physiopathology of TTS (1 record) • studies describing health services (1 record)
Week 4	All subgroups submit a zero draft with feedback from the meeting on 17 May
Week 5	Zero draft harmonized and posted on SharePoint for feedback from all GDG members
Week 6	Expert discussion

*WHO Science Division

A rapid review of the literature, based on the key questions, was performed on 6 May 2021 and updated on 22 May 2021 to identify existing publications on TTS in patients with COVID-19 and those who had been vaccinated with a COVID-19 vaccine. The search strategies were developed by members of the WHO secretariat. (The search terms are available in [Search strategies for bibliographic databases: PubMed, WHO COVID-19 Database and Global Index Medicus](#)). Three electronic databases were searched, WHO's COVID-19 database, PubMed and the Global Index Medicus (GIM) database. Screening of these results to select potential studies was performed by two reviewers, members of the WHO secretariat.

The first strategy, which included COVID-19 populations with and without vaccination, retrieved 404 citations. A total of 257 were excluded by screening the titles and abstracts. After the second screen of the full text, 40 studies in COVID-19-vaccinated populations and 107 studies in non-vaccinated COVID-19 populations.

The second search strategy, which only included COVID-19-vaccinated populations, retrieved 381 citations. A total of 353 were excluded after screening the titles and abstracts. After the second screen of the full text, 28 were included.

In total, 785 citations were retrieved. References from the included studies were also reviewed and the 'similar articles' function in PubMed was used to identify additional records, leading to a total of 804 citations retrieved that were screened by the subject matter expert, who reviewed and extracted the information and summarized the evidence. The documents created by the experts were collated, and all the comments and changes were tracked.

Treatment guidelines

Rapid review for treatment

For the treatment guidelines, two PICO questions were formulated:

- 1) Should heparin-based anticoagulants (I) versus no heparin or other anticoagulants (C) be administered to individuals diagnosed with TTS following COVID-19 vaccination (P)?
- 2) Should specific drugs or procedures (intravenous immunoglobulin (IVIG), steroids, anticoagulants excluding heparin-based anticoagulants, blood products transfusion) (I) versus none or other drugs or procedures (C) be administered to individuals who present with TTS following COVID-19 vaccination (P)?

The outcomes of interests were: recovery, death and intracranial haemorrhage.

The risk of bias in the treatment guidelines was assessed for each study included using the GRADE Handbook¹. Biases specific to observational studies were analysed, including failure to develop and apply appropriate eligibility criteria, presence of control populations, flawed measurement of both exposure and outcome, failure to adequately control confounding and incomplete follow-up. The data from the included studies were analysed descriptively and the certainty of evidence, which included assessment of the limitations of study design or execution, inconsistency of results, indirectness of evidence, imprecision and publication bias, was evaluated using GRADEPro².

Three outcomes were considered to be critical; according to the GRADE approach (i.e., most important to the patient who will be affected by the recommendations):

- 1) recovery, defined as the explicit mention of discharge of the patient in a recovered status;
- 2) mortality, including all-cause mortality and not just treatment-specific mortality; and
- 3) intracranial haemorrhage.

Patients with uncertain outcomes were not classified as recovery or death. Studies and patients in the studies with valid information for each of the different outcomes were analysed. The outcome rates were calculated for all patients in the individual studies regardless of treatment received and only for patients who had received the treatment of interest. The outcome rates for all patients were calculated by dividing the total number of patients with the outcome by the total number of patients included in each study. The outcome rates for each specific treatment were calculated by dividing the total of patients who received the treatment with outcome of interest by the total number of patients in the studies that provided valid data for the treatment. Only the data available in the publications were analysed, and no attempt to find missing information was made. Summary of findings (SoF) are presented in GRADE Evidence Profile Tables ([Evidence tables](#))

Recommendation formulation

Two virtual meetings were held via Zoom on 7 and 8 June 2021. The meetings were chaired by a member of the GDG approved by the group in advance of the first meeting. An experienced guidelines methodologist facilitated the evidence-to-decision-making (EtD) process as described in the WHO Handbook for Guideline Development.³ Although the original aim was to base all decisions on a consensus, at the beginning of the meeting the GDG members agreed that if any decisions required a vote, the vote would need to be carried by a 60% majority.

The GDG reviewed the evidence contained in the systematic reviews and in the GRADE EtD tables, and discussed the topics under consideration, facilitated by the guideline methodologist. The GRADE EtD communicate the GDG's judgements about several factors as well as their judgements on the benefits and harms and their certainty. These factors include:

- the values and preferences of end-users;
- resource use, including costs and cost-effectiveness;
- potential impact on human rights and equity; and
- acceptability and feasibility.

1 GRADE Handbook, available from <https://gdt.gradepr.org/app/handbook/handbook.html#h.ged5uqebmir9>. Accessed 30 May 2021.

2 GRADEpro GDT, available from <https://gradepr.org/>. Accessed 28 June 2021.

3 World Health Organization. WHO handbook for guideline development – 2nd ed, available from <https://www.who.int/publications/i/item/9789241548960>. Accessed 28 June 2021.

During the virtual meets, care was taken to ensure that all members of the GDG gave their responses through regular unofficial votes and use of the chat function to gain an initial hint about the GDG members' views on the direction of each recommendation (i.e., for or against an intervention), and on the strength of each recommendation (strong or conditional). The methodologist also asked participants to raise their hands to show support for each separate option. Although there was no formal vote system, this approach enabled the methodologist and the chair to assess the distribution of opinions and to prompt further discussion with the aim of reaching consensus.

The strength of the recommendation was established by considering both the certainty of the evidence and the availability and feasibility of the interventions. A recommendation **for** an intervention indicates that it should be implemented and a recommendation **against** an intervention indicates that it should not be implemented. The strength of a recommendation, which was either 'strong' or 'conditional', reflects the degree of confidence the GDG had that the desirable effects of the recommendation outweighed the undesirable effects for a positive recommendation, or the reverse (that the undesirable effects outweigh the desirable effects) for a negative recommendation.

The final wording of each recommendation, including an indication of its direction and strength, was confirmed by consensus between all GDG members and each member of the GDG was asked to express their decision verbally. The judgements made by the GDG related to each recommendation are summarized in the section [Evidence to decision tables framework](#).

