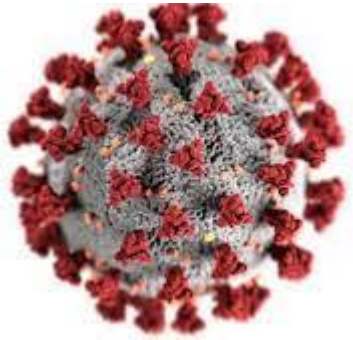
FORTE-U

Forum pour la Recherche Thrombo-Embolique aux Urgences

Vaccination COVID-19 et thromboses



Cedric HERMANS

UCLouvain

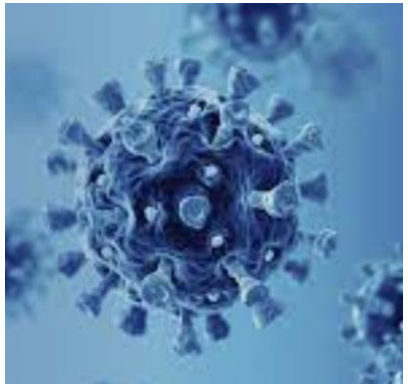
Cliniques universitaires SAINT-LUC UCL BRUXELLES

VACCINE-INDUCED IMMUNE THROMBOCYTOPENIA AND THROMBOSIS (VITT)

Globally, as of **9:17am CEST, 13 October 2021**, there have been **238,229,951 confirmed cases** of COVID-19, including **4,859,277 deaths**, reported to WHO. As of **10 October 2021**, a total of **6,364,021,792 vaccine doses** have been administered.

WHO Health Emergency Dashboard WHO (COVID-19) Homepage

- **March 2021: first cases of thrombosis at unusual sites associated with thrombocytopenia among fit and healthy young persons vaccinated with the AZ.**



Pavord S, et al. N Engl J Med. 2021 Aug 11.

MARCH 2021 : FIRST CASE

- 18 year old girl
- Headache
- Cerebral venous sinus thrombosis (CVST) with intracerebral haemorrhage
- Thrombocytopenia
- AstraZeneca vaccination 2 weeks earlier

- **Diagnoses considered**
  - Immune thrombocytopenia (ITP) with thrombosis
  - Thrombotic thrombocytopenic purpura (TTP)
  - Catastrophic antiphospholipid syndrome (CAPS)
  - Spontaneaous Heparin Induced Thrombocytopenia (HIT)
  - *Advance cancer*
  - *Disseminated (or localized) intravascular coagulation*

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

ABSTRACT

BACKGROUND

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

METHODS

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.

RESULTS

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Additional studies with PF4–heparin affinity purified antibodies in patient sera confirmed PF4-dependent platelet activation.

CONCLUSIONS

Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)

GERMANY

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

SUMMARY

We report findings in five patients who presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against coronavirus disease 2019 (Covid-19). The patients were health care workers who were 32 to 54 years of age. All the patients had high levels of antibodies to platelet factor 4–polyanion complexes; however, they had had no previous exposure to heparin. Because the five cases occurred in a population of more than 130,000 vaccinated persons, we propose that they represent a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia.

THE EUROPEAN MEDICINES AGENCY HAS APPROVED FIVE VACCINES against coronavirus disease 2019 (Covid-19), and more than 600 million doses have been administered globally.[1] In Norway, older adults living in institutional settings and health care professionals who are in close contact with patients with Covid-19 have been prioritized to receive the BNT162b2 mRNA Covid-19 vaccine (Pfizer–BioNTech). In addition, the ChAdOx1 nCoV-19 vaccine (AstraZeneca) has been administered to health care professionals younger than 65 years of age who do not have close contact with patients with Covid-19. As of March 20, 2021, when administration of the vaccine was paused, a total of 132,686 persons in Norway had received the first dose of the ChAdOx1 nCoV-19 vaccine and none had received the second dose.[2]

Within 10 days after receiving a first immunization with ChAdOx1 nCoV-19, five health care workers 32 to 54 years of age presented with thrombosis in unusual sites and severe thrombocytopenia. Four of the patients had major cerebral hemorrhage. Here we describe this vaccine-induced syndrome of severe thrombosis and thrombocytopenia found among these five patients admitted to Oslo University Hospital

NORWAY

ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Tom Solomon, M.D., Marcel Levi, M.D., David Goldblatt, M.D., Ph.D., Pavel Kotoucek, M.D., William Thomas, M.D., and William Lester, M.D.

