Cardiovascular complications of covid vaccines

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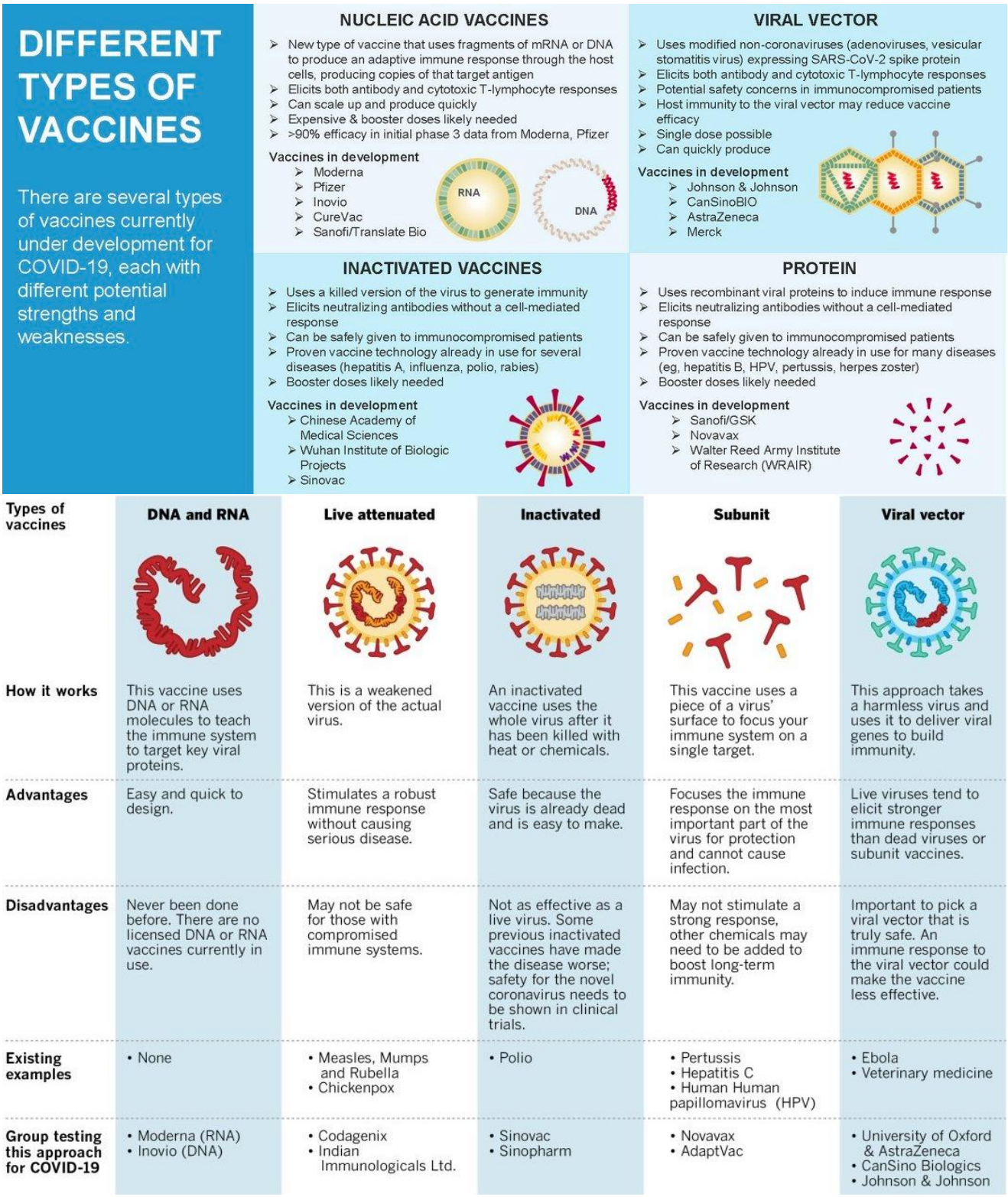
Types of Covid vaccines



Types of vaccines	DNA and RNA	Live attenuated	Inactivated	Subunit	Viral vector
How it works	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Advantages	Easy and quick to design.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Disadvantages	Never been done before. There are no licensed DNA or RNA vaccines currently in use.	May not be safe for those with compromised immune systems.	Not as effective as a live virus. Some previous inactivated vaccines have made the disease worse; safety for the novel coronavirus needs to be shown in clinical trials.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.
Existing examples	• None	• Measles, Mumps and Rubella • Chickenpox	• Polio	• Pertussis • Hepatitis C • Human Human papillomavirus (HPV)	• Ebola • Veterinary medicine
Group testing this approach for COVID-19	• Moderna (RNA) • Inovio (DNA)	• Codagenix • Indian Immunologicals Ltd.	• Sinovac • Sinopharm	• Novavax • AdaptVac	• University of Oxford & AstraZeneca • CanSino Biologics • Johnson & Johnson

Figure 1: Different types of covid vaccines

(Centers for Disease Control and Prevention)

Vaccine developer	Pfizer	Moderna	AstraZeneca	Johnson & Johnson	Novavax
When approved/expected approval	Given full FDA approval Aug. 23, 2021	Dec. 18, 2021	Not yet available. Phase III clinical trials in progress as of Feb. 27	Feb. 27	Not yet available. Results from phase III clinical trials published June 14.
Protection %	95%	94.1%	70%	66.1% globally; 72% in the U.S. 86% effective against severe disease	89.7%
Recommended for?	12 years and older	18 years and older	Not yet available	18 years and older	Not yet available
Doses	Two doses, 3 weeks apart	Two doses, 4 weeks apart	Two doses, a month apart	One dose	Two doses, 21 days apart
Time for a booster dose?	8 months after your second dose	8 months after your second dose		To be determined	
Side effects	Fatigue, headache, chills, muscle pain, especially after the second dose	Fever, muscle aches, headaches lasting a few days. Effects worse after second dose.	Local Pain, fever, muscle aches, headache	Local Pain, headache, fatigue, muscle pain	Local Pain, fatigue, headache, muscle pain
Any warnings?	The FDA issued a warning in June about myocarditis.	The FDA issued a warning in June about myocarditis.		In July, the FDA issued a warning about an increased risk for developing Guillain-Barre syndrome.	
Pregnant women and nursing moms?	Pregnant women or nursing moms who want the COVID-19 vaccine should get one.	The CDC says pregnant women may choose to receive the vaccine.		Discuss with your health care provider.	Not yet available
Contraindications	People with a history of serious allergic reactions, anyone with a history of allergic reactions to vaccine ingredients, including polyethylene glycol, and anyone with a history of allergic reactions to polysorbate			Anyone who's had an allergic reaction to an ingredient in the vaccine, like polysorbate	Not yet available
Any significant side effects?	Extremely rare cases of anaphylaxis in people who received the vaccine. Extremely rare cases of Bell's palsy		Four total serious side effects, including two cases of transverse myelitis	TTS	Not yet available
What about people with lowered immune function?	OK for people whose immune function is lowered by HIV or immunosuppressing drugs if they have no other reasons to avoid it.		Not yet available	Not yet available	Not yet available
What about people with autoimmune diseases?	No data is available on the safety or effectiveness of mRNA vaccines in people with autoimmune disease. People with autoimmune conditions may still get the shots if they have no other reasons to avoid vaccination.		Not yet available	Not yet available	Not yet available
Is the vaccine safe for people with a history of Guillain-Barre syndrome (GBS)?	To date, no cases of GBS have been seen in people vaccinated for COVID-19. The CDC says a history of GBS is not a reason to avoid vaccination.		Not yet available	There's a possible, but rare risk in developing Guillain-Barre syndrome after this vaccine.	Not yet available

Table 1: comparison between different types of covid vaccines [227].

Possible side effect of the vaccines

COVID-19 vaccination will help protect against COVID-19 infection. Some side effects may develop, which are normal signs that the body is building protection. These side effects may affect the ability to do the daily activities, but they should go away in a few days. Some people have no side effects [(70).]

Serious side effects that could cause a long-term health problem are extremely unlikely following any vaccination, including COVID-19 vaccination. Vaccine monitoring has historically shown that side effects generally happen within six weeks of receiving a vaccine dose. For this reason, the FDA required each of the authorized COVID-19 vaccines to be studied for at least two months (eight weeks) after the final dose. [(70).]

- Local side effects at the site of injection:
  - Pain. – Redness. - Swelling
- General side effects:
  - Tiredness. – Headache. - Muscle pain
  - Chills. – Fever. – Nausea

- Treatment:
  - To reduce pain and discomfort at the site of injection:
    - Apply a clean, cool, wet washcloth over the area.
    - Use or exercise the arm.
  - To reduce discomfort from fever
    - Drink plenty of fluids.
    - Dress lightly.
  - NSAIDs and antihistamines:
    - Ibuprofen, acetaminophen, aspirin, or antihistamines

Side effects after the second shot may be more intense than the ones experienced after the first shot. These side effects are normal signs that the body is building protection and should go away within a few days. [(70).]

Side effects after getting a booster shot are similar to side effects after the 2-shot series. The most common side effects after a booster shot are fatigue and pain at the injection site and overall, most side effects were mild to moderate. Like the 2-shot primary series, serious side effects are rare, but may occur. [(70).]

If a severe or immediate allergic reaction developed after getting the first dose of an mRNA COVID-19 vaccine, the second dose of either of the mRNA COVID-19 vaccines is contraindicated.

Need to contact health care provider:

- In most cases, discomfort from pain or fever is a normal sign that the body is building protection.
- Contact healthcare provider:
  - If the redness or tenderness at the site of injection gets worse after 24 hours.
  - If side effects are worrying or do not seem to be going away after a few days[(70).]

Myocarditis and pericarditis.

Epidemiology:

Historically, postvaccination myocarditis has been reported as a rare adverse event after vaccinations, especially smallpox vaccination, influenza, hepatitis B, or other vaccinations.[1]

In the general population, myocarditis is diagnosed in approximately 10 to 20 individuals per 100 000 per year,[2] and occurs more commonly and at younger ages in males compared with females.[3]

In the pre–COVID-19 era, among 620 195 reports filed at the Vaccine Adverse Event Reporting System (VAERS) between 1990 and 2018, 0.1% were attributable to myopericarditis. Of those myopericarditis reports, 79% were in males.[1]

Recently, a Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices identified a likely association between the 2 COVID-19 mRNA vaccines from Pfizer-BioNTech and Moderna and cases of myocarditis and pericarditis.[5]

Patient reports in VAERS were categorized according to CDC work case definitions as probable myocarditis, confirmed myocarditis, or acute pericarditis[5].

According to the Advisory Committee on Immunization Practices, after ≈300 million COVID-19 mRNA vaccine doses administered through June 11, 2021, there were 1226 reports of probable myocarditis/pericarditis cases in VAERS, 67% of which followed the second dose.[5] Seventy-nine percent were in males, with the majority in individuals <30 years of age with a median age of 24.

Age groups	Females			Males		
	Doses administered	Expected	Observed	Doses administered	Expected	Observed
12–17 y	2 189 726	0–2	19	2 039 871	0–4	128
18–24 y	5 237 262	1–6	23	4 337 287	1–8	219
25–29 y	4 151 975	0–5	7	3 625 574	1–7	59
30–39 y	9 356 296	2–18	11	8 311 301	2–16	61
40–49 y	9 927 773	2–19	18	8 577 766	2–16	34
50–64 y	18 696 450	4–36	18	16 255 927	3–31	18
65+ y	21 708 975	4–42	10	18 041 547	3–35	11

Table 2. Expected Versus Observed Number of Myocarditis/Pericarditis Cases in 7-Day Risk Window After Dose 2 of mRNA Covid-19 Vaccination(228)

Age groups	**Female rates per million doses**			**Male rates per million doses**		
	All doses	**Dose 1**	**Dose 2**	**All doses**	**Dose 1**	**Dose 2**
12–17 y	4.2	1.1	9.1	32.4	9.8	66.7
18–24 y	3.6	1.5	5.5	30.7	8.7	56.3
25–29 y	2.0	0.8	2.6	12.2	4.5	20.4
30–39 y	1.8	1.4	1.8	6.9	2.0	10.0
40–49 y	2.0	0.9	2.8	3.5	1.0	5.1
50–64 y	1.6	1.0	1.8	1.9	1.0	2.3
65+ y	1.1	0.6	1.2	1.2	0.7	1.4

Table 3: Crude Reporting Rates of Myocarditis/Pericarditis Cases per Million Doses After mRNA COVID-19 Vaccination (228)