As new data continues to emerge, these observations and recommendations may change. Therefore, these guidelines have a shelf-life of 3-6 months and clinicians should be aware of this.

External review

Seven external reviewers (from Argentina, China, Ghana, Iraq, Morocco, Myanmar and Russia), were invited to review the pre-final version of the guidelines to ensure readability and geographic relevance. All experts signed a confidentiality agreement and were assessed for any conflict of interest.

Limitations

The main limitations of the present guidelines are related to the quality and quantity of the existing evidence., often based on single cases or case series. The degree of certainty was affected by the presence of biases that should be better managed in future studies. In addition, the number of patients represented in the analysis of the different treatment modalities was not balanced and in some cases was significantly low. Evidence regarding some treatment options for LMIC settings was also limited and should be properly evaluated, ideally with well-designed observational studies or with randomized-controlled trials.

The GDG did not include patient representatives, which should be addressed in future updates.

Annex 6: Supplementary information on literature review methods and results

Thrombosis with thrombocytopenia syndrome (TTS) in the context of post-COVID-19 vaccination

Rapid Review Group Team Members: Mónica Ballesteros, Jesús López Alcalde, Kavita Kothari.

Last Date of Search: 22 May 2021

Date of Report: 23 May 2021

1. Objective:

To update the evidence available on TTS in the context of post-COVID-19 vaccination.

2. PICO:

The unique component of PICO structure included was population because the clinical questions require a comprehensive literature search strategy.

Population (in the context of post COVID-19 vaccination): Adult population who have received a COVID-19 vaccine with clinical signs and symptoms of thrombosis and associated novel thrombocytopenia within 4 to 28 days of vaccination. In this updated version, we have included the following terms without being associated with a new episode of thrombocytopenia: cerebral venous sinus thrombosis (CVST), Splanchnic vein thrombosis (intra-abdominal), deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), pulmonary embolism (PE), stroke and myocardial infarction.

3. Methods

3.1 Search methods for study identification

This updated search strategy was developed by a WHO librarian taking into account comments and recommendations from clinical experts. More details can be found in the section [Search strategies for bibliographic databases: PubMed, WHO COVID-19 Database and Global Index Medicus](#).

3.2 Electronic databases:

- WHO COVID-19 database
- PubMed
- Global Index Medicus

3.3 Methods for screening search results

The screening was performed by two reviewers (MB, JLA), who classified the results according to the type of data present in the publication ([Table S1](#)).

[Table S1](#). Classification of studies by data type

Data type	Definition
Epidemiology	Study describes burden of disease or describes the distribution of disease
Mechanism	The study describes the possible underlying causes of TTS or its physiopathology
Clinical characteristics	Study describes clinical characteristics of inpatients or outpatients
Diagnosis	Study describes clinical signs and symptoms, laboratory tests, imaging examinations, or any other test to establish the diagnosis of TTS
Prognosis	The study provides data on the predicted prognosis of an outcome of interest
Treatment	The study describes the assessment of a treatment or management intervention for TTS (e.g., treatment, maximize comfort, alleviate symptoms or side effects).
Health services	The study describes the assessment of the delivery, processes, management, organization, or financing of healthcare.

Selected PICO questions used in the rapid review of evidence

Selected PICO questions used in the rapid review of evidence on TTS indications and treatment in the context of post-COVID-19 vaccination: a rapid review of evidence. Search Strategy Development.

05 May 2021

- What is the global aetiology, baseline epidemiology of TTS in adults post-COVID-19 vaccination?
- What is the clinical presentation of TTS in patients post-COVID-19 vaccination?
- Is an internationally agreed case definition for patients presenting with TTS post vaccination emerging in the literature? What definitions are currently available, including clinical features and laboratory diagnosis?
- **What algorithm is most suitable for triaging and case management of patients with Covid-19 vaccine-related TTS and thrombosis/thromboembolism after vaccination with an adenovirus vector-based COVID-19 vaccine?**
- The main component of the PICO question was population, because the clinical questions required a comprehensive literature search strategy.
- The second search strategy included the following terms: Cerebral Venous Sinus Thrombosis (CVST), splanchnic vein thrombosis (intra-abdominal), deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), pulmonary embolism (PE), stroke and myocardial infarction.

Search strategies for bibliographic databases: PubMed, WHO COVID-19 Database and Global Index Medicus