ABSTRACT

BACKGROUND

The mainstay of control of the coronavirus disease 2019 (Covid-19) pandemic is vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within a year, several vaccines have been developed and millions of doses delivered. Reporting of adverse events is a critical postmarketing activity.

METHODS

We report findings in 23 patients who presented with thrombosis and thrombocytopenia 6 to 24 days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine (AstraZeneca). On the basis of their clinical and laboratory features, we identify a novel underlying mechanism and address the therapeutic implications.

RESULTS

In the absence of previous prothrombotic medical conditions, 22 patients presented with acute thrombocytopenia and thrombosis, primarily cerebral venous thrombosis, and 1 patient presented with isolated thrombocytopenia and a hemorrhagic phenotype. All the patients had low or normal fibrinogen levels and elevated D-dimer levels at presentation. No evidence of thrombophilia or causative precipitants was identified. Testing for antibodies to platelet factor 4 (PF4) was positive in 22 patients (with 1 equivocal result) and negative in 1 patient. On the basis of the pathophysiological features observed in these patients, we recommend that treatment with platelet transfusions be avoided because of the risk of progression in thrombotic symptoms and that the administration of a nonheparin anticoagulant agent and intravenous immune globulin be considered for the first occurrence of these symptoms.

CONCLUSIONS

Vaccination against SARS-CoV-2 remains critical for control of the Covid-19 pandemic. A pathogenic PF4-dependent syndrome, unrelated to the use of heparin therapy, can occur after the administration of the ChAdOx1 nCoV-19 vaccine. Rapid identification of this rare syndrome is important because of the therapeutic implications.

UK

VACCINE-INDUCED IMMUNE THROMBOCYTOPENIA AND THROMBOSIS

ORIGINAL ARTICLE

April 9, 2021

(AZ)

Thrombotic Thrombocytopenia
after ChAdOx1 nCov-19 Vaccination

BRIEF REPORT

April 9, 2021

Thrombosis and Thrombocytopenia
after ChAdOx1 nCoV-19 Vaccination

(AZ)

CORRESPONDENCE

(J&J)

April 14, 2021

Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination

ORIGINAL ARTICLE

April 16, 2021

Pathologic Antibodies to Platelet Factor 4
after ChAdOx1 nCoV-19 Vaccination

Greinacher NEJM, 2021; Schultz NEJM, 2021; Muir NEJM, 2021; Scully NEJM, 2021.

Reference	Vaccine	Country/Area	Number	Age mean (range) in years	Sex	Primary thrombosis type	Platelet count mean (range) x109/l	Outcome
Schultz NEJM	AZ	Norway	5	40.8 (32-54)	4 F, 1 M	4 CVST 1 Portal vein	27 (10-70)	Fatal 60%
Greinacher NEJM	AZ	Germany and Austria	11	36 (22-49)	9 F, 2 M	9 CVST 1 PE	35 (8-107)	Fatal 55%
Scully NEJM	AZ	UK	23	46 (21-77)	13 F, 10 M	13 CVST 4 PE 1 DVT 2 MCA strokes 2 Portal vein	44 (7-113)	Fatal 30%
JAMA	J&J	USA	12	<40 in 9	12 F	12 CVST	46 (9-127)	Fatal 25% Still in hospital 42%
Tiede Blood	AZ	Germany	5	58.6 (41-67)	5 F	1 CVST 3 Arterial strokes 1 Splanchnic	39 (12-105)	Fatal 0%

Reported patients had low platelets + PF4 antibodies

Clinical workup in patients with clinical symptoms and signs suggestive of thrombosis with 30 days of vaccination with a COVID-19