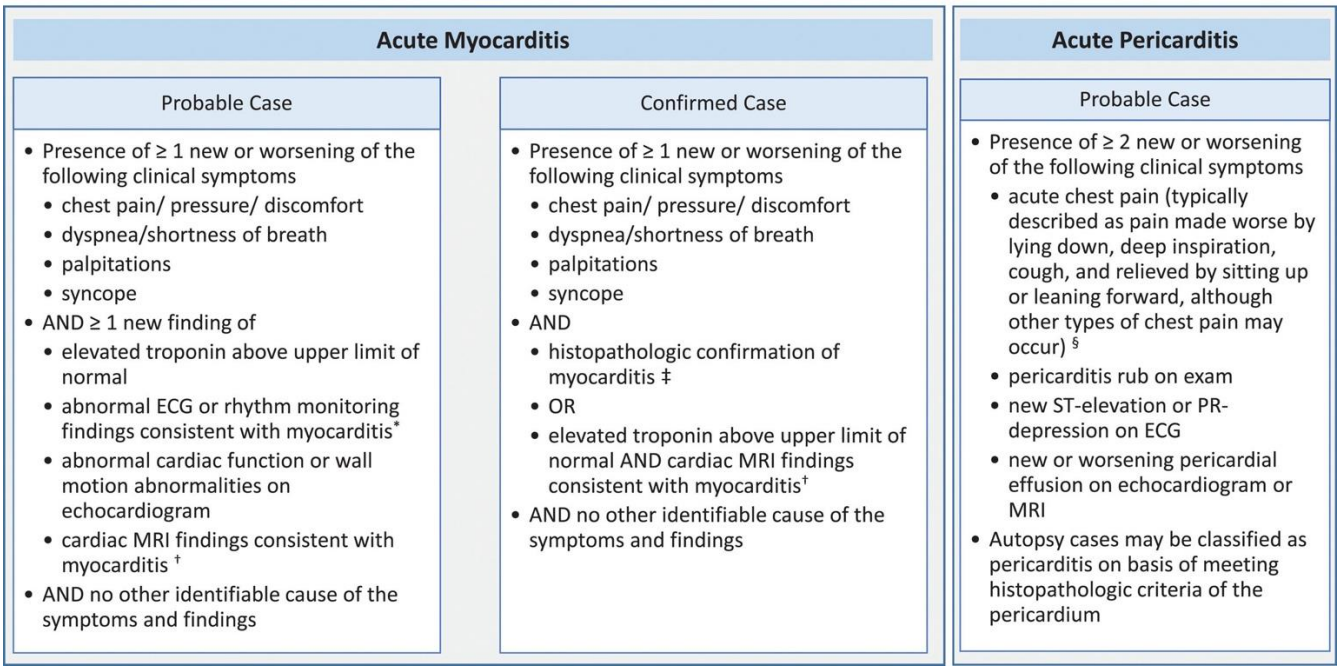


Figure 2. Centers for Disease Control and Prevention working case definitions for acute myocarditis and acute pericarditis[70].

additional analyses of CDC Vaccine Safety Datalink with data from 9 participating integrated health care organizations revealed an increased risk of myocarditis/pericarditis events among individuals 12 to 39 years of age in the 7-day risk interval after vaccination with mRNA COVID-19 vaccines compared with unvaccinated individuals or individuals vaccinated with non-mRNA COVID-19 vaccines on the same calendar days (rate ratio of 10.8 [95% CI, 3.2–49.0], adjusted for site, age, sex, race/ethnicity, and calendar date).[5]

The estimated myocarditis/pericarditis chart-confirmed rate was 12.6 cases per million doses with second-dose mRNA vaccine among individuals 12 to 39 years of age.[5] The rates based on International Classification of Diseases, 10th Revision–coded cases were also higher in males than in females. [5]

All chart-confirmed cases with follow-up had resolution of symptoms; and among those who had follow-up ECG/echocardiography and laboratory testing, most had returned to normal or baseline.[5]

On this basis, the Food and Drug Administration will add a warning to the product label of both mRNA vaccines regarding the risk of myocarditis.[7]

Age group 12-39 y	Female cases	Female rates per million doses	Male cases	Male rates per million doses
Any mRNA both doses	6	3.2 (1.2–6.9)	26	16.9 (11.0–24.8)
Any mRNA dose 1	2	1.9 (0.2–7.0)	4	4.7 (1.3–12.0)
Any mRNA dose 2	4	4.7 (1.3–12.0)	22	32.0 (20.1–48.5)

Table 4. Myocarditis/Pericarditis Rates Based on International Classification of Diseases, 10th Revision Codes(228)

Clinical Presentation of Myocarditis After COVID-19 Vaccination:

Time to onset of symptoms was a median of 3 days, with the highest rate at day 2 after vaccination and among patients 16 to 18 years of age. In 484 probable myocarditis/pericarditis cases among patients ≤29 years of age that were reviewed and characterized by the CDC, 86% had reports of chest pain on presentation, 61% had reports of ST- or T-wave changes on ECG, 64% had reports of elevated cardiac enzymes, and 17% had reports of abnormal cardiac imaging. In 323 of the reports that met the CDC

definition of confirmed myocarditis/pericarditis, 96% were hospitalized, but most were discharged with a resolution of symptoms. The observed myocarditis/pericarditis reports were higher than expected case rates for males compared with females, and higher at younger ages compared with older ages [5].

Several myocarditis cases after COVID-19 vaccination have been published in peer-reviewed journals, with reports predominantly after the second dose of mRNA COVID-19 vaccines (BNT162b2 mRNA-Pfizer-BioNTech and the mRNA-1273-Moderna [8–19].

Patients in these reports invariably presented with chest pain, usually 2 to 3 days after a second dose of mRNA vaccination, some preceded with fever and myalgia 1 day after vaccination. These were predominantly young males requiring hospitalization for myocarditis and without a history of COVID-19 or comorbidities. All tested negative for current COVID-19 by polymerase chain reaction testing. A majority had spike antibody levels for SARS-CoV-2 suggesting effective immunization. All had elevated cardiac troponin, the highest-level peaking usually 3 days after vaccination. ECG was abnormal with ST elevations in most presentations. An echocardiogram was abnormal in only 40%, with only a small percentage having a left ventricular ejection fraction<50% on presentation. Cardiac MRI was abnormal in all tested patients, with findings suggestive of myocarditis such as late gadolinium enhancement and myocardial edema. B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide levels were only mildly elevated in approximately two-thirds of the patients when measured. C-reactive protein levels were elevated in most and decreased along with troponin through the hospital stay. Almost all patients had resolution of symptoms and signs and improvement in diagnostic markers and imaging with or without treatment [8–19].

COVID-19–Associated Myocarditis

With the emergence of COVID-19 in Hubei Province, China, there was an expectation that the SARS-CoV-2 would cause predominantly respiratory illness, similar to that seen with SAR) in 2002 to 2003.[21]

However, with the next phase of the COVID-19 epidemic in Southern Europe and later New York City, it became apparent that there were cardiovascular involvement and thromboembolic complications.[22] Therefore, COVID-19 emerged as a virus pathogen affecting the vasculature and resulting in myocardial injury, requiring far different therapeutic approaches compared with SARS.[22,23]

Historically, pre–COVID-19, coronaviruses have not been commonly associated with significant myocardial damage. SARS infected >8000 individuals without significant incidence of myocarditis. In 1 autopsy series, SARS-CoV-1 was polymerase chain reaction amplifiable in 7 of 20 (35%) hearts, but was not associated with lymphocytic myocarditis, the hallmark of classic viral myocarditis.[24]

Similarly, Middle East respiratory syndrome coronavirus infected >2000 individuals, with only 1 case report of MRI-diagnosed Middle East respiratory syndrome coronavirus myocarditis.[25] On the other hand, epidemiological data suggest that ≈12% to 20% of hospitalized patients with COVID-19 have evidence of cardiac injury as indicated by elevated levels of cardiac troponin.[23,26]

Furthermore in young athletes recovering from COVID-19 infection,[27] cardiac MRI abnormalities consistent with myocarditis have been reported at a higher prevalence than expected, in ≈1% to 3% of the athletes.[28–32]

It was also recognized that COVID-19 can result in a multisystem inflammatory syndrome in children and younger adults. This rare but serious condition is defined by an excessive hyperinflammatory response that can affect multiple organs including the lungs, kidneys, brain, skin, eyes, the gastrointestinal system, and the cardiovascular system, resulting in ventricular dysfunction, coronary aneurysms, and shock.[33,34]

Although some investigators have proposed direct virus invasion as the most likely mechanism, others focus more on host inflammatory cell responses. Emerging data indicate that a maladaptive host immune response fueled by excessive activation of innate immune pathways along with proinflammatory cytokine surge, deregulated thromboinflammation, thrombotic microangiopathy, and endothelial dysfunction may play a role in pathogenesis of cardiac injury related to COVID-19.[35,36]

Other hypothesized mechanisms include demand ischemia, and stress- and hypoxia-induced myocardial injury.[23] Baseline comorbidities including metabolic syndrome, hypertension, and cardiovascular disease likely also play a role.

Although SARS-CoV-2 can enter the cardiomyocyte through an angiotensin-converting enzyme 2–mediated entry and SARS-CoV-2 copies have been detected in heart tissue,[37–39] cardiac histopathology studies have reported the absence of diffuse lymphocytic myocarditis traditionally seen in viral myocarditis or confluent myocyte necrosis expected in fulminant myocarditis.[38,40–43]

It is important to note that macrophages can mediate both local and systemic responses to viral infection, are also capable of fixing complement, and therefore could cause the direct death of nearby myocytes through the activation of apoptotic attack complexes.[35]

These findings suggest that COVID-19 may incite a form of myocarditis that is different from the typical lymphocytic myocarditis associated with other viral myocarditis presentations and may instead be associated with diffusely infiltrative cells of monocyte/macrophage lineage.[35,41,44]

Potential Mechanisms of COVID-19 Vaccine Myocarditis

SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA, encoding the viral spike glycoprotein of SARS-CoV-2, but not live virus or DNA. They are encapsulated in lipid nanoparticles that act as delivery vehicles to transport mRNA into the cells and may include inactive ingredients such as buffer and salts. Once inside the host cells, the vaccine's mRNA causes the cells to build the spike protein which then stimulates an adaptive immune response to identify and destroy a virus expressing spike protein. Vaccine-induced spike protein IgG antibodies prevent attachment of SARS-COV-2 to its host cell via spike protein binding to the angiotensin-converting enzyme 2 receptor, and thereby neutralizes the virus.[228]

Selected RNA molecules can be immunogenic and stimulate the mammalian innate immune system, destroying the mRNA before it reaches target cells, preventing the spike protein and neutralizing antibody production. Nucleoside modifications of mRNA have been groundbreaking, shown to reduce innate immunogenicity, and result in less activation of cytokines, paving the path for mRNA vaccine development.[45]

COVID-19 mRNA vaccines have been shown to be highly effective and safe in large-scale trials.[46,47] Systemic reactions to the vaccine, which are usually mild and transient, were reported more commonly among the younger population and more often after the second dose. Adverse cardiovascular effects in these trials were isolated, with incidences <0.05%, and did not include myocarditis.[46,47]

Although nucleoside modifications of mRNA have been shown to reduce their innate immunogenicity,[45] in certain individuals with genetic predisposition,[48] the immune response to mRNA may not be turned down and may drive the activation of an aberrant innate and acquired immune response. The dendritic cells or Toll-like receptor expressing cells exposed to RNA may still have the capacity to express cytokines and activation markers in certain individuals, although this may be markedly less when exposed to mRNA with nucleoside modifications than when treated with unmodified RNA.[45]

The immune system may therefore detect the mRNA in the vaccine as an antigen, resulting in activation of proinflammatory cascades and immunologic pathways that may play a role in the development of myocarditis as part of a systemic reaction in certain individuals.[45,48]

In published reports of myocarditis after COVID-19 vaccination, cardiac biopsy was reported in only 2 cases and did not demonstrate myocardial infiltrate[11] or any evidence of myocarditis.[9] This could be attributable to a sampling error in these few cases, or a different mechanism causing myocardial injury detected by cardiac biomarkers and MRI not manifest as traditional lymphocytic or eosinophilic myocarditis or myonecrosis on cardiac histopathology.

SARS-COV-2 polymerase chain reaction and viral serology for other causes including hepatitis, Epstein-Barr virus, cytomegalovirus, parvovirus, mycoplasma, HIV, influenza A/B, respiratory syncytial virus, rhinovirus, enterovirus (Coxsackie A, Coxsackie B), adenovirus, and other causes were negative for acute or active infection, when tested, arguing against myocarditis caused by COVID-19 or other infections.[10,14–18]

Serology for autoimmune disorders with antinuclear antibodies and rheumatoid factor were negative, with no evidence of predilection to individuals with preexisting autoimmune disorders.[10]

There was also no evidence of leukocytosis, eosinophilia, anemia, thrombocytopenia, or transaminase elevation.[19,12]

D-Dimer was slightly elevated in 2 patients without evidence of pulmonary embolus or venous thromboembolic events,[12,14] and erythrocyte sedimentation rate was mildly elevated in some cases.[14]

In 1 case report, a panel testing for variants in 121 genes potentially linked to cardiomyopathy was negative,[17] arguing against an existing predisposition to cardiomyopathy attributable to known gene variants in that case.