Population	Patients with vaccine-related TTS. Similar pathophysiology as that for heparin—induced thrombocytopenia
Intervention	Non-heparin-based anticoagulant (NHAC)s, high-dose intravenous immunoglobulin (IVIG), and prednisolone, thromboprophylaxis, steroids, folate, platelet transfusion, splenectomy Platelet count <50 000/ μ L
Full PubMed search strategy	<p>((("Heparin induced thrombocytopenia"[tiab] OR ((prothrombotic OR thrombosis[tiab] OR thrombotic[tiab] OR thromboembolism[tiab]) AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab]))) AND systematic[sb]) (157)</p> <p>((prothrombotic OR thrombosis[tiab] OR thrombotic[tiab] OR thromboembolism[tiab]) AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab])) AND (2020:2021[pdat]) AND (Coronavirus*[TIAB] OR corona?virus[Tiab] OR "Coronavirus"[Mesh] OR coronavirinae[tiab] OR coronaviridae[tiab] OR betacoronavirus[tiab] OR "corona pandemic"[tiab] OR COVID OR Covid19[TW] OR NCov[Tiab] OR 2019ncov[TW] OR (SARS AND COV) OR SARS2 OR "CoV 2"[tiab] OR CoV2[tiab] OR "Coronavirus Infections"[Mesh] OR NCOV19[tiab] OR "solidarity trial"[tiab]) (142)</p> <p>OR "Vaccine Induced Thrombocytopenia Syndrome"[tiab] OR "vaccine-induced prothrombotic immune thrombocytopenia"[tiab] OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia"[tiab] OR " inflammatory and thrombotic response to vaccination"[tiab] OR "Rare thromboembolic syndrome"[tiab] OR VIPIT[tiab] OR</p> <p>((("Cerebral venous sinus thrombosis"[tiab] OR " Cerebral venous thrombosis"[tiab] OR " Sinus Thrombosis, Intracranial"[tiab] OR "cerebral sinovenous thrombosis"[tiab] OR "cerebral vein thrombosis"[tiab] OR "cerebral venous and sinus thrombosis"[tiab] OR "cerebral vein and dural sinus thrombosis"[tiab] OR " cavernous sinus thrombosis"[tiab] OR CVST[tiab] OR "Anti PF4 antibodies") AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab])))</p>
Full String WHO COVID-19 Database	<p>"Heparin induced thrombocytopenia" OR ((prothrombotic OR thrombosis OR thrombotic OR thromboembolism) AND ("thrombocytopenia" OR thrombocytopenic))</p> <p>OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR VIPIT OR</p> <p>((("Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR " Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR " cavernous sinus thrombosis" OR CVST OR "Anti PF4 antibodies") AND ("thrombocytopenia" OR thrombocytopenic))</p>
WHO Database Link	<p>https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/?output=site&lang=en&from=0&sort=&format=summary&count=20&fb=&page=1&skfp=&index=tw&q=%22Heparin+induced+thrombocytopenia%22+OR+%28%28prothrombotic+OR+thrombosis+OR+thrombotic+OR+thromboembolism%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29+++OR+%22Vaccine+Induced+Thrombocytopenia+Syndrome%22+OR+%22vaccine-induced+prothrombotic+immune+thrombocytopenia%22+OR+%22Vaccine-Induced+Immune+Thrombotic+Thrombocytopenia%22+OR+%22inflammatory+and+thrombotic+response+to+vaccination%22+OR+%22Rare+thromboembolic+syndrome%22+OR+VIPIT+OR+%28%28%22Cerebral+venous+sinus+thrombosis%22+OR+%22+Cerebral+venous+thrombosis%22+OR+%22+Sinus+Thrombosis%2C+Intracranial%22+OR+%22cerebral+sinovenous+thrombosis%22+OR+%22cerebral+vein+thrombosis%22+OR+%22cerebral+venous+and+sinus+thrombosis%22+OR+%22cerebral+vein+and+dural+sinus+thrombosis%22+OR+%22+cavernous+sinus+thrombosis%22+OR+CVST%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29&search_form_submit=</p>

<p>Global Index Medicus</p>	<p>tw:(("Heparin induced thrombocytopenia" OR ((prothrombotic OR thrombosis OR thrombotic) AND ("thrombocytopenia" OR thrombocytopenic)) OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR vipit OR (("Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR " Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR " cavernous sinus thrombosis" OR cvst) AND ("thrombocytopenia" OR thrombocytopenic))) AND (type_of_study:(("guideline" OR "policy_brief" OR "systematic reviews")))</p>
<p>GIM LINK</p>	<p>https://pesquisa.bvsalud.org/gim/?output=site&lang=en&from=0&sort=&format=summary&count=20&fb=&page=1&filter%5Btype_of_study%5D%5B%5D=guideline&filter%5Btype_of_study%5D%5B%5D=policy_brief&filter%5Btype_of_study%5D%5B%5D=systematic_reviews&index=tw&q=tw%3A%28%22Heparin+induced+thrombocytopenia%22+OR+%28%28prothrombotic+OR+thrombosis+OR+thrombotic%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29+++OR+%22Vaccine+Induced+Thrombocytopenia+Syndrome%22+OR+%22vaccine-induced+prothrombotic+immune+thrombocytopenia%22+OR+%22Vaccine-Induced+Immune+Thrombotic+Thrombocytopenia%22+OR+%22inflammatory+and+thrombotic+response+to+vaccination%22+OR+%22Rare+thromboembolic+syndrome%22+OR+vipit+OR++%28%28%22Cerebral+venous+sinus+thrombosis%22+OR+%22+Cerebral+venous+thrombosis%22+OR+%22+Sinus+Thrombosis%2C+Intracranial%22+OR+%22cerebral+sinovenous+thrombosis%22+OR+%22cerebral+vein+thrombosis%22+OR+%22cerebral+venous+and+sinus+thrombosis%22+OR+%22cerebral+vein+and+dural+sinus+thrombosis%22+OR+%22+cavernous+sinus+thrombosis%22+OR+cvst%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29%29+AND+%28+type_of_study%3A%28%22guideline%22+OR+%22policy_brief%22+OR+%22systematic_reviews%22%29%29&search_form_submit=</p>

Rapid Review Group

Research Topic

Thrombosis with Thrombocytopenia Syndrome

WHO COVID-19 Database

<https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/>

Concept	Search string	Results 22.05.2021
#1- TTS in COVID-19	<p>((prothrombotic OR thrombosis OR thrombotic OR thromboembolism OR embolism OR thrombus OR D-dimer OR "Splanchnic vein" OR SVT OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "Myocardial Infarction" OR "coronary infarction") AND ("thrombocytopenia" OR thrombocytopenic OR "Anti PF4 antibodies" OR "platelet factor 4" OR "low platelet"))</p> <p>OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR VIPIT OR "Heparin induced thrombocytopenia"</p>	353
# 2 – Thrombosis after COVID-19 vaccination	<p>("Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR "Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR " cavernous sinus thrombosis" OR "deep venous thrombosis" OR "deep vein thrombosis" OR "diffuse intravascular thrombosis" OR "arterial thrombosis" OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR "splanchnic vein" OR SVT OR "intra-abdominal thrombosis" OR "intra-abdominal venous thrombosis" OR "intra-abdominal vein thrombosis" OR "abdominal thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "pulmonary thromboembolism" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "myocardial infarction" OR "coronary infarction") AND</p> <p>(Innoculation* OR Immuniz* OR Vaccin* OR BNT162b2 OR "comirnaty" OR "mRNA-1273" OR CoviShield OR AZD1222 OR "Sputnik V" OR CoronaVac OR "BBIBP-CorV" OR "Ad26.CoV2.S" OR "JNJ-78436735" OR Ad26COVS1 OR VAC31518 OR EpiVacCorona OR Convidicea OR Ad5-nCoV OR Covaxin OR CoviVac OR ZF2001 OR "NVX-CoV2373" OR "ZyCoV-D" OR CIGB 66 OR "CVnCoV" OR "INO-4800" OR "VIR-7831" OR "UB-612" OR BNT162 OR "Soberana 1" OR "Soberana 2" OR Pzifer OR Moderna OR "Pzifer/bioNtech" OR AstraZeneca OR Gamaleya OR Sinovac OR Sinopharm OR "johnson & Johnson" OR Janssen OR "CanSino Biologics" OR "Bharat Biotech" OR "wuhan institute" OR Chumakov OR "Longcom Biopharmaceutical" OR "Finlay Institute of Vaccines" OR Novavax OR "Zydus Cadila" OR "Center for Genetic Engineering and Biotechnology" OR CureVac OR "University of Melbourne" OR "Murdoch Children's Research Institute" OR "Radboud University Medical Center" OR "Faustman Lab" OR "Inovio Pharmaceuticals" OR Dynavax OR ImmunityBio OR NantKwest OR COVAXX OR "adenovirus vector")</p>	256