By 1 case report, SARS-CoV-2 spike IgM and IgG neutralizing antibody levels were not significantly different in the patient with myocarditis than in individuals without myocarditis post–COVID-19 mRNA vaccination,[17] arguing against a hyperimmune response.[17]

In the same report, the patient with myocarditis had elevated levels of IL-1 (interleukin 1) receptor antagonist, IL-5, IL-16, but not proinflammatory cytokines such as IL-6, tumor necrosis factor, IL-1B, IL-2, or interferon-γ levels. However, the patient had diminished levels of leukemia inhibitory factor, varying bidirectional profiles for IL-10, macrophage migration inhibitory factor, and vascular endothelial growth factor relative to an unvaccinated individual or a vaccinated individual without myocarditis.[17] This patient also had higher levels of antibodies against some self-antigens such as aquaporin 4, endothelial cell antigen, and proteolipid protein 1.[17]

Historically, circulating heart-reactive autoantibodies have been reported at a higher frequency in patients with myocarditis and have been implicated in pathogenesis.[49] These autoantibodies are usually directed against multiple antigens, some of which may have functional effects on cardiac myocytes.[49] Thus, autoantibody generation could be one of the mechanisms whereby myocarditis may develop in susceptible individuals after vaccination. However, it should be noted that in the patient studied, autoantibody levels peaked on day 2 along with symptoms, but they did not recede as expected, as the clinical condition improved, although the follow-up was rather short.[49]

Another important potential mechanism for myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens.[50]

Antibodies against SARS-CoV-2 spike glycoproteins have been experimentally shown to cross-react with structurally similar human peptide protein sequences, including α-myosin.[50]

However, severe adverse events or autoimmune reactions have been very rare.[46,47] Although COVID-19 vaccination does not appear to provoke de novo immune-mediated adverse events, it is possible that it may trigger preexisting dysregulated pathways in certain individuals with predisposition, resulting in a polyclonal B-cell expansion, immune complex formation, and inflammation.[48]

Reports to date also do not suggest a delayed hypersensitivity reaction, such as serum sickness–like reaction or eosinophilic myocarditis as a cause for myocarditis after mRNA COVID-19 vaccination.[15]

Although rare, delayed localized skin hypersensitivity reactions have been described with mRNA COVID-19 vaccination with a median latency of 7 days,[59]

unlike myocarditis emerging earlier within 3 to 4 days after vaccination. None of the case reports published to date had evidence of eosinophilia in peripheral blood or immune complex deposition or eosinophilic infiltrates in endomyocardial biopsy samples arguing against hypersensitivity, allergic or eosinophilic myocarditis.[8–17] Lipid nanoparticles or adjuvants used in mRNA vaccines have not been shown to result in an immune or inflammatory response and have not been associated with myocarditis either. [8–17]

Rare occurrences of vaccine-induced immune thrombotic thrombocytopenia have been reported after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of SARS-COV-2.[60] Although very rare thrombotic complications have been reported after mRNA COVID-19 vaccinations, these patients did not have thrombocytopenia or antiplatelet antibodies.[61,62]

None of the myocarditis cases reported after mRNA vaccination had evidence of thrombotic events, thrombocytopenia, or disseminated intravascular coagulation. These patients also did not have persistent fever beyond the first few days, lymphadenopathy, hepatosplenomegaly, cytopenias (anemia, leukopenia, and thrombocytopenia), hypofibrinogenemia, transaminitis, extreme elevation in ferritin or multiorgan impairment to suggest a cytokine storm, hemophagocytic lymphohistiocytosis, or macrophage activation syndrome that results from overactivation of T lymphocytes and macrophages.[63,64]

Male predominance in myocarditis/pericarditis cases has been described in clinical and experimental studies before, and the reasons are unknown. An important possible explanation relates to sex hormone differences.[3,65,66] Testosterone is thought to play a role, by a combined mechanism of inhibition of anti-inflammatory cells[3,65–67] and commitment to a Th1-type immune response.[68] Estrogen has inhibitory effects on proinflammatory T cells, resulting in a decrease in cell-mediated immune responses; and pericarditis incidence is higher in women during the postmenopausal period. Another contributing factor could be underdiagnosis in women. [69]

Assessing the risk

Despite these rare cases of myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups[5].

Given the known potential risk of complications with COVID-19 infection, including hospitalizations and death even in younger adults (mortality remains 0.1–1 per 100 000 for persons 12–29 years of age), the risk-benefit decision remains overwhelmingly favorable for vaccination. Therefore, COVID-19 vaccination is currently recommended for everyone ≥12 years of age[5] .

COVID-19 vaccination not only prevents COVID-19–related hospitalizations and death, but also COVID-19–related complications such as myocarditis, multisystem inflammatory syndrome,[33] and post–acute sequelae of SARS-CoV-2 infection or long COVID-19.[74]

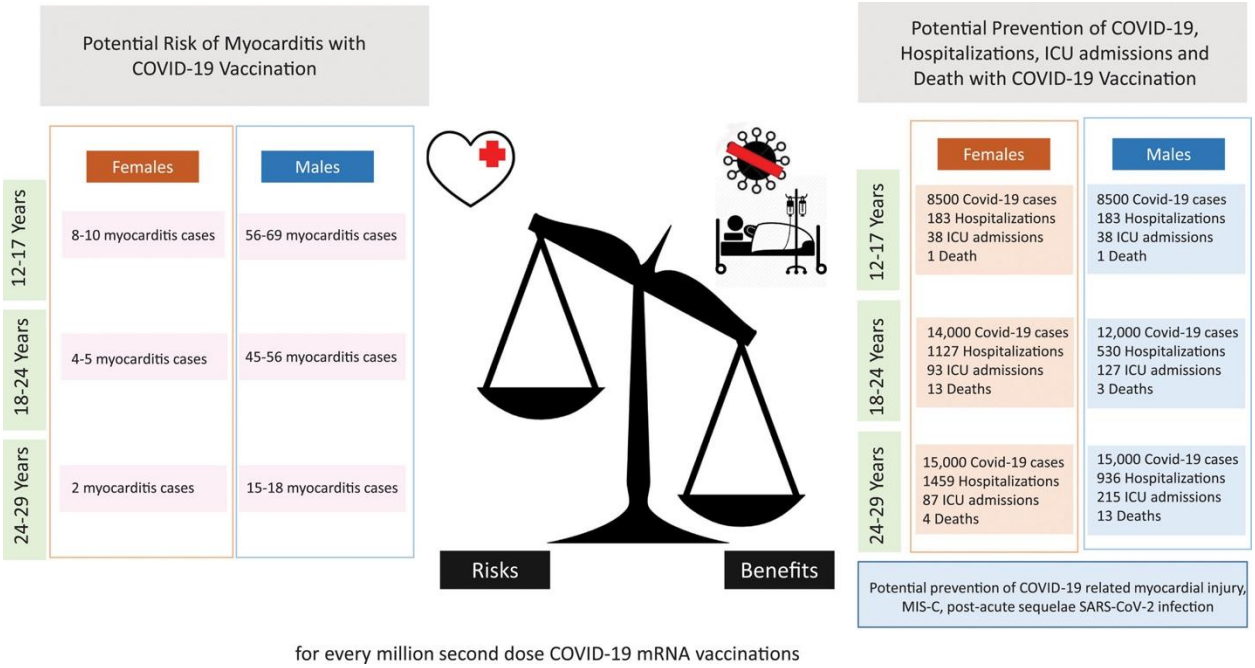


Figure 3: Predicted benefits of reduction in COVID-19–related hospitalizations and death and risks of myocarditis after second dose of mRNA COVID-19 vaccination by age group.

Adapted from Centers for Disease Control and Prevention[5] with permission. Predictions for hospitalization and myocarditis rates were calculated for every million doses of mRNA vaccine based on hospitalization rates from Coronavirus Disease 2019 (COVID-19)–Associated Hospitalization Surveillance Network (COVID-NET) as of May 22. Benefit/risk were calculated over 120 days. [71]

To meet the ECG or rhythm-monitoring criterion, at least 1 of the following must be included: ST-segment or T-wave abnormalities, paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias, atrioventricular nodal conduction delays or intraventricular conduction defects. [226] COVID-19 indicates coronavirus disease 2019; ICU, intensive care unit; MIS-C, multisystem inflammatory syndrome in children; and SARS-CoV-2, severe acute respiratory syndrome coronavirus-2. †Using either the original or revised Lake Louise criteria.[72] ‡Using the Dallas criteria.[73] §Autopsy cases may be classified as pericarditis on the basis of meeting histopathologic criteria of the pericardium.

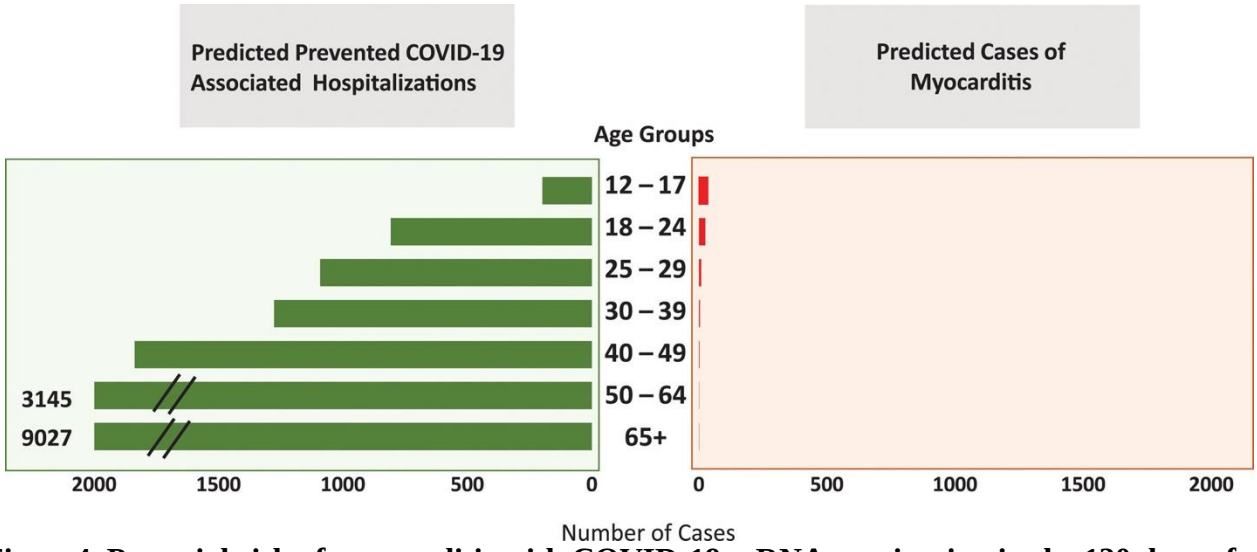


Figure4. Potential risk of myocarditis with COVID-19 mRNA vaccination in the 120 days after vaccination and predicted prevention of COVID-19 cases, COVID-19–related hospitalizations, intensive care unit admissions, and deaths according to age groups and sex.

Adapted from Centers for Disease Control and Prevention[5] with permission.
Predictions for hospitalization and myocarditis rates were calculated for every million doses of mRNA vaccine based on hospitalization rates from Coronavirus Disease 2019 (COVID-19)–Associated Hospitalization Surveillance Network (COVID-NET) as of May 22, 2021. Benefit/risk was calculated over 120 days.

Management Strategies

Although rare, clinicians should be aware of the myocarditis and pericarditis risk, which should be considered in individuals presenting with chest pain within a week after vaccination, especially in the younger population.[226]

For initial evaluation, ECG and cardiac troponin level should be obtained, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate can be helpful.[5]

For suspected cases, cardiology consultation and evaluation with echocardiography and cardiac MRI should be considered. [226]

An evaluation for acute COVID-19 infection (via polymerase chain reaction of respiratory tract sample) and past disease (via SARS-CoV-2 nucleocapsid and spike protein antibodies) would be helpful. [226]

Evaluation and management may vary depending on the patient's age, clinical presentation, potential other causes and comorbidities, hemodynamic and rhythm stability, and clinical course. [226]

Patients with chest pain, evidence of myocardial injury, ECG changes, cardiac imaging abnormality, arrhythmia, hemodynamic instability after COVID-19 vaccination likely will require hospitalization and close follow-up. [226]

In published case reports, in addition to supportive care, nonsteroidal anti-inflammatory drugs, steroids, and colchicine were used for management of some of the patients with myocarditis after COVID-19 vaccination. [226]

A few patients were treated with intravenous immunoglobulin and aspirin, and some were initiated on β-blocker and angiotensin-converting enzyme inhibitor therapy because of left ventricular systolic dysfunction. [226]

Although there are no prospective or randomized studies, it is reasonable to consider these therapies, especially in patients with significant symptoms and findings. [226]

Among patients with rapid resolution of symptoms, with preserved cardiac function and normal biomarkers or resolving cardiac biomarker abnormality, therapy may be deferred. [226]

In patients with persistent mild symptoms without hemodynamic instability, arrhythmia, significant left ventricular dysfunction or heart failure, colchicine, nonsteroidal anti-inflammatory drugs, and steroids may be considered. [226]

In patients with left ventricular dysfunction, heart failure, new-onset arrhythmia, or hemodynamic instability, intravenous steroids and intravenous immunoglobulin along with other cardiac or circulatory supportive measures can be considered. [226]

In patients with left ventricular systolic dysfunction, guideline-directed therapy including β-blockers and angiotensin-converting enzyme inhibitors should be initiated. [226]

Management should include a cardiologist for initial assessment, evaluation, treatment, and follow-up, and an infection disease specialist for guidance on subsequent immunization strategies. [226]

Although the clinical course appears mild with likely resolution of symptoms and signs, it is reasonable to restrict or defer strenuous physical activity and competitive sports until after complete resolution of symptoms, signs, hemodynamic, rhythm, diagnostic, and biomarker abnormalities. [226]

If a person develops myocarditis or pericarditis after the first dose of an mRNA vaccine, CDC recommends that their second dose be delayed and that the second dose could be reconsidered on resolution of symptoms, signs, and findings, under certain circumstances.[75]

There is evolving evidence that a single-dose mRNA vaccine does not offer adequate protection in the general population against new SARS-COV-2 variants, and further studies are needed to determine efficacy of a single versus 2 doses of mRNA vaccination in different age groups.[75]

CDC recommends that all cases of myocarditis and pericarditis post–COVID-19 vaccination be reported to VAERS.[5]

Future Directions and Research Priorities

Studies are needed to elucidate the incidence, risk factors including genetic predisposition, prognosis, potential mechanisms, reasons for sex differences, clinical course, treatment strategies, and the long-term impact of myocarditis after COVID-19 vaccination.[5]

Future research studies should be designed and supported specifically to:

(1) Characterize the role of specific immune cell populations, their similarities and differences in the development of COVID-19, immunity post–COVID-19 vaccinations, myocardial injury and

multisystem inflammatory syndrome in children related to COVID-19, and myocarditis related to COVID-19 vaccines. [228]

(2) Characterize histopathology, immunohistochemistry, ultrastructural, and functional changes of the myocardium in the setting of myocardial injury related to COVID-19, and myocarditis related to COVID-19 vaccines, and their correlation with cardiac imaging and cardiac biomarker findings. [228]

(3) Prospectively screen for the development of myocarditis and myocardial injury after COVID-19 vaccinations in different populations with specific emphasis on sex- and age-related differences. [228]

(4) Explore predisposing factors for the development of myocardial injury with COVID-19 or myocarditis with COVID-19 vaccines (eg, genetic factors, comorbidities, immunity or autoimmunity profile). [228]

(5) Explore the mechanisms for development of myocarditis related to COVID-19 mRNA vaccination, including but not limited to molecular mimicry, autoantibody formation, mRNA immune reactivity, trigger of preexisting dysregulated immune processes; it is also important to determine whether these factors are specific for spike delivery through the mRNA technology or possibly a rare event from mRNA vaccinations. [228]

(6) Prospectively characterize the clinical course and short- and long-term outcomes of myocardial injury related to COVID-19, and myocarditis related to COVID-19 vaccines. [228]

(7) Explore appropriate treatment and management strategies for myocardial injury related to COVID-19 and myocarditis related to COVID-19 vaccines. [228]

(8) Characterize cardiac biomarkers, cardiac function and structure in patients with prolonged symptoms after COVID-19, or myocarditis related to COVID-19 vaccine. [228]

(9) Determine a risk-benefit ratio for different age and sex groups with different doses of COVID-19 vaccination. [228]

(10) Provide guidance on return to play and return to activity for patients with evidence of myocardial injury related to COVID-19 and myocarditis related to COVID-19 vaccines. [228]

Conclusions

In summary, >177 million people have received at least 1 dose of COVID-19 vaccine (>300 million doses) in the United States, and CDC and other international organizations continue to monitor the safety of COVID-19 vaccines for any health problems including rare cases of myocarditis after vaccination.[75] Despite rare cases of self-limited myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups; therefore, COVID-19 vaccination is currently recommended for everyone 12 years of age and older. [228]

Vascular thrombosis
Thrombosis with thrombocytopenia syndrome (TTS)

Other names:

- Vaccine induced thrombocytopenia thrombosis (VITT).
- Vaccine-induced immune thrombotic thrombocytopenia (VIITT)
- Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) [226].

Background:

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.COV2-S 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 [76-78].

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 [76-106].

TTS is a very rare adverse event following immunization (AEFI) and the benefits of COVID-19 vaccination clearly outweigh the potential risks [226].

Case definition

The definition of TTS is based on the combined presence of a thrombosis and new onset thrombocytopenia. Three levels of certainty are proposed, based on the anatomical location of the thrombosis, the severity of thrombocytopenia and the outcome of laboratory investigations [226].

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[226].

WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty **(**Table 7). 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 6**:

A. Vaccination against COVID within last 30 days.
B. No alternative explanation for the condition (i.e., no heparin exposure within the previous
C. Combination of thrombosis and thrombocytopenia [226].

Classification	Major criteria	Minor criteria
Thrombosis	**CONFIRMED** diagnosis of thrombosis by imaging study, surgical, or pathology findings consistent with thrombosis / thromboembolism in an **uncommon location**: • Cerebral veins OR • Splanchnic veins OR • Multiple organ	**CONFIRMED** diagnosis of thrombosis by imaging study,surgical, or pathology consistent with thrombosis / thromboembolism in a **common location:** • Pulmonary arteries/veins OR • Limb veins OR • Coronary arteries OR • Cerebral arteries OR • Other arteries/veins OR **SUGGESTIVE** thrombosis by supporting imaging or laboratory findings **suggestive but not definitive** of thrombosis/thromboembolism in any location OR **SUGGESTIVE** thrombosis by specific **clinical syndromes** consistent with thrombosis or thromboembolism event in any location
Thrombocytopenia	Platelet count: < 50 x 10^9 /L AND Confirmatory peripheral smear showing reduced platelets AND No evidence of platelet clumping	Platelet count: > 50 x 10^9/L - <150 x 10^9/L OR >50% decrease from baseline platelet count
Laboratory (other than thrombocytopenia)	Positive anti-platelet factor 4 antibodies (with ELISA) OR platelet functional assay (i.e., serotonin release assay)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)

Table 6: Major and minor criteria for thrombocytopenia, thrombotic events and laboratory examinations [226].

Classification	Level 1 (Confirmed case)		Level 2 (Probable case)		Level 3 (Possible case)
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

Table 7. WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty [226].

Cases with incomplete investigation or the presence of other possible explanations should be classified as possible cases of TTS until better evidence is available [226].

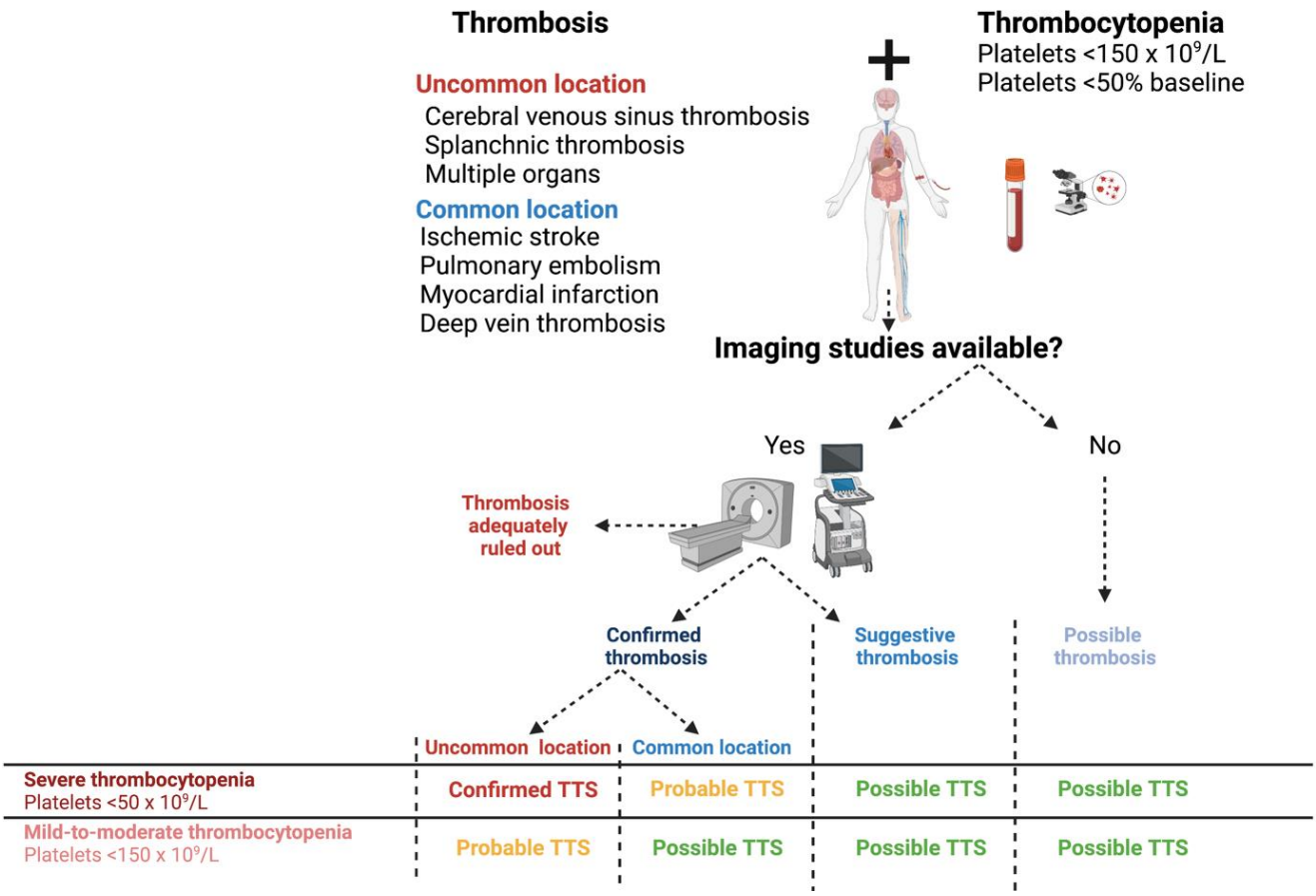


Figure 5: Algorithm for the clinical diagnosis of thrombosis thrombocytopenia syndrome [226].

Incidence

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 [111]. 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 [111].

Thrombotic complications are frequent in patients with active or recent SARS-CoV-2 infection [112]. Thrombocytopenia (<150 000 platelets/µL) 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 analyzed 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) [110].

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 [112]. The presence of an active SARS-CoV-2 infection was ruled out in most TTS cases reported to date [76-105].

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

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 [82].

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 [113].

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 [76, 77].

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 [93]. 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 yeas (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[93].

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-1vaccine have been given. The Ad26.COV2-S vaccine is administered as a single dose. Data about Ad26.COV2-S 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 [114]. No TTS cases have been reported following vaccination with other adenovirus vector-based COVID-19 vaccines or mRNA COVID-19 vaccines. 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 [115].

First author/source	Date of publication	Study period	Country	Vaccine	Dose	Cumulative incidence per 100 000 vaccinees
Schultz	9/4/21	Unknown-20/03/2021	Norway	ChAdOx-1	First	3.8 (95% CI 1.4-9.3)
Spanish Medicines Agency	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	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	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	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	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 8. Cumulative incidence of TTS following vaccination with a non-replicant adenovirus vector-based vaccine [226].

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 [76-105].

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 [124-133]. 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) [226].

Pathophysiology

The etiology of TTS is thought to be immune-mediated. 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 [134].

Since there are several similarities with autoimmune heparin-induced thrombocytopenia (aHIT), it is thought that the pathophysiology of TTS is similar to that of a HIT's. Hence, like for aHIT, TTS may be caused by the binding of PF4 antibodies to an unknown 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 [79–81, 85, 134–139]. 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 [134-144].

There are clinical and laboratory similarities between TTS and a HIT, 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 [76–105].

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 [144–149].

Clinical presentation

The most specific elements of TTS are the **delayed onset** after vaccination and **greater severity**. 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 [76–105].

The median time from vaccination to symptom onset is 8-9 days with a range of 1 to 37 days. As of 27 May 2021, only one of the 21 case series reported cases that occurred within the first 72 hours [93].

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 [93], 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 [76–105].

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 [226].

TTS is associated with a more severe thrombosis profile, with greater extension of thrombi and a higher frequency of concomitant intracranial hemorrhage in the case of CVST. Mortality rates (20-25%) are two-to- three times higher compared with non-vaccine related thrombotic events. 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 [150-157].

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. Vaccine-related CVST presents with an increased rate of intracranial hemorrhage (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) [226].

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 etiology, with the most frequent symptom being abdominal pain [(226).]

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[(226).]

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 [(226).]

Thrombosis location	Symptoms	Signs

Cerebral venous sinus	• New onset/unexplained headache:
	  • 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.
		• 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 ↑ICP:
		  • Bradycardia
		  • Badypnea
		  • Arterial hypertension.

Abdominal veins (portal, superior mesenteric, splenic, hepatic)	• Abdominal pain • Bloating, nausea, vomiting • Diarrhea /increased frequency of bowel movements • Constipation • Fever, anorexia • Back pain • Gastrointestinal bleeding.	• Portal hypertension signs • Abdominal distension/ascites • Hepatomegaly • Jaundice
Deep vein	• Unilateral or bilateral swelling • Painful and tenderness • Limb swelling • Redness, distended veins	• 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	• Dyspnea, with sudden onset, shortness of breath, cough • Chest pain, with pleuritic characteristics • Difficulty to perform any physical exercises • Hemoptysis • Syncope palpitations	• Tachypnea. • Tachycardia • Arterial hypotension

Table 9. Clinical syndromes suggestive of thrombosis or thromboembolism [226].

Laboratory diagnosis

1. **Platelet count**

Complete blood count must be done for all patients. Thrombocytopenia is defined as a platelet count <150 000/µL or a 50% decrease from a recent previous platelet count. In most of the reported cases, the platelet nadir was <50 000 platelets/µL, with a median value around 25 000 platelets/µL [158-163].

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 CBC 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 [76-105].

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 RBCs) was reported in one case of TTS [81].

3. **D-dimer**

A D-dimer value of four times the upper limit of the normal range (i.e., usually >4000 µg/L FEU (fibrinogen equivale is also highly suggestive, and a value of between 2000 and 4000 µg/L FEU may be suggestive [78-81].

4. **Anti-platelet factor 4 antibodies**

The presence of anti-PF4 antibodies, in the absence of heparin therapy, is highly specific for TTS. 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) 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 [79-81].

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 [226].

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[226].

7. **SARS-CoV-2 tests**

SARS-CoV-2 real-time polymerase chain reaction (PCR) test on an 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 [226].

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	Initially increased, then decreased	Normal	Normal	Decreased
D-dimer	Increased (>4 times ULN)	Normal	Normal to increased	Increased
Other			ADAMST13 <10%	

Table 10. Laboratory tests for the differential diagnosis of TTS [226].

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.*

Conditions	Key elements
Autoimmune heparin-induced thrombocytopenia	Heparin use during the past 4-30 days.
Atypical hemolytic 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
Hemophagocytic 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, clopidogrel, trimethoprim-sulfamethoxazole, alendronate, vancomycin, pentostatin, chemotherapy (mitomycin, cyclosporine, tacrolimus, gemcitabine, carmustine, cytarabine, Taxotere), illicit drugs (cocaine, ecstasy)

Table 11. Other conditions that should be included in the differential diagnosis of thrombosis/disseminated thrombosis and thrombocytopenia [226].

Imaging diagnosis

Imaging and clinical workup for thrombosis should be based on the symptoms and location [164-173].