Pubmed

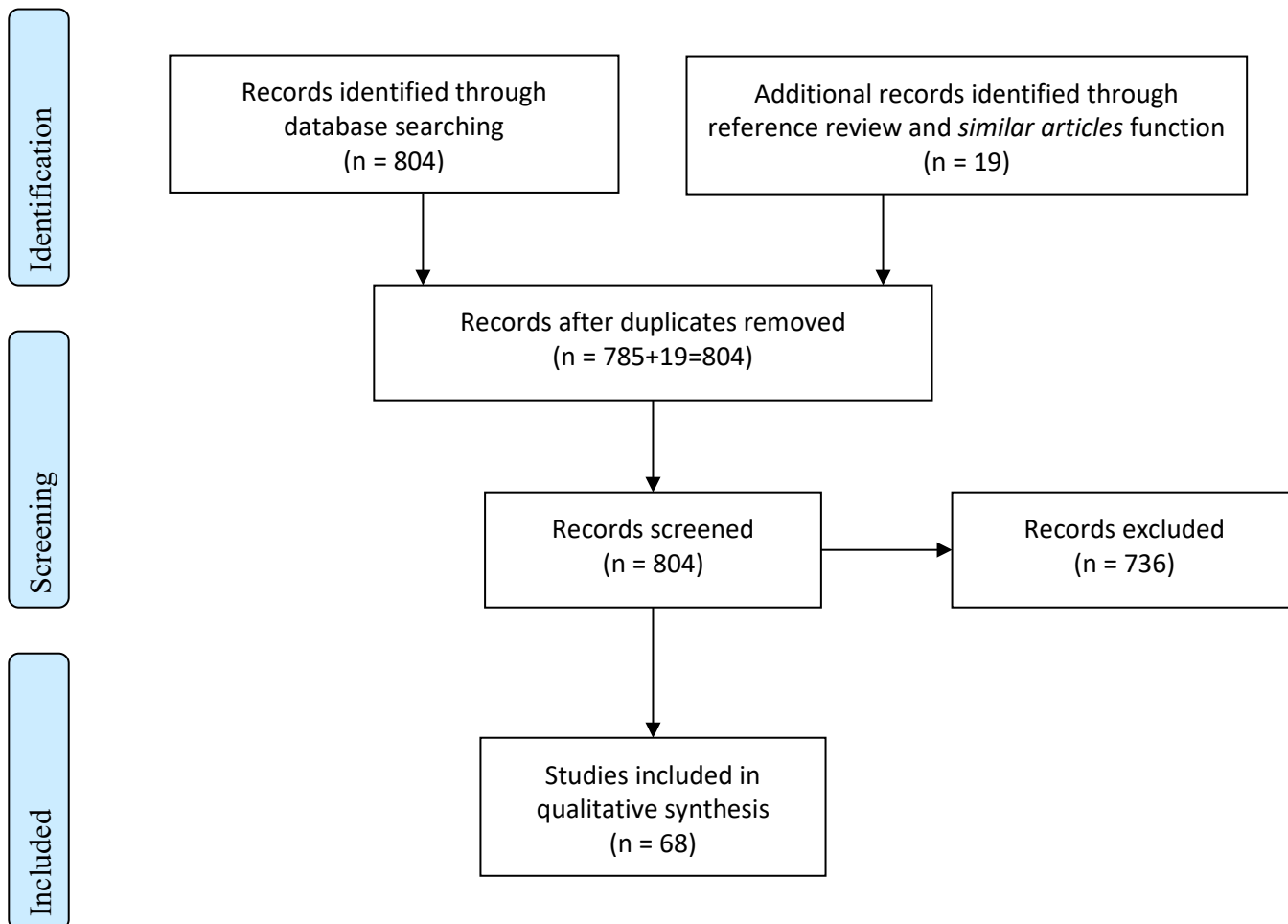
<https://pubmed.ncbi.nlm.nih.gov/>

Concept	Search string	Results
#3 - SR on TTS-like syndromes	"Heparin induced thrombocytopenia"[tiab] OR "Vaccine Induced Thrombocytopenia Syndrome"[tiab] OR "vaccine-induced prothrombotic immune thrombocytopenia"[tiab] OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia"[tiab] OR " inflammatory and thrombotic response to vaccination"[tiab] OR "Rare thromboembolic syndrome"[tiab] OR VIPIT[tiab] OR ((prothrombotic[tiab] OR thrombosis[tiab] OR thrombotic[tiab] OR thromboembolism[tiab] OR embolism[tiab] OR thrombus[tiab] OR D-dimer[tiab] OR "Splanchnic vein"[tiab] OR SVT[tiab] OR CVST[tiab] OR DVT[tiab] OR "Disseminated Intravascular coagulation"[tiab] OR "consumptive coagulopathy"[tiab] OR "disseminated intravascular coagulopathy"[tiab] OR "defibrination syndrome"[tiab] OR "defibrinogenation syndrome"[tiab] OR "acquired afibrinogenemia"[tiab] OR Stroke[tiab] OR "cerebrovascular accident"[tiab] OR "CVA"[tiab] OR "cerebral infarct"[tiab] OR "ischemic infarctions"[tiab] OR "CNS infarction"[tiab] OR "Myocardial Infarction"[tiab] OR "coronary infarction"[tiab]) AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab] OR "Anti PF4 antibodies"[tiab] OR "platelet factor 4"[tiab] OR "low platelet"[tiab])) AND systematic[sb]	181

Global Index Medicus
<https://pubmed.ncbi.nlm.nih.gov/>

Concept	Search string	Results
#4 - SR on TTS-like syndromes	"Heparin induced thrombocytopenia" OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR VIPIT OR ((prothrombotic OR thrombosis OR thrombotic OR thromboembolism OR embolism OR thrombus OR D-dimer OR "Splanchnic vein" OR SVT OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "Myocardial Infarction" OR "coronary infarction") AND ("thrombocytopenia" OR thrombocytopenic OR "Anti PF4 antibodies" OR "platelet factor 4" OR "low platelet")) AND (type_of_study:("guideline" OR "policy_brief" OR "systematic_reviews"))	14

Flowchart of the identified, screened and included studies.