Specific diagnostic methods consistent with confirmed thrombosis/thromboembolism	• Ultrasound - Doppler • CT scan - contrast/angiography • Magnetic resonance venography or arteriography • Echocardiogram • Perfusion V/Q scan • Conventional angiography / digital subtraction angiography
Procedures consistent with the presence of a thrombus	• Surgery • Thrombectomy
Pathologic examination that confirmed the presence of a thrombus	• Biopsy • Autopsy
Specific diagnostic modalities supportive of the presence of thrombosis/thromboembolism	• Chest radiography • Echocardiogram • CT scan without contrast • D-dimer (elevated above upper limit of normal for age)

Table 12. Specific diagnostic methods that provide results that may be consistent or suggestive of thrombosis/thromboembolism [226].

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	• **CT/MR venogram**: Filling defect in sinus (empty delta sign) • **Non- contrast CT**: ○ 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 hea ○ Intracranial hemorrhage with early oedema in parasagittal locations • **Fundoscopy**: papilledema
Splanchnic thrombosis	• CT angiography	• Doppler ultrasound	• **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	• **Doppler ultrasound**: intraluminal echogenic material, absent signal on color 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 maneuver or with calf squeeze.
Pulmonary thrombosis	• CTPA	• Echocardiogram • Chest X ray • ECG • V/Q scan	• **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 angiography		• **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	• **CT:** loss of grey-white matter differentiation, hypoattenuation of deep nuclei, cortical hypodensity, gyral effacement

Table 13: Optimal and alternative investigational tests used in TTS workups and typical diagnostic findings [226].

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

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 hematology, 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. (158, 159, 174–177).

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, diarrhea/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, hemoptysis, 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 (226).

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. Patients must be monitored closely, since new-onset thrombosis might occur, and multiple thromboses have been reported in 20-25% of patients. (226).

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, with at least a CBC, 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. 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. (226).

Treatment 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)* (226).
- **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)* (226).
    - 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)* (226).

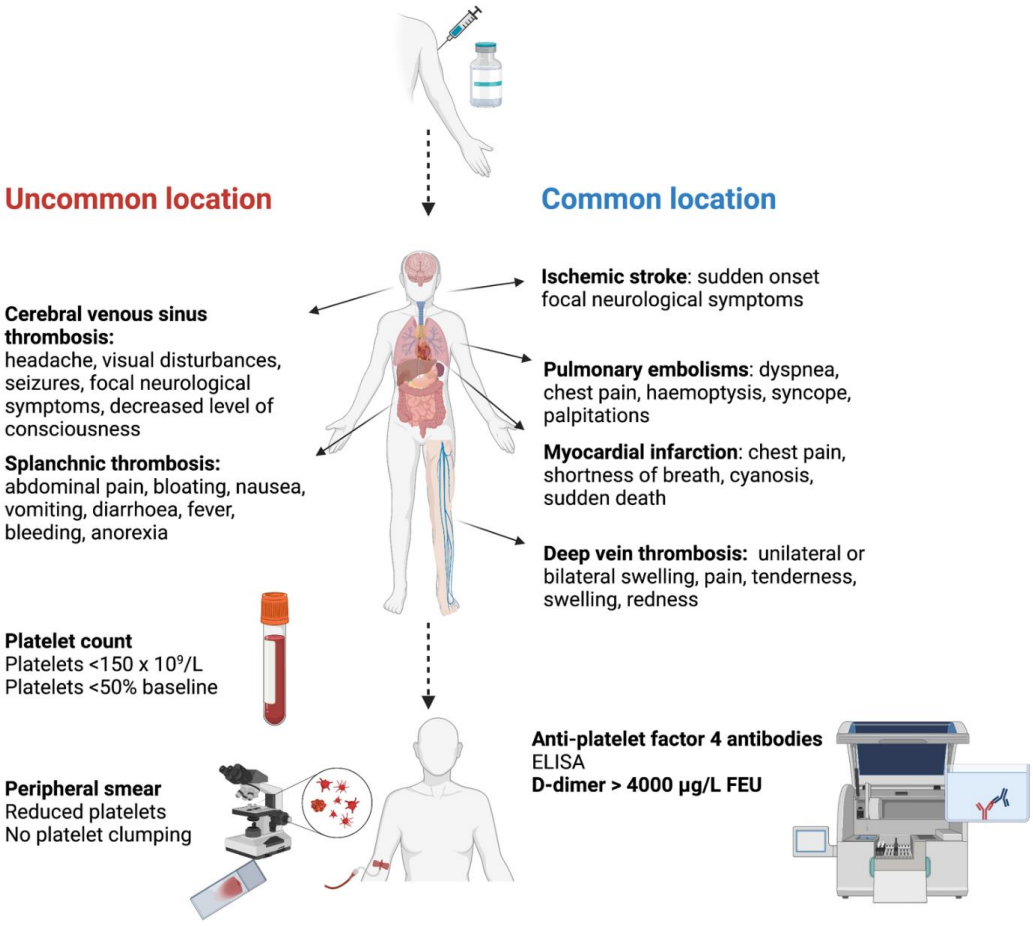


Figure 6: Clinical workup in patients with clinical symptoms and signs suggestive of thrombosis with 30 days of vaccination with a COVID-19 adenovirus vector-based vaccine [226].

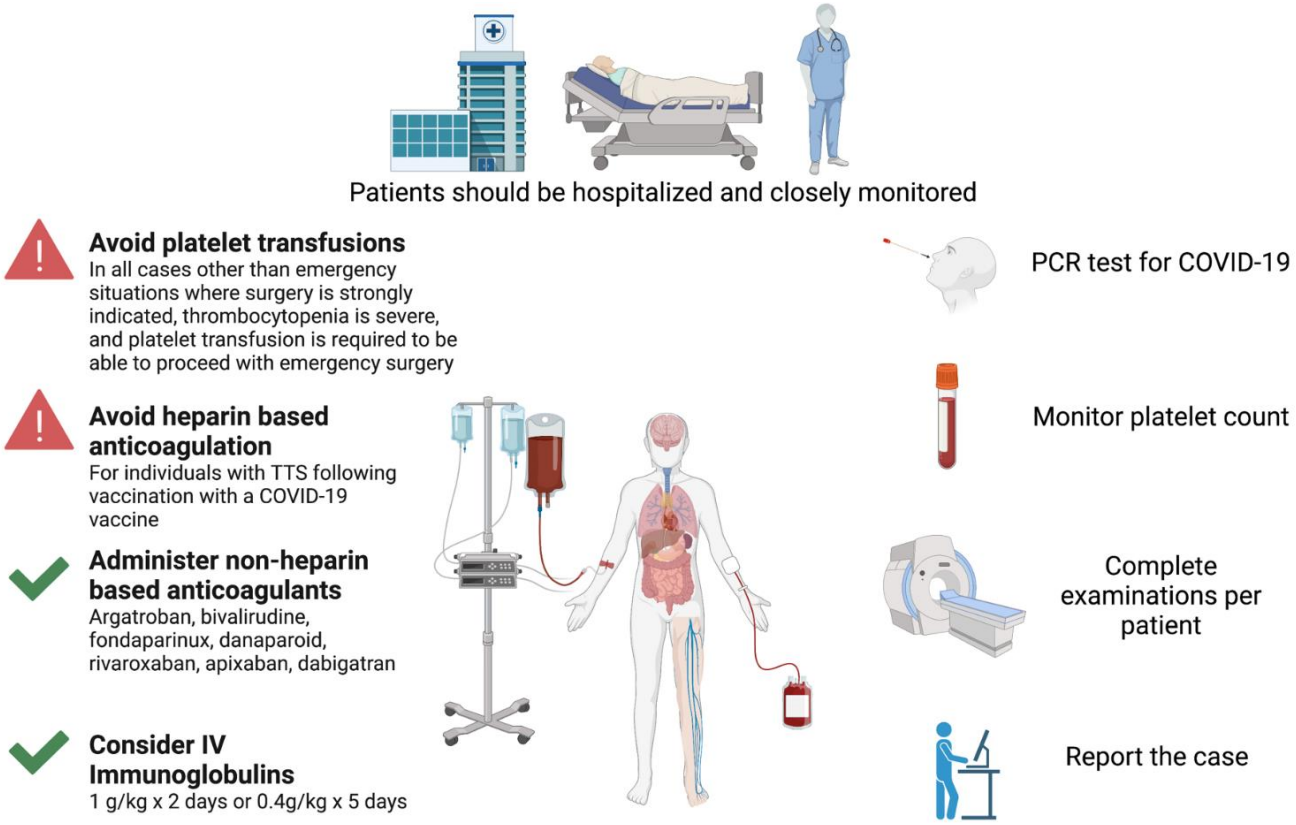


Figure 3: Clinical management of patients with confirmed, probable or possible vaccine related TTS [226].

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 1.75mg/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 1500IU60-75 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	CSVT or DVT or PE	According to GFR and patient's weight

Table 14: Examples of non-heparin anticoagulant treatments for TTS [226].

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

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. [226].

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

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. [226].

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. [226].

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. [226].

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.

Possible research gaps for future prophylactic management: [226].

1. Should hydroxychloroquine be used in patients having TTS?
2. Genetic markers for ‘at risk’ patients.
3. Risk factors for TTS and the role of other thrombotic risk factors.
4. 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.
5. 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.
6. Duration of immunosuppressive treatments.
7. Management of treatment-resistant cases.
8. Possibility of organ donation in TTS-deceased patients.
9. Consider rapid literature search to identify the most common cause of hypercoagulability.
10. Research on increase in hypercoagulopathy in patients with a previous of COVID-19 infection, given any COVID-19 vaccine.
11. 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.
12. 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).

References

1. Su JR, McNeil MM, Welsh KJ, Marquez PL, Ng C, Yan M, Cano MV. Myopericarditis after vaccination, Vaccine Adverse Event Reporting System (VAERS), 1990–2018.**Vaccine**. 2021; 39:839–845. doi: 10.1016/j.vaccine.2020.12.046
2. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hübner N, et al.. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions.**Nat Rev Cardiol**. 2021; 18:169–193. doi: 10.1038/s41569-020-00435-x
3. Fairweather D, Cooper LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy.**Curr Probl Cardiol**. 2013; 38:7–46. doi: 10.1016/j.cpcardiol.2012.07.003
4. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS).**Vaccine**. 2015; 33:4398–4405. doi: 10.1016/j.vaccine.2015.07.035
5. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Coronavirus disease 2019 (COVID-19) vaccines.Accessed July 6, 2021.
6. Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, Duffy J, Harrington T, McNeil MM, Broder K, et al.. U.S. population-based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines.**Vaccine**. 2021; 39:3666–3677. doi: 10.1016/j.vaccine.2021.05.016
7. Marill MC. FDA to add myocarditis warning to mRNA COVID-19 vaccines.**Medscape**. June 23, 2021. Accessed July 6, 2021.
8. Marshall M, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, Shaughnessya R, Carona R, Fuss C, Corbin KJE, et al.. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination.**Pediatrics**. Published online June 4, 2021. doi: 10.1542/peds.2021-052478
9. Rosner CM, Genovese L, Tehrani BN, Atkins M, Bakhshi H, Chaudhri S, Damluji AA, de Lemos JA, Desai SS, Emaminia A, et al.. Myocarditis temporally associated with COVID-19 vaccination.**Circulation**. 2021; 144:503–506. doi: 10.1161/CIRCULATIONAHA.121.055891
10. Abu Mouch S, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, Zoabi M, Aisman M, Goldschmid N, Berar Yanay N. Myocarditis followin COVID-19 mRNA vaccination.**Vaccine**. 2021; 39:3790–3793. doi: 10.1016/j.vaccine.2021.05.087
11. Larson KF, Ammirati E, Adler ED, Cooper LT, Hong KN, Saponara G, Couri D, Cereda A, Procopio A, Cavalotti C, et al.. Myocarditis after BNT162b2 and mRNA-1273 vaccination.**Circulation**. 2021; 144:507–509. doi: 10.1161/CIRCULATIONAHA.121.055913
12. Ammirati E, Cavalotti C, Milazzo A, Pedrotti P, Soriano F, Schroeder JW, Morici N, Giannattasio C, Frigerio M, Metra M, et al.. Temporal relation between second dose BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection.**Int J Cardiol Heart Vasc**. 2021; 34:100774. doi: 10.1016/j.ijcha.2021.100774
13. Bautista GJ, Pena OP, Bonilla Fernandez JA, Cardenes LA, Ramirez BL, Caballero DE. Acute myocarditis after administration of the BNT162b2 vaccine against COVID-19.**Rev Esp Cardiol (Engl Ed)**. Published online April 27, 2021; S1885–5857(21)00133–X. doi: 10.1016/j.rec.2021.04.005
14. Mclean K, Johnson T. Myopericarditis in a previously healthy adolescent male following COVID-19 vaccination: a case report.**Acad Emerg Med**. Published online June 16, 2021. doi: 10.1111/acem.14322
15. D'Angelo T, Cattafi A, Carerj ML, Booz C, Ascenti G, Cicero G, Blandino A, Mazziotti S. Myocarditis after SARS-CoV-2 vaccination: a vaccine-induced reaction?**Can J Cardiol**. Published online June 9, 2021;S0828–282X(21)00286–5. doi: 10.1016/j.cjca.2021.05.010
16. Albert E, Aurigemma G, Saucedo J, Gerson DS. Myocarditis following COVID-19 vaccination.**Radiol Case Rep**. 2021; 16:2142–2145. doi: 10.1016/j.radcr.2021.05.033

17. Muthukumar A, Narasimhan M, Li QZ, Mahimainathan L, Hitto I, Fuda F, Batra K, Jiang X, Zhu C, Schoggins J, et al.. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine.**Circulation**. 2021; 144:487–498. doi: 10.1161/CIRCULATIONAHA.121.056038

18. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, Loran D, Hrncir D, Herring K, Platzer M, et al.. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military.**JAMA Cardiol**. Published online June 29, 2021. doi: 10.1001/jamacardio.2021.2833

19. Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, Parker MA, Kim RJ. Patients with acute myocarditis following mRNA COVID-19 vaccination.**JAMA Cardiol**. Published online June 29, 2021. doi: 10.1001/jamacardio.2021.2828

20. Israel Ministry of Health. Surveillance of myocarditis (inflammation of the heart muscle) cases between December 2020 and May 2021 (including).June 2, 2021. Accessed July 6, 2021.

21. World Health Organization. Severe acute respiratory syndrome (SARS).2021. Accessed July 6, 2021.

22. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, et al.. COVID-19 and cardiovascular disease.**Circulation**. 2020; 141:1648–1655. doi: 10.1161/CIRCULATIONAHA.120.046941

23. Hendren NS, Drazner MH, Bozkurt B, Cooper LT. Description and proposed management of the acute COVID-19 cardiovascular syndrome.**Circulation**. 2020; 141:1903–1914. doi: 10.1161/CIRCULATIONAHA.120.047349

24. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS.**Eur J Clin Invest**. 2009; 39:618–625. doi: 10.1111/j.1365-2362.2009.02153.x

25. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus.**Ann Saudi Med**. 2016; 36:78–80. doi: 10.5144/0256-4947.2016.78

26. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: implications for long-term surveillance and outcomes in survivors.**Heart Rhythm**. 2020; 17:1984–1990. doi: 10.1016/j.hrthm.2020.06.026

27. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, et al.. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19).**JAMA Cardiol**. 2020; 5:1265–1273. doi: 10.1001/jamacardio.2020.3557

28. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, Daniels CJ. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection.**JAMA Cardiol**. 2021; 6:116–118. doi: 10.1001/jamacardio.2020.4916

29. Clark DE, Parikh A, Dendy JM, Diamond AB, George-Durrett K, Fish FA, Slaughter JC, Fitch W, Hughes SG, Soslow JH. COVID-19 myocardial pathology evaluation in athletes with cardiac magnetic resonance (COMPETE CMR).**Circulation**. 2021; 143:609–612. doi: 10.1161/CIRCULATIONAHA.120.052573

30. Martinez MW, Tucker AM, Bloom OJ, Green G, DiFiori JP, Solomon G, Phelan D, Kim JH, Meeuwisse W, Sills AK, et al.. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening.**JAMA Cardiol**. 2021; 6:745–752. doi: 10.1001/jamacardio.2021.0565

31. Starekova J, Bluemke DA, Bradham WS, Eckhardt LL, Grist TM, Kusmirek JE, Purtell CS, Schiebler ML, Reeder SB. Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging.**JAMA Cardiol**. Published online January 14, 2021; e207444. doi: 10.1001/jamacardio.2020.7444

32. Daniels CJ, Rajpal S, Greenshields JT, Rosenthal GL, Chung EH, Terrin M, Jeudy J, Mattson SE, Law IH, Borchers J, et al.. Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: results from the Big Ten COVID-19 Cardiac Registry.**JAMA Cardiol**. Published online May 27, 2021; e212065. doi: 10.1001/jamacardio.2021.2065

33. Most ZM, Hendren N, Drazner MH, Perl TM. Striking similarities of multisystem inflammatory syndrome in children and a myocarditis-like syndrome in adults: overlapping manifestations of COVID-19.**Circulation**. 2021; 143:4–6. doi: 10.1161/CIRCULATIONAHA.120.050166

34. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, Soma VL, Maddux AB, Mourani PM, Bowens C, et al.; Overcoming COVID-19 Investigators. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19.**JAMA**. 2021; 325:1074–1087. doi: 10.1001/jama.2021.2091

35. Fox SE, Falgout L, Vander Heide RS. COVID-19 myocarditis: quantitative analysis of the inflammatory infiltrate and a proposed mechanism.**Cardiovasc Pathol**. Published online June 23, 2021; 107361. doi: 10.1016/j.carpath.2021.107361

36. Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, Ntinopoulou M, Sertaridou E, Tsironidou V, Tsigalou C, et al.. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis.**J Clin Invest**. 2020; 130:6151–6157. doi: 10.1172/JCI141374

37. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, et al.. Multiorgan and renal tropism of SARS-CoV-2.**N Engl J Med**. 2020; 383:590–592. doi: 10.1056/NEJMc2011400

38. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, et al.. Myocardial localization of coronavirus in COVID-19 cardiogenic shock.**Eur J Heart Fail**. 2020; 22:911–915. doi: 10.1002/ejhf.1828

39. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, et al.. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases.**JAMA Cardiol**. 2020; 5:1281–1285. doi: 10.1001/jamacardio.2020.3551

40. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, et al.. Pathological findings of COVID-19 associated with acute respiratory distress syndrome.**Lancet Respir Med**. 2020; 8:420–422. doi: 10.1016/S2213-2600(20)30076-X

41. Kawakami R, Sakamoto A, Kawai K, Gianatti A, Pellegrini D, Nasr A, Kutys B, Guo L, Cornelissen A, Mori M, et al.. Pathological evidence for SARS-CoV-2 as a cause of myocarditis: JACC Review Topic of the Week.**J Am Coll Cardiol**. 2021; 77:314–325. doi: 10.1016/j.jacc.2020.11.031

42. Fox SE, Li G, Akmatbekov A, Harbert JL, Lameira FS, Brown JQ, Vander Heide RS. Unexpected features of cardiac pathology in COVID-19 infection.**Circulation**. 2020; 142:1123–1125. doi: 10.1161/CIRCULATIONAHA.120.049465

43. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations.**Cardiovasc Pathol**. 2021; 50:107300. doi: 10.1016/j.carpath.2020.107300

44. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study.**Eur Heart J**. 2020; 41:3827–3835. doi: 10.1093/eurheartj/ehaa664

45. Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA.**Immunity**. 2005; 23:165–175. doi: 10.1016/j.immuni.2005.06.008

46. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al.; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine.**N Engl J Med**. 2020; 383:2603–2615. doi: 10.1056/NEJMoa2034577

47. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al.; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine.**N Engl J Med**. 2021; 384:403–416. doi: 10.1056/NEJMoa2035389

48. Caso F, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, Scarpa R. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects?**Autoimmun Rev**. 2020; 19:102524. doi: 10.1016/j.autrev.2020.102524

49. Caforio AL, Mahon NJ, Tona F, McKenna WJ. Circulating cardiac autoantibodies in dilated cardiomyopathy and myocarditis: pathogenetic and clinical significance.**Eur J Heart Fail**. 2002; 4:411–417. doi: 10.1016/s1388-9842(02)00010-7

50. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases.**Clin Immunol**. 2020; 217:108480. doi: 10.1016/j.clim.2020.108480

51. Graham BS. Rapid COVID-19 vaccine development.**Science**. 2020; 368:945–946. doi: 10.1126/science.abb8923

52. Jaume M, Yip MS, Cheung CY, Leung HL, Li PH, Kien F, Dutry I, Callendret B, Escriou N, Altmeyer R, et al.. Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent FcγR pathway.**J Virol**. 2011; 85:10582–10597. doi: 10.1128/JVI.00671-11

53. Sedova ES, Scherbinin DN, Lysenko AA, Alekseeva SV, Artemova EA, Shmarov MM. Non-neutralizing antibodies directed at conservative influenza antigens.**Acta Naturae**. 2019; 11:22–32. doi: 10.32607/20758251-2019-11-4-22-32

54. Halstead SB, Katzelnick L. COVID-19 vaccines: should we fear ADE?**J Infect Dis**. 2020; 222:1946–1950. doi: 10.1093/infdis/jiaa518

55. Hotez PJ, Bottazzi ME, Corry DB. The potential role of Th17 immune responses in coronavirus immunopathology and vaccine-induced immune enhancement.**Microbes Infect**. 2020; 22:165–167. doi: 10.1016/j.micinf.2020.04.005

56. Hotez PJ, Corry DB, Bottazzi ME. COVID-19 vaccine design: the Janus face of immune enhancement.**Nat Rev Immunol**. 2020; 20:347–348. doi: 10.1038/s41577-020-0323-4

57. De Swart RL, Kuiken T, Timmerman HH, van Amerongen G, Van Den Hoogen BG, Vos HW, Neijens HJ, Andeweg AC, Osterhaus AD. Immunization of macaques with formalin-inactivated respiratory syncytial virus (RSV) induces interleukin-13-associated hypersensitivity to subsequent RSV infection.**J Virol**. 2002; 76:11561–11569. doi: 10.1128/jvi.76.22.11561-11569.2002

58. Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, Santos MR, Schuitemaker H, Watson M, Arvin A. Prospects for a safe COVID-19 vaccine.**Sci Transl Med**. 2020; 12:eabe0948. doi: 10.1126/scitranslmed.abe0948

59. Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series.**JAMA Dermatol**. 2021; 157:716–720. doi: 10.1001/jamadermatol.2021.1214

60. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination.**N Engl J Med**. 2021; 384:2092–2101. doi: 10.1056/NEJMoa2104840

61. Dias L, Soares-Dos-Reis R, Meira J, Ferrão D, Soares PR, Pastor A, Gama G, Fonseca L, Fagundes V, Carvalho M. Cerebral venous thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine.**J Stroke Cerebrovasc Dis**. 2021; 30:105906. doi: 10.1016/j.jstrokecerebrovasdis.2021.105906

62. Carli G, Nichele I, Ruggeri M, Barra S, Tosetto A. Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine.**Intern Emerg Med**. 2021; 16:803–804. doi: 10.1007/s11739-021-02685-0

63. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies.**Annu Rev Med**. 2015; 66:145–159. doi: 10.1146/annurev-med-061813-012806

64. Tang LV, Hu Y. Hemophagocytic lymphohistiocytosis after COVID-19 vaccination.**J Hematol Oncol**. 2021; 14:87. doi: 10.1186/s13045-021-01100-7

65. Lyden DC, Olszewski J, Feran M, Job LP, Huber SA. Coxsackievirus B-3-induced myocarditis. Effect of sex steroids on viremia and infectivity of cardiocytes.**Am J Pathol**. 1987; 126:432–438.

66. Girón-González JA, Moral FJ, Elvira J, García-Gil D, Guerrero F, Gavilán I, Escobar L. Consistent production of a higher TH1:TH2 cytokine ratio by stimulated T cells in men compared with women.**Eur J Endocrinol**. 2000; 143:31–36. doi: 10.1530/eje.0.1430031

67. Frisancho-Kiss S, Coronado MJ, Frisancho JA, Lau VM, Rose NR, Klein SL, Fairweather D. Gonadectomy of male BALB/c mice increases Tim-3(+) alternatively activated M2 macrophages, Tim-3(+) T cells, Th2 cells and Treg in the heart during acute coxsackievirus-induced myocarditis.**Brain Behav Immun**. 2009; 23:649–657. doi: 10.1016/j.bbi.2008.12.002

68. Huber SA, Pfaeffle B. Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3.**J Virol**. 1994; 68:5126–5132. doi: 10.1128/JVI.68.8.5126-5132.1994

69. Kytö V, Sipilä J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis.**Circulation**. 2014; 130:1601–1606. doi: 10.1161/CIRCULATIONAHA.114.010376

70. Centers for Disease Control and Prevention. The Vaccine Adverse Event Reporting System (VAERS) results.June 6, 2021. Accessed July 6, 2021.

71. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET).2021. Accessed July 6, 2021.

72. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, et al.. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations.**J Am Coll Cardiol**. 2018; 72:3158–3176. doi: 10.1016/j.jacc.2018.09.072

73. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ, Olsen EG, Schoen FJ. Myocarditis. A histopathologic definition and classification.**Am J Cardiovasc Pathol**. 1987; 1:3–14.

74. Hageman JR. Long COVID-19 or post-acute sequelae of SARS-CoV-2 infection in children, adolescents, and young adults.**Pediatr Ann**. 2021; 50:e232–e233. doi: 10.3928/19382359-20210519-02

75. Centers for Disease Control and Prevention. Clinical considerations; myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults.May 28, 2021. Accessed July 6, 2021.

76. European Medicines Agency. 29 March 2021 update. COVID-19 vaccine safety update VAXZEVRIA AstraZeneca AB.

77. European Medicines Agency. COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 20 April 2021.

78. European Medicines Agency.14 April 2021 update. COVID-19 vaccine safety update VAXZEVRIA AstraZeneca AB.

79. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021;384(23):2202-2211.

80. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021;384(22):2092-2101.

81. Tiede A, Sachs UJ, Czwalinna 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.

82. European Medicines Agency. Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – Vaxzevria (previously COVID-19 Vaccine AstraZeneca) (Other viral vaccines).

83. 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.

84. D'Agostino V, Caranci F, Negro A, Piscitelli V, Tuccillo B, Fasano F, et al. A rare case of cerebral venous thrombosis and disseminated intravascular coagulation temporally associated to the COVID-19 vaccine administration. J Pers Med. 2021;11(4):285

85. 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.

86. Wolf ME, Luz B, Niehaus L, Bhogal P, Bäzner H, Henkes H. Thrombocytopenia and intracranial venous sinus thrombosis after "COVID-19 Vaccine AstraZeneca" exposure. J Clin Med. 2021;10(8):1599.

87. Castelli GP, Pognani C, Sozzi C, Franchini M, Vivona L. Cerebral venous sinus thrombosis associated with thrombocytopenia post-vaccination for COVID-19. Crit Care. 2021;25(1):137.

88. Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med. 2021;384(20):1964-1965.