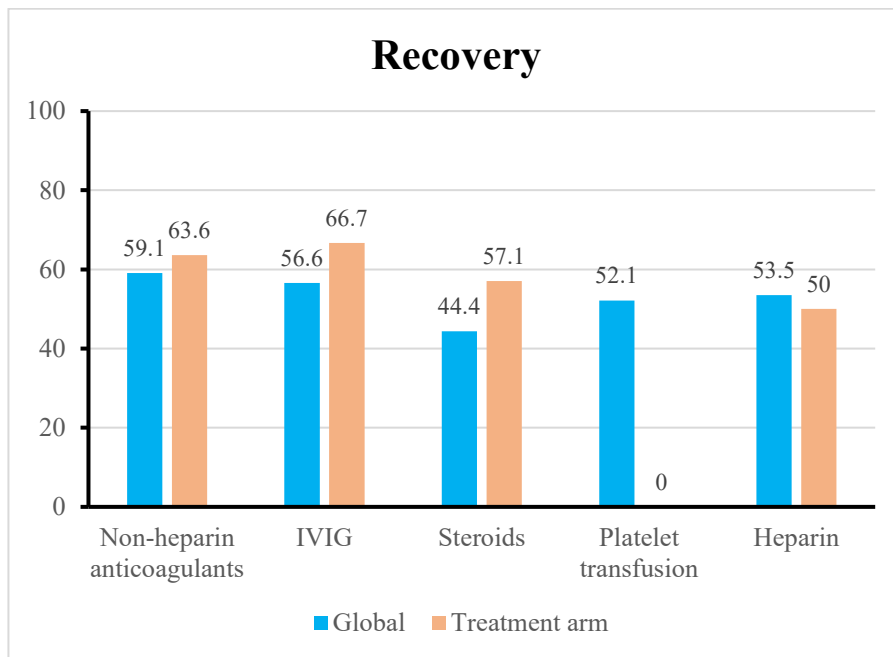


Evidence to decision tables framework⁴

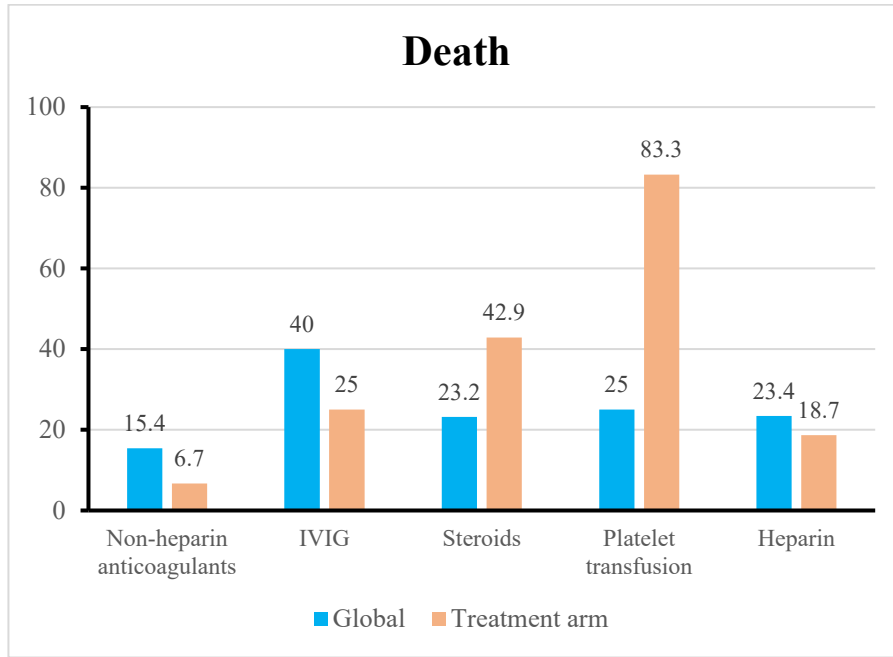
Question	Judgement
1. Is the problem a priority?	No, Yes, Varies, Uncertain
2. How substantial are the Benefits?	Large, Moderate, Small, Trivial, Varies, Uncertain
3. How substantial are the Harms?	Large, Moderate, Small, Trivial, Varies, Uncertain
4. What is the overall certainty of the evidence?	High, Moderate, Low, Very Low
5. What is the balance between benefits and harms?	Favours intervention, Against intervention
6. How do people value treatment for TTS?	Degree of Variability or Uncertainty
7. How large are the resource requirements (costs)?	Large, Moderate, Negligible costs or savings
8. What is the certainty of the evidence for the costs?	High, Moderate, Low, Very Low
9. Are treatments for TTS cost-effective?	Favours intervention, Against intervention
10. What would the impact be on health equity?	Reduced, Increased, Varies, Uncertain
11. Are treatments for TTS acceptable to all stakeholders?	No, Yes, Varies, Uncertain
12. Are treatments for TTS feasible to implement?	No, Yes, Varies, Uncertain

4 GRADE Handbook. Available from: <https://gdt.grade.pro.org/app/handbook/handbook.html>. Accessed 1 July 2021

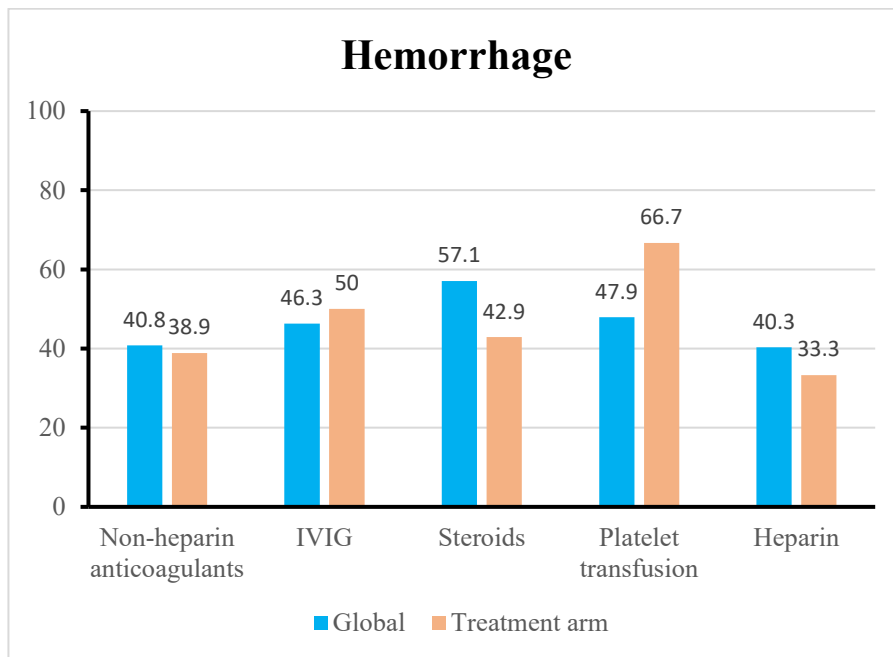
Summary of findings



Drug	Number of studies	Global rate	Number of studies with valid data	Treated rate
Non-heparin anticoagulants	6	65/110	5	28/44
IVIG	7	64/113	4	6/9
Steroids	4	4/9	4	4/7
Platelet transfusion	5	25/48	3	0/6
Heparin	8	68/127	4	7/14



Drug	Number of studies	Global rate	Number of studies with valid data	Treated rate
Non-heparin anticoagulants	6	17/110	4	1/15
IVIG	8	22/55	5	4/16
Steroids	6	19/82	4	3/7
Platelet transfusion	5	12/48	3	5/6
Heparin	9	30/128	5	6/32



Drug	Number of studies	Global rate	Number of studies with valid data	Treated rate
Non-heparin anticoagulants	5	20/49	4	7/18
IVIG	7	25/54	5	5/10
Steroids	5	12/21	4	3/7
Platelet transfusion	5	23/48	3	4/6
Heparin	8	27/67	6	7/21

Possible research gaps for future prophylactic management:

- Should hydroxychloroquine be used in patients having TTS?
- Genetic markers for 'at risk' patients.
- Risk factors for TTS and the role of other thrombotic risk factors.
- Role of point-of-care devices and diagnostics like the thromboelastography (TEG), that gives an indication of fibrinogen levels, or point-of-care ultrasound (POCUS) which would enable frequent testing of coagulation/bleeding profiles.
- Duration and persistence of anti-PF4 antibodies in COVID-19 vaccine-related TTS. In patients with HIT, the median time to antibody clearance is 50 days for platelet activation assays and 85 to 90 days by immunoassays. Immunoassays may remain positive in ~35% of patients for up to 1 year, with levels decreasing over time. Hence patients may be at risk for thrombosis because of circulating anti-PF4/heparin antibodies.
- Duration of immunosuppressive treatments.
- Management of treatment-resistant cases.
- Possibility of organ donation in TTS-deceased patients.
- Consider rapid literature search to identify the most common cause of hypercoagulability.
- Research on increase in hypercoagulopathy in patients with a previous of COVID-19 infection, given any COVID-19 vaccine.
- Randomized controlled trials (RCTs) to determine the safety of proposed anticoagulation, alternate anticoagulants and the role for anti-platelets, such as Ticagrelor, in patient management.
- RCTs to evaluate the efficacy of using new oral anticoagulants (NOACS) as prophylaxis in patients recovering from TTS after COVID-19 vaccine? (If anti-PF 4 antibodies are present).

Evidence tables

Question: Heparin compared with no heparin or other anticoagulants for patients diagnosed with TTS following COVID-19 vaccination **Outcome:** death (all-cause)

Certainty assessment							Impact	Certainty	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Death (All-cause)									
9	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 9 studies providing valid data [7 case series and 2 case reports], including 128 patients, 46 of them treated with heparin. Global death rate was 30/128 (23.4%). Information about death in patients treated with heparin was available in 5 studies including 32 patients. Death rate in patients treated with heparin was 6/32 (18.7%).	⊕○○○ VERY LOW	CRITICAL

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Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Heparin compared with no heparin or other anticoagulants for patients diagnosed with TTS following COVID-19 vaccination **Outcome:** intracranial haemorrhage

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Intracranial haemorrhage									
8	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 8 studies providing valid data [6 case series and 2 case reports], including 67 patients, 34 of them treated with heparin. Global intracranial hemorrhage rate was 27/67 (40.3%). Information about intracranial hemorrhage rate in patients treated with heparin was available in 6 studies, and was 7/21 (33.3%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

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Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Heparin compared with no heparin or other anticoagulants for patients diagnosed with TTS following COVID-19 vaccination – Outcome: recovery

Certainty assessment							Impact	Certainty	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
8	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 8 studies providing valid data [7 case series and 1 case report], including 127 patients, 45 of them treated with heparin. 68/127 (53.5%) patients were recovered by the time the study was published. Information about recovery in patients treated with heparin was available in 4 studies, including 14 patients. Recovery rate was 7/14 (50%).	⊕○○○ VERY LOW	CRITICAL

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- Schultz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. *medRxiv* doi: <https://doi.org/10.1101/2021.04.30.21256383>; version posted May 13, 2021.
- See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, 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;325(24):2448-56.
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- 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(8):1599.

Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Non-heparin-based anticoagulants compared with heparin or no anticoagulation for patients diagnosed with TTS following COVID-19 vaccination **Outcome:** death (all-cause)

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Death (all-cause death)									
6	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 6 studies providing valid data, all case series, including 110 patients, 77 of them treated with non-heparin anticoagulants. Global death rate was 17/110 (15.4%). Information about death in patients treated with non-heparin anticoagulants was available in 4 studies including 15 patients. Death rate in patients treated with non-heparin anticoagulants was 1/15 (6.7%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

- George G, Friedman KD, Curtis BR, Lind SE. Successful treatment of thrombotic thrombocytopenia with cerebral sinus venous thrombosis following Ad26.COVS.2.S vaccination. Am J Hematol. 2021. doi: 10.1002/ajh.26237.
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- 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(8):1599.

Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Non-heparin-based anticoagulants compared with heparin or no anticoagulation for patients diagnosed with TTS following COVID-19 vaccination –
Outcome: intracranial haemorrhage

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Intracranial haemorrhage									
5	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 5 studies providing valid data, all case series, including 49 patients, 44 of them treated with non-heparin anticoagulants. Global haemorrhage rate was 20/49 (40.8%). Information about haemorrhage in patients treated with non-heparin anticoagulants was available in 4 studies including 18 patients. Death rate in patients treated with non-heparin anticoagulants was 7/18 (38.9%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

- George G, Friedman KD, Curtis BR, Lind SE. Successful treatment of thrombotic thrombocytopenia with cerebral sinus venous thrombosis following Ad26.COVID.S vaccination. Am J Hematol. 2021. doi: 10.1002/ajh.26237.
- See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COVID.S vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
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Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Non-heparin-based anticoagulants compared with heparin or no anticoagulation for patients diagnosed with TTS following COVID-19 vaccination – Outcome: recovery

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
6	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 6 studies providing valid data, all case series, including 110 patients, 77 of them treated with non-heparin anticoagulants. Global recovery rate was 65/110 (59.1%). Information about recovery in patients treated with non-heparin anticoagulants was available in 5 studies including 44 patients. Recovery rate in patients treated with non-heparin anticoagulants was 28/44 (63.6%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

- George G, Friedman KD, Curtis BR, Lind SE. Successful treatment of thrombotic thrombocytopenia with cerebral sinus venous thrombosis following Ad26.COVS.2 vaccination. Am J Hematol. 2021. doi: 10.1002/ajh.26237.
- Schultz JB, Berlitz P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. medRxiv doi: <https://doi.org/10.1101/2021.04.30.21256383>; version posted May 13, 2021.
- See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COVS.2 vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448-56.
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Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: IVIG compared with no treatment or other drugs or procedures for patients diagnosed with TTS following COVID-19 vaccination Outcome: death (all cause)

Certainty assessment							Impact	Certainty	Importance
N ^o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Death (all-cause)									
8	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 8 studies reporting use of IVIG, [3 case reports and 5 case series], including 114 patients, 55 of them treated with IVIG. Global death rate was 22/55 (40.0%). Information about death in patients treated with IVIG was available in 5 studies including 16 patients. Death rate in patients treated with IVIG was 4/16 (25.0%).	⊕○○○ VERY LOW	CRITICAL

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- Tiede A, Sachs UJ, Czwalińska A, Werwitzke S, Bikker R, Krauss JK, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccine. Blood 2021;blood.2021011958. doi: 10.1182/blood.2021011958.

Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: IVIG compared with no treatment or other drugs or procedures for patients diagnosed with TTS following COVID-19 vaccination – Outcome: intracranial haemorrhage

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Intracranial haemorrhage									
7	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 7 studies reporting use of IVIG, [3 case reports and 4 case series], including 54 patients, 35 of them treated with IVIG. Global haemorrhage rate was 25/54 (46.3%). Information about haemorrhage in patients treated with IVIG was available in 5 studies including 10 patients. Haemorrhage rate in patients treated with IVIG was 5/10 (50.0%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

- George G, Friedman KD, Curtis BR, Lind SE. Successful treatment of thrombotic thrombocytopenia with cerebral sinus venous thrombosis following Ad26.COV2.S vaccination. Am J Hematol. 2021. doi: 10.1002/ajh.26237.
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- See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, 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;325(24):2448-56.
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- Tiede A, Sachs UJ, Czwalińska A, Werwitzke S, Bikker R, Krauss JK, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccine. Blood 2021;blood.2021011958. doi: 10.1182/blood.2021011958.

Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: IVIG compared with no treatment or other drugs or procedures for patients diagnosed with TTS following COVID-19 vaccination – Outcome: Recovery

Certainty assessment							Impact	Certainty	Importance
N ^o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
7	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 7 studies reporting use of IVIG, [2 case reports and 5 case series], including 113 patients, 55 of them treated with IVIG. Global recovery rate was 64/113 (56.6%). Information about recovery in patients treated with IVIG was available in 4 studies including 9 patients. Recovery rate in patients treated with IVIG was 6/9 (66.7%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

- George G, Friedman KD, Curtis BR, Lind SE. Successful treatment of thrombotic thrombocytopenia with cerebral sinus venous thrombosis following Ad26.COV2.S vaccination. *Am J Hematol.* 2021. doi: 10.1002/ajh.26237.
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- 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(22):2124-2130.
- Schultz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. *medRxiv* doi: <https://doi.org/10.1101/2021.04.30.21256383>; version posted May 13, 2021.
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Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Platelet transfusion compared with no platelet transfusion for patients diagnosed with TTS following COVID-19 – Outcome: death (all-cause)

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality (all-cause)									
5	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 5 studies providing valid data, 2 case reports and 3 case series, including 48 patients, 16 of them treated with platelet transfusions. Global mortality rate was 12/48 (25.0%). Information about mortality in patients treated with platelet transfusions was available in 3 studies including 6 patients. Mortality rate in patients treated with platelet transfusions was 5/6 (83.3%).	⊕○○○ VERY LOW	CRITICAL

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1. Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenziani I, et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. *Thromb Res.* 2021;202:182-183.
2. Mehta PR, Apap Mangion S, Bengner M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. *Brain Behav Immun.* 2021;95:514-517.
3. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COVS.2.S vaccination, March 2 to April 21, 2021. *JAMA.* 2021;325(24):2448-56.
4. 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(22):2124-2130.
5. Centers for Disease Control and Prevention. National Center for Immunization & Respiratory Diseases. Update: Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination Advisory Committee on Immunization Practices (ACIP) May 12, 2021. Available at: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf>, accessed 30 May 2021.

Explanations

- a. Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- b. The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- c. The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- d. Outcome was not available at the moment of publication in many cases.