89. 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.

90. 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.

91. Yocum A, Simon EL. Thrombotic thrombocytopenic purpura after Ad26.COV2-S vaccination. Am J Emerg Med. 2021:S0735-6757(21)00376-4. doi: 10.1016/j.ajem.2021.05.001.

92. Jamme M, Mosnino E, Hayon J, Franchineau G. Fatal cerebral venous sinus thrombosis after COVID-19 vaccination. Intensive Care Med. 2021:1–2. doi: 10.1007/s00134-021-06425-y.

93. Schultz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany.

94. Bjørnstad-Tuveng TH, Rudjord A, Anker P. Fatal cerebral haemorrhage after COVID-19 vaccine. Tidsskr Nor Laegeforen. 2021;141. 10.4045/tidsskr.21.0312.

95. Blauenfeldt RA, Kristensen SR, Ernstsen SL, Kristensen CCH, Simonsen CZ, Hvas AM. Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine. J Thromb Haemost. 2021;19(7):1771-1775.

96. Porres-Aguilar M, Lazo-Langner A, Panduro A, Uribe M. COVID-19 vaccine-induced immune thrombotic thrombocytopenia: An emerging cause of splanchnic vein thrombosis. Ann Hepatol. 2021;23:100356. doi: 10.1016/j.aohep.2021.100356.

97. Hocking J, Chunilal SD, Chen V, Brighton T, Nguyen J, Tan J, et al. The first known ChAdOx1 nCoV-19 vaccine-induced thrombotic thrombocytopenia in Australia. Preprint. Med J Austral.

98. Chatterjee S, Ojha UK, Vardhan B, Tiwari A. Myocardial infarction after COVID-19 vaccination-casual or causal? Diabetes Metab Syndr. 2021;15(3):1055–1056.

99. McCrae KR. Thrombotic thrombocytopenia due to SARS-CoV-2 vaccination. Cleve Clin J Med. 2021. doi: 10.3949/ccjm.88a.ccc078.

100. Colarossi G, Schnöring H, Trivellas A, Betsch M, Hatam N, Eschweiler J, et al. Prognostic factors for patients with heparin-induced thrombocytopenia: a systematic review. Int J Clin Pharm. 2020;43(3):449-460.

101. Borhani Haghighi A, Edgell RC, Cruz-Flores S, Feen E, Piriyawat P, Vora N, et al. Mortality of cerebral venous-sinus thrombosis in a large national sample. Stroke. 2012 Jan;43(1):262-264.

102. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004 Mar;35(3):664-670.

103. Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet. 2020;395(10240):1845-1854.

104. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al.; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-478.

105. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020;396(10249):479-488.

106. GRADE Handbook.

107. Brighton Collaboration. Interim case definition of thrombosis with thrombocytopenia syndrome.

108. Burn E, Li X, Kotska K, Stewart HM, Reich C, Seager S, et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: incidence between 2017 and 2019 and patient profiles from 20.6 million people in six European countries.

109. Li X, Ostropolets A, Makadia R, Shaoibi A, Rao G, Sena AG, et al. Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study.

110. Smadja DM, Yue QY, Chocron R, Sanchez O, Lillo-Le Louet A. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. Eur Respir J. 2021:2100956. doi: 10.1183/13993003.00956-2021.

111. Otite FO, Patel S, Sharma R, Khandwala P, Desai D, Latorre JG, et al. Trends in incidence and epidemiologic characteristics of cerebral venous thrombosis in the United States. Neurology. 2020 Oct 20;95(16):e2200-e2213.

112. Thakur KT, Tamborska A, Wood GK, McNeill E, Roh D, Akpan IJ, et al. Clinical review of cerebral venous thrombosis in the context of COVID-19 vaccinations: Evaluation, management, and scientific questions. J Neurol Sci. 2021;427:117532.

113. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021;373:n1114.

114. 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.

115. Pawlowski C, Rincon-Hekking J, Awasthi S, Pandey V, Lenehan P, Venkatakrishnan AJ, et al. Cerebral venous sinus thrombosis (CVST) is not significantly linked to COVID-19 vaccines or non-COVID vaccines in a large multi-state US health system.

116. Spanish Agency of Medicine and Healthcare products. Pharmacovigilance report, published on 9 April 2021.

117. Medicines & Healthcare products Regulatory Agency. Coronavirus vaccine - weekly summary of Yellow Card reporting. Updated 27 May 2021.

118. Chan BTB, Bobos P, Odutayo A, Pai M. Meta-analysis of risk of vaccine-induced immune thrombotic thrombocytopenia following ChAdOx1-S recombinant vaccine.

119. Shay DK, Gee J, Su JR, Myers TR, Marquez P, Liu R, et al. Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine - United States, March-April 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):680-684.

120. MacNeil JR, Su JR, Broder KR, Guh AY, Gargano JW, Wallace M, et al. Updated recommendations from the Advisory Committee on Immunization Practices for use of the Janssen (Johnson & Johnson) COVID-19

vaccine after reports of thrombosis with thrombocytopenia syndrome among vaccine recipients - United States, April 2021. MMWR Morb Mortal Wkly Rep. 2021;70(17):651-656.

121. Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers) emergency use authorization (EUA) of the JANSSEN COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19).

122. Australian Government, Department of Health. ATAGI update following weekly COVID-19 meeting – 23 June 2021.

123. Medicines & Healthcare products Regulatory Agency. Coronavirus vaccine – summary of yellow card reporting. First published on 5 February 2021, Updated on 10 June 2021.

124. Valeriani E, Riva N, Di Nisio M, Ageno W. Splanchnic vein thrombosis: current perspectives. Vasc Health Risk Manag. 2019;15:449-461.

125. Qi X, De Stefano V, Senzolo M, Xu H, Mancuso A. Splanchnic vein thrombosis: etiology, diagnosis, and treatment. Gastroenterol Res Pract. 2015;2015:506136.

126. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med. 2001;344(17):1286-1292.

127. De Stefano V, Qi X, Betti S, Rossi E. Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment. Thromb Haemost. 2016;115(2):240-249.

128. Ramrakhiani N, Sharma DK, Dubey R, Gupta P, Sharma A, Sharma KK. Clinical profile, risk factors and outcomes in patients with cerebral venous sinus thrombosis: a study from Western India. J Assoc Physicians India. 2019;67(9):49-53.

129. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664-670.

130. Kalita J, Misra UK, Singh RK. Do the risk factors determine the severity and outcome of cerebral venous sinus thrombosis? Transl Stroke Res. 2018;9(6):575-581.

131. Pan L, Ding J, Ya J, Zhou D, Hu Y, Fan C, et al. Risk factors and predictors of outcomes in 243 Chinese patients with cerebral venous sinus thrombosis: A retrospective analysis. Clin Neurol Neurosurg. 2019;183:105384.

132. McBane RD 2nd, Tafur A, Wysokinski WE. Acquired and congenital risk factors associated with cerebral venous sinus thrombosis. Thromb Res. 2010;126(2):81-87.

133. Saadatnia M, Fatehi F, Basiri K, Mousavi SA, Mehr GK. Cerebral venous sinus thrombosis risk factors. Int J Stroke. 2009;4(2):111-123.

134. Greinacher A, Selleng K, Wesche J, Handtke S, Palankar R, Aurich K, et al. Towards understanding ChAdOx1 nCov-19 vaccine immune thrombotic thrombocytopenia (VITT). Preprint. Research Square. 10.21203/rs.3.rs-440461/v1. Posted 20 April 2021.

135. Greinacher A. Heparin-Induced Thrombocytopenia. N Engl J Med. 2015;373(19):1883-1884.

136. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost. 2017;15(11):2099-2114.

137. Hofherr SE, Mok H, Gushiken FC, Lopez JA, Barry MA. Polyethylene glycol modification of adenovirus reduces platelet activation, endothelial cell activation, and thrombocytopenia. Hum Gene Ther. 2007;18(9):837-838.

138. Cichon G, Schmidt HH, Benhidjeb T, Löser P, Ziemer S, Haas R, et al. Intravenous administration of recombinant adenoviruses causes thrombocytopenia, anemia and erythroblastosis in rabbits. J Gene Med. 1999;1(5):360-371.

139. Schnell MA, Zhang Y, Tazelaar J, Gao GP, Yu QC, Qian R, et al. Activation of innate immunity in nonhuman primates following intraportal administration of adenoviral vectors. Mol Ther. 2001;3(5 Pt 1):708-722.

140. Wolins N, Lozier J, Eggerman TL, Jones E, Aguilar-Córdova E, Vostal JG. Intravenous administration of replication-incompetent adenovirus to rhesus monkeys induces thrombocytopenia by increasing in vivo platelet clearance. Br J Haematol. 2003;123(5):903-905.

141. Varnavski AN, Calcedo R, Bove M, Gao G, Wilson JM. Evaluation of toxicity from high-dose systemic administration of recombinant adenovirus vector in vector-naive and pre-immunized mice. Gene Ther. 2005;12(5):427-436.

142. AbdelMassih A, Hozaien R, El Shershaby M, Kamel A, Ismail HA, Fouda R. Is the heparin-induced thrombocytopenia-like syndrome associated with ChAdOx vaccine related to the vaccine itself or to an autoimmune reaction to severe acute respiratory syndrome 2 coronavirus: insights and implications from previous reports in infected cases? New Microbes New Infect. 2021;41:100884.

143. Smith CW, Kardeby C, Di Y, Lowe GC, Lester WA, Watson SP. Platelet activation by vaccine-induced immune thrombotic thrombocytopenia (VITT) patient serum is blocked by COX, P2Y12 and kinase inhibitors. medRxiv. Doi: https://doi.org/10.1101/2021.04.24.21255655. Version posted April 27, 2021.

144. Kadkhoda K. Post-adenoviral-based COVID-19 vaccines thrombosis: A proposed mechanism. J Thromb Haemost. 2021;19(7):1831-1832.

145. Parums DV. Editorial: SARS-CoV-2 mRNA Vaccines and the possible mechanism of vaccine-induced immune thrombotic thrombocytopenia (VITT). Med Sci Monit. 2021;27:e932899.

146. von Hundelshausen P, Lorenz R, Siess W, Weber C. Vaccine-induced immune thrombotic thrombocytopenia (VITT): targeting pathomechanisms with bruton tyrosine kinase inhibitors. Thromb Haemost. 2021. doi: 10.1055/a-1481-3039.

147. Xie C, Vincent L, Chadwick A, Peschl H. COVID-19 vaccine induced prothrombotic immune thrombocytopenia. Eur Heart J. 2021:ehab237. doi: 10.1093/eurheartj/ehab237.

148. Elalamy I, Gerotziafas G, Alamowitch S, Laroche JP, van Dreden P, Ageno W, et al. SARS-CoV-2 vaccine and thrombosis: an expert consensus on vaccine-induced immune thrombotic thrombocytopenia. Thromb Haemost. 2021. doi: 10.1055/a-1499-0119.

149. Mattioli AV, Bonetti L, Zennaro M, Ambrosio G, Mattioli G. Heparin/PF4 antibodies formation after heparin treatment: temporal aspects and long-term follow-up. Am Heart J. 2009;157(3):589-595.

150. Kiliç T, Akakin A. Anatomy of cerebral veins and sinuses. Front Neurol Neurosci. 2008;23:4-15.

151. Singh RJ, Saini J, Varadharajan S, Kulkarni GB, Veerendrakumar M. Headache in cerebral venous sinus thrombosis revisited: Exploring the role of vascular congestion and cortical vein thrombosis. Cephalalgia. 2018;38(3):503-510.

152. Wasay M, Kojan S, Dai AI, Bobustuc G, Sheikh Z. Headache in cerebral venous thrombosis: incidence, pattern and location in 200 consecutive patients. J Headache Pain 2010;11(2):137-139.

153. García-Azorín D, Monje MHG, González-García N, Guerrero ÁL, Porta-Etessam J. Presence of red flags in patients with cerebral venous sinus thrombosis admitted to the emergency department because of headache: A STROBE compliant cohort-study. Medicine (Baltimore). 2020;99(29):e20900.

154. Mehta A, Danesh J, Kuruvilla D. Cerebral venous thrombosis headache. Curr Pain Headache Rep. 2019;23(7):47.

155. Silvis SM, de Sousa DA, Ferro JM, Coutinho JM. Cerebral venous thrombosis. Nat Rev Neurol. 2017;13(9):555-565.

156. Bayas A, Menacher M, Christ M, Behrens L, Rank A, Naumann M. Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination. Lancet. 2021;397(10285):e11. doi: 10.1016/S0140-6736(21)00872-2.

157. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost. 2005;94(1):132-5.

158. Avendaño-Solá C, Cámara R, Castellanos M, Ezpeleta D, García-Azorín D, Martínez CI, et al. Diagnostic and treatment recommendations from the FACME ad-hoc expert working group on the management of cerebral venous sinus thrombosis associated with COVID-19 vaccination. Neurologia. 2021 doi: 10.1016/j.nrl.2021.05.001.

159. Thakur KT, Tamborska A, Wood GK, McNeill E, Roh D, Akpan IJ. Clinical review of cerebral venous thrombosis in the context of COVID-19 vaccinations: Evaluation, management, and scientific questions. J Neurol Sci. 2021;427:117532. doi: 10.1016/j.jns.2021.117532.

160. Sørvoll IH, Horvei KD, Ernstsen SL, Laegreid IJ, Lund S, Grønli RH, et al. An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination. J Thromb Haemost. 2021;19(7):1813-1818.

161. Nazy I, Sachs UJ, Arnold DM, McKenzie SE, Choi P, Althaus K, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: Communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost. 2021;19(6):1585-1588.

162. Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, et al. Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH. Hamostaseologie. 2021;41(3):184-189.

163. Platton S, Bartlett A, MacCallum P, Makris M, McDonald V, Singh D, et al. Evaluation of laboratory assays for anti-Platelet Factor 4 antibodies after ChAdOx1 nCOV-19 vaccination. J Thromb Haemost. 2021. doi: 10.1111/jth.15362.

164. Linn J, Pfefferkorn T, Ivanicova K, Müller-Schunk S, Hartz S, Wiesmann M, et al. Noncontrast CT in deep cerebral venous thrombosis and sinus thrombosis: comparison of its diagnostic value for both entities. AJNR Am J Neuroradiol. 2009;30(4):728-735.

165. Buyck PJ, Zuurbier SM, Garcia-Esperon C, Barboza MA, Costa P, Escudero I, et al. Diagnostic accuracy of noncontrast CT imaging markers in cerebral venous thrombosis. Neurology. 2019;92(8):e841-e851.

166. Bonatti M, Valletta R, Lombardo F, Zamboni GA, Turri E, Avesani G, et al. Accuracy of unenhanced CT in the diagnosis of cerebral venous sinus thrombosis. Radiol Med. 2021;126(3):399-404.

167. Tayyebi S, Akhavan R, Shams M, Salehi M, Farrokh D, Yousefi F, et al. Diagnostic value of non-contrast brain computed tomography in the evaluation of acute cerebral venous thrombosis. Sci Rep. 2020;10(1):883.

168. Xu W, Gao L, Li T, Ramdoyal ND, Zhang J, Shao A. The performance of CT versus MRI in the differential diagnosis of cerebral venous thrombosis. Thromb Haemost. 2018;118(6):1067-1077.

169. Gao L, Xu W, Li T, Yu X, Cao S, Xu H, et al. Accuracy of magnetic resonance venography in diagnosing cerebral venous sinus thrombosis. Thromb Res. 2018;167:64-73.

170. Sato T, Terasawa Y, Mitsumura H, Komatsu T, Sakuta K, Sakai K, et al. Venous stasis and cerebrovascular complications in cerebral venous sinus thrombosis. Eur Neurol. 2017;78(3-4):154-160.

171. Weimar C. Diagnosis and treatment of cerebral venous and sinus thrombosis. Curr Neurol Neurosci Rep. 2014;14(1):417.

172. Ferro JM, Aguiar de Sousa D. Cerebral venous thrombosis: an update. Curr Neurol Neurosci Rep. 2019;19(10):74.

173. Ciccone A, Zanotti B; working group on cerebral venous thrombosis after COVID-19 vaccination. The importance of recognizing cerebral venous thrombosis following anti-COVID-19 vaccination. Eur J Intern Med. 2021:89:115-117.

174. British Society of Haemotology. Guidance produced from the Expert Haematology Panel (EHP) focused on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus vaccination. Updated guidance on management. Version 1.7.

175. Brasil. Ministério da Saúde. Coordenação Geral do Programa Nacional de I. Orientações para identificação investigação e manejo da síndrome de trombose e trombocitopenia (TTS) no contexto da vacinação contra o COVID-19 no Brasil. 2021.

176. Franchini M, Liumbruno GM, Pezzo M. COVID-19 vaccine-associated immune thrombosis and thrombocytopenia (VITT): Diagnostic and therapeutic recommendations for a new syndrome. Eur J Haematol. 2021. doi: 10.1111/ejh.13665.

177. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2(22):3360-3392.

178. 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.

179. Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost 2021. doi: 10.1111/jth.15346.

180. Einhäupl K, Stam J, Bousser MG, De Bruijn SF, Ferro JM, Martinelli I, et al. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol. 2010;17(10):1229-1235.

181. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-1192.

182. Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - Endorsed by the European Academy of Neurology. Eur Stroke J. 2017;2(3):195-221.

183. Einhäupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, et al. Heparin treatment in sinus venous thrombosis. Lancet. 1991;338(8767):597-600.

184. Mehraein S, Schmidtke K, Villringer A, Valdueza JM, Masuhr F. Heparin treatment in cerebral sinus and venous thrombosis: patients at risk of fatal outcome. Cerebrovasc Dis. 2003;15(1-2):17-21.

185. Busch MA, Hoffmann O, Einhäupl KM, Masuhr F. Outcome of heparin-treated patients with acute cerebral venous sinus thrombosis: influence of the temporal pattern of intracerebral haemorrhage. Eur J Neurol. 2016;23(9):1387-1392.

186. Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Bousser MG, Stam J, et al. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. Stroke. 2010;41(11):2575-2580.

187. Misra UK, Kalita J, Chandra S, Kumar B, Bansal V. Low molecular weight heparin versus unfractionated heparin in cerebral venous sinus thrombosis: a randomized controlled trial. Eur J Neurol. 2012;19(7):1030-1036.

188. Afshari D, Moradian N, Nasiri F, Razazian N, Bostani A, Sariaslani P. The efficacy and safety of low-molecular-weight heparin and unfractionated heparin in the treatment of cerebral venous sinus thrombosis. Neurosciences (Riyadh). 2015;20(4):357-361.

189. Qureshi A, Perera A. Low molecular weight heparin versus unfractionated heparin in the management of cerebral venous thrombosis: A systematic review and meta-analysis. Ann Med Surg (Lond). 2017;17:22-26.

190. Furie KL, Cushman M, Elkind MSV, Lyden PD, Saposnik G; American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced immune thrombotic thrombocytopenia. Stroke. 2021;52(7):2478-2482.

191. Matthai WH Jr, Hursting MJ, Lewis BE, Kelton JG. Argatroban anticoagulation in patients with a history of heparin-induced thrombocytopenia. Thromb Res. 2005;116(2):121-126.

192. Colarossi G, Maffulli N, Trivellas A, Schnöring H, Hatam N, Tingart M, et al. Superior outcomes with Argatroban for heparin-induced thrombocytopenia: a Bayesian network meta-analysis. Int J Clin Pharm. 2021 doi: 10.1007/s11096-021-01260-z.

193. Gleichgerrcht E, Lim MY, Turan TN. Cerebral venous sinus thrombosis due to low-molecular-weight heparin-induced thrombocytopenia. Neurologist. 2017;22(6):241-244.

194. Barreto AD, Alexandrov AV, Lyden P, Lee J, Martin-Schild S, Shen L, et al. The argatroban and tissue-type plasminogen activator stroke study: final results of a pilot safety study. Stroke. 2012;43(3):770-775.

195. Barreto AD, Ford GA, Shen L, Pedroza C, Tyson J, Cai C, et al.; ARTSS-2 Investigators. Randomized, multicenter Trial of ARTSS-2 (Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke). Stroke. 2017;48(6):1608-1616.

196. Berekashvili K, Soomro J, Shen L, Misra V, Chen PR, Blackburn S, et al. Safety and feasibility of argatroban, recombinant tissue plasminogen activator, and intra-arterial therapy in stroke (ARTSS-IA Study). J Stroke Cerebrovasc Dis. 2018;27(12):3647-3651.

197. Hwang SR, Wang Y, Weil EL, Padmanabhan A, Warkentin TE, Pruthi RK. Cerebral venous sinus thrombosis associated with spontaneous heparin-induced thrombocytopenia syndrome after total knee arthroplasty. Platelets. 2020:1-5. doi: 10.1080/09537104.2020.1828574.

198. Sun Z, Lan X, Li S, Zhao H, Tang Z, Xi Y. Comparisons of argatroban to lepirudin and bivalirudin in the treatment of heparin-induced thrombocytopenia: a systematic review and meta-analysis. Int J Hematol. 2017;106(4):476-483.

199. Thorsteinsson GS, Magnussson M, Hallberg LM, Wahlgren NG, Lindgren F, Malmborg P, et al. Cerebral venous thrombosis and heparin-induced thrombocytopenia in an 18-year old male with severe ulcerative colitis. World J Gastroenterol. 2008;14(28):4576-4579.

200. Kuo KH, Kovacs MJ. Fondaparinux: a potential new therapy for HIT. Hematology. 2005;10(4):271-275.

201. Shankar Iyer R, Tcr R, Akhtar S, Muthukalathi K, Kumar P, Muthukumar K. Is it safe to treat cerebral venous thrombosis with oral rivaroxaban without heparin? A preliminary study from 20 patients. Clin Neurol Neurosurg. 2018;175:108-111.

202. Fayyaz M, Abbas F, Kashif T. The role of warfarin and rivaroxaban in the treatment of cerebral venous thrombosis. Cureus. 2019;11(5):e4589.

203. Maqsood M, Imran Hasan Khan M, Yameen M, Aziz Ahmed K, Hussain N, Hussain S. Use of oral rivaroxaban in cerebral venous thrombosis. J Drug Assess. 2020;10(1):1-6.

204. Connor P, Sánchez van Kammen M, Lensing AWA, Chalmers E, Kállay K, Hege K, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). Blood Adv. 2020;4(24):6250-6258.

205. Fatima M, Asghar MS, Abbas S, Iltaf S, Ali A. An observational study to evaluate the effectiveness of rivaroxaban in the management of cerebral venous sinus thrombosis. Cureus 2021;13(3):e13663.

206. Esmaeili S, Abolmaali M, Aarabi S, Motamed MR, Chaibakhsh S, Joghataei MT, et al. Rivaroxaban for the treatment of cerebral venous thrombosis. BMC Neurol. 2021;21(1):73.

207. Covut F, Kewan T, Perez O, Flores M, Haddad A, Daw H. Apixaban and rivaroxaban in patients with cerebral venous thrombosis. Thromb Res. 2019;173:77-78.

208. Rao SK, Ibrahim M, Hanni CM, Suchdev K, Parker D, Rajamani K, et al. Apixaban for the treatment of cerebral venous thrombosis: A case series. J Neurol Sci. 2017;381:318-320.

209. Li H, Yao M, Liao S, Chen J, Yu J. Comparison of novel oral anticoagulants and vitamin K antagonists in patients with cerebral venous sinus thrombosis on efficacy and safety: A systematic review. Front Neurol. 2020;11:597623.

210. Bose G, Graveline J, Yogendrakumar V, Shorr R, Fergusson DA, Le Gal G, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review. BMJ Open. 2021;11(2):e040212.

211. Riva N, Ageno W. Direct oral anticoagulants for unusual-site venous thromboembolism. Res Pract Thromb Haemost. 2021;5(2):265-277.

212. Riva N, Carrier M, Gatt A, Ageno W. Anticoagulation in splanchnic and cerebral vein thrombosis: An international vignette-based survey. Res Pract Thromb Haemost. 2020;4(7):1192-1202.

213. Stam J, Majoie CB, van Delden OM, van Lienden KP, Reekers JA. Endovascular thrombectomy and thrombolysis for severe cerebral sinus thrombosis: a prospective study. Stroke. 2008;39(5):1487-1490.

214. Salottolo K, Wagner J, Frei DF, Loy D, Bellon RJ, McCarthy K, et al. Epidemiology, endovascular treatment, and prognosis of cerebral venous thrombosis: US center study of 152 patients. J Am Heart Assoc. 2017;6(6):e005480.

215. Liao CH, Liao NC, Chen WH, Chen HC, Shen CC, Yang SF, et al. Endovascular mechanical thrombectomy and on-site chemical thrombolysis for severe cerebral venous sinus thrombosis. Sci Rep. 2020;10(1):4937.

216. Keller E, Pangalu A, Fandino J, Könü D, Yonekawa Y. Decompressive craniectomy in severe cerebral venous and dural sinus thrombosis. Acta Neurochir Suppl. 2005;94:177-183.

217. Riva N, Ageno W. Cerebral and splanchnic vein thrombosis: advances, challenges, and unanswered questions. J Clin Med. 2020;9(3):743.

218. Karnam A, Lacroix-Desmazes S, Kaveri SV, Bayry J. Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT): Consider IVIG batch in the treatment. J Thromb Haemost. 2021;19(7):1838-1839.

219. Aryal MR, Gosain R, Donato A, Katel A, Chakradhar R, Dhital R, et al. Effectiveness of intravenous immunoglobulin use in heparin-induced thrombocytopenia. Blood Coagul Fibrinolysis. 2020;31(5):287-292.

220. Dougherty JA, Yarsley RL. Intravenous immune globulin (IVIG) for treatment of autoimmune heparin-induced thrombocytopenia: a systematic review. Ann Pharmacother. 2021;55(2):198-215.

221. Onuoha C, Barton KD, Wong ECC, Raval JS, Rollins-Raval MA, Ipe TS, et al. Therapeutic plasma exchange and intravenous immune globulin in the treatment of heparin-induced thrombocytopenia: A systematic review. Transfusion. 2020;60(11):2714-2736.

222. Guetl K, Gary T, Raggam RB, Schmid J, Wölfler A, Brodmann M. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia treated with immunoglobulin and argatroban. Lancet. 2021;397(10293):e19.

223. Greinacher A, Eichler P, Lubenow N, Kwasny H, Luz M. Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. Blood. 2000;96(3):846-851.

224. Treschan TA, Schaefer MS, Geib J, Bahlmann A, Brezina T, Werner P, et al. Argatroban versus Lepirudin in critically ill patients (ALicia): a randomized controlled trial. Crit Care. 2014;18(5):588.

225. Bourguignon A, Arnold DM, Warkentin TE, Smith JW, Pannu T, Shrum JM, et al. Adjunct immune globulin for vaccine-induced thrombotic thrombocytopenia. N Engl J Med. 2021. doi: 10.1056/NEJMoa2107051.

226. World Health Organization. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19): interim guidance. July 19, 2021.

227. WebMD Medical Reference, Brunilda Nazario, MD on August 27, 2021

228. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA Vaccines. Circulation. 2021.