Question: Platelet transfusion compared with no platelet transfusion for patients diagnosed with TTS following COVID-19 – Outcome: intracranial haemorrhage

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Intracranial haemorrhage									
5	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 5 studies providing valid data, 2 case reports and 3 case series, including 48 patients, 16 of them treated with platelet transfusions. Global intracranial haemorrhage rate was 23/48 (47.9%). Information about intracranial haemorrhage in patients treated with platelet transfusions was available in 3 studies including 6 patients. Haemorrhage rate in patients treated with platelet transfusions was 4/6 (66.7%).	⊕○○○ VERY LOW	CRITICAL

Bibliography:

1. Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenziani I, et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. *Thromb Res.* 2021;202:182-183.
2. Mehta PR, Apap Mangion S, Bengner M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. *Brain Behav Immun.* 2021;95:514-517.
3. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, 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;325(24):2448-56.
4. 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(22):2124-2130.
5. Centers for Disease Control and Prevention. National Center for Immunization & Respiratory Diseases. Update: Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination Advisory Committee on Immunization Practices (ACIP) May 12, 2021. Available at: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf>, accessed 30 May 2021.

Explanations

- a. Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- b. The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- c. The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- d. Outcome was not available at the moment of publication in many cases.

Question: Platelet transfusion compared with no platelet transfusion for patients diagnosed with TTS following COVID-19 – Outcome: recovery

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
5	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 5 studies providing valid data, 2 case reports and 3 case series, including 48 patients, 16 of them treated with platelet transfusions. Global recovery rate was 25/48 (52.1%). Information about recovery in patients treated with platelet transfusions was available in 3 studies including 6 patients. Recovery rate in patients treated with platelet transfusions was 0/6 (0%).	⊕○○○ VERY LOW	CRITICAL

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1. Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenzi I, et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. *Thromb Res.* 2021;202:182-183.
2. Mehta PR, Apap Mangion S, Bengner M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. *Brain Behav Immun.* 2021;95:514-517.
3. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, 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;325(24):2448-56.
4. 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(22):2124-2130.
5. Centers for Disease Control and Prevention. National Center for Immunization & Respiratory Diseases. Update: Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination Advisory Committee on Immunization Practices (ACIP) May 12, 2021. Available at: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf>, accessed 30 May 2021.

Explanations

- a. Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- b. The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- c. The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- d. Outcome was not available at the moment of publication in many cases.

Question: Steroids compared with no steroids or other treatments for patients diagnosed with TTS following COVID-19 vaccination – Outcome; death (all cause)

Certainty assessment							Impact	Certainty	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Death (all-cause)									
6	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 6 studies providing valid data, 4 case reports and 2 case series, including 82 patients, 14 of them treated with steroids. Global death rate was 19/82 (23.2%). Information about death in patients treated with steroids was available in 4 studies including 7 patients. Death rate in patients treated with steroids was 3/7 (42.9%).	⊕○○○ VERY LOW	CRITICAL

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- George G, Friedman KD, Curtis BR, Lind SE. Successful treatment of thrombotic thrombocytopenia with cerebral sinus venous thrombosis following Ad26.COV2.S vaccination. Am J Hematol. 2021. doi: 10.1002/ajh.26237.
- Mehta PR, Apap Mangion S, Bengner M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. Brain Behav Immun. 2021;95:514-517.
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- Schultz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. medRxiv doi: <https://doi.org/10.1101/2021.04.30.21256383>; version posted May 13, 2021.
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Explanations

- Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- Outcome was not available at the moment of publication in many cases.

Question: Steroids compared with no steroids or other treatments for diagnosed with TTS following COVID-19 vaccination – Outcome: intracranial haemorrhage

Certainty assessment							Impact	Certainty	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Intracranial haemorrhage									
5	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 5 studies providing valid data, 4 case reports and 1 case series, including 21 patients, 10 of them treated with steroids. Global haemorrhage rate was 12/21 (57.1%). Information about haemorrhage rate in patients treated with steroids was available in 4 studies including 7 patients. Haemorrhage rate in patients treated with steroids was 3/7 (42.9%).	⊕○○○ VERY LOW	CRITICAL

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1. Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenziani I, et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. *Thromb Res.* 2021;202:182-183.
2. Mehta PR, Apap Mangion S, Bengner M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. *Brain Behav Immun.* 2021;95:514-517.
3. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, 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;325(24):2448-56.
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Explanations

- a. Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- b. The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- c. The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- d. Outcome was not available at the moment of publication in many cases.

Question: Steroids compared with no steroids or other treatments for patients diagnosed with TTS following COVID-19 vaccination – Outcome: recovery

Certainty assessment							Impact	Certainty	Importance
N ^o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			

Recovery

4	observational studies	very serious ^a	serious ^b	not serious	very serious ^c	publication bias strongly suspected ^d	There were 4 studies providing valid data, all case reports, including 9 patients, 7 of them treated with steroids. Global recovery rate was 4/9 (44.4%). Information about recovery in patients treated with steroids was available in 4 studies including 7 patients. Recovery rate in patients treated with steroids was 4/7 (57.1%).	⊕○○○ VERY LOW	CRITICAL
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Bibliography:

1. Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenziani I, et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. *Thromb Res.* 2021;202:182-183.
2. Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. *Brain Behav Immun.* 2021;95:514-517.
3. 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(22):2124-2130.
4. Centers for Disease Control and Prevention. National Center for Immunization & Respiratory Diseases. Update: Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination Advisory Committee on Immunization Practices (ACIP) May 12, 2021. Available at: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf>, accessed 30 May 2021.

Explanations

- a. Selection bias: Fatal cases were more likely to be quickly published as case reports (range 5-8 days) than large case series. Not all confounding factors influencing the prognosis were analyzed (age, time between symptom onset and treatment, other treatments, presence of multiple organ thrombosis), incomplete follow-up in most cases
- b. The dose was not described in studies. Duration of follow-up was different. There is heterogeneity clinically (different treatment paradigms, location and severity of thromboses) and methodologically between studies, and there is limited certainty regarding that the differences explain the observed differences in effects.
- c. The total number of patients included is less than the number of patients that should be included according to a sample size calculation for a single adequately powered trial
- d. Outcome was not available at the moment of publication in many cases.