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

Interim guidance

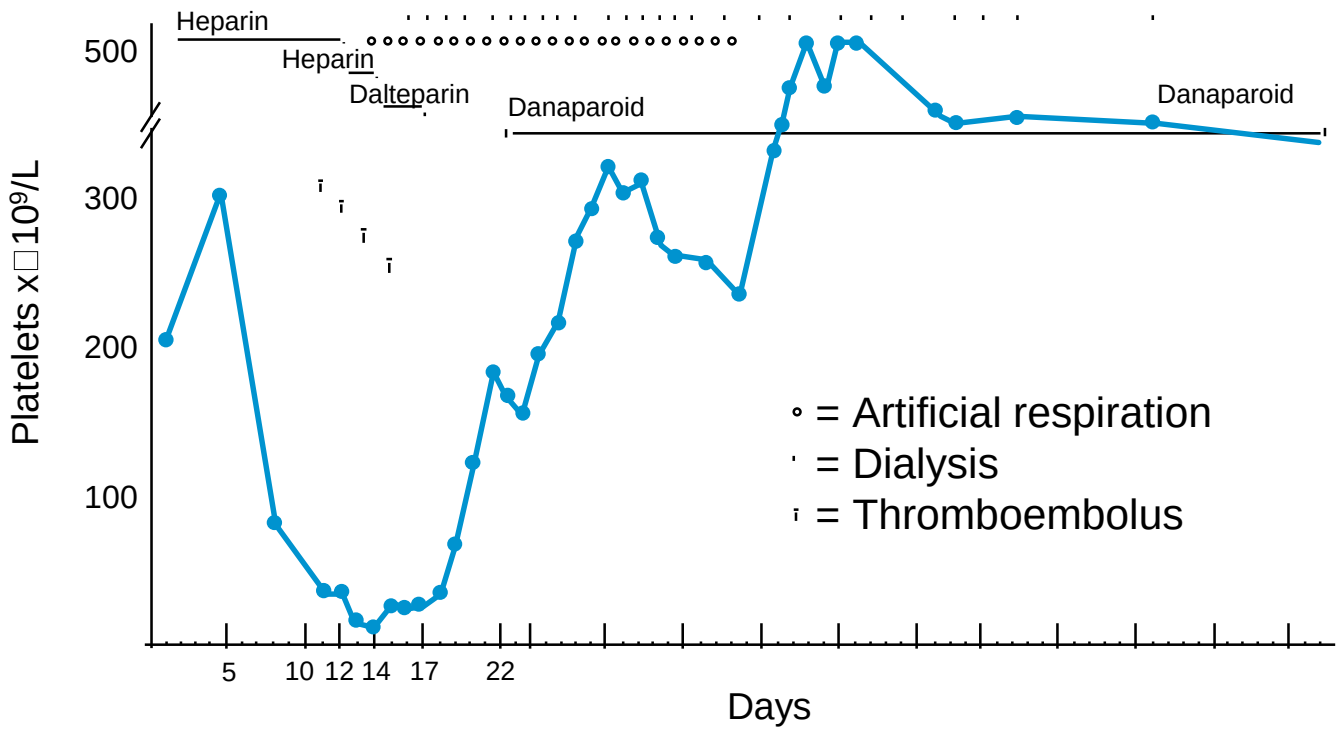
19 July 2021

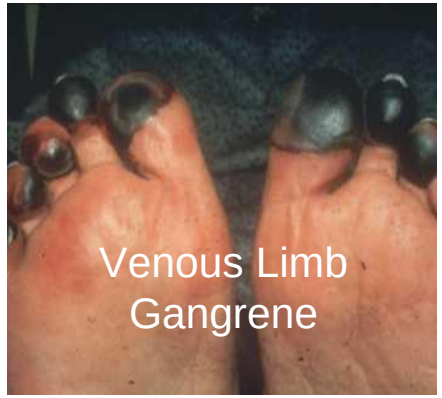
World Health Organization

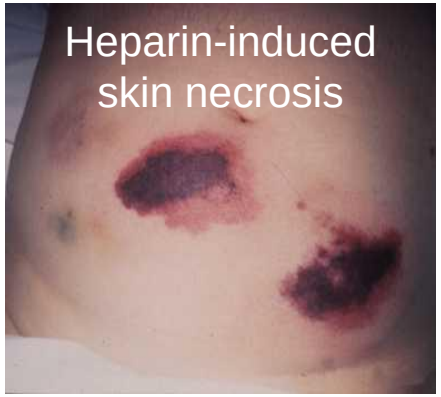
VITT : vaccine-induced immune thrombotic thrombocytopenia

HITT : heparin-induced thrombocytopenia with thrombosis

HIT (Heparin-Induced Thrombocytopaenia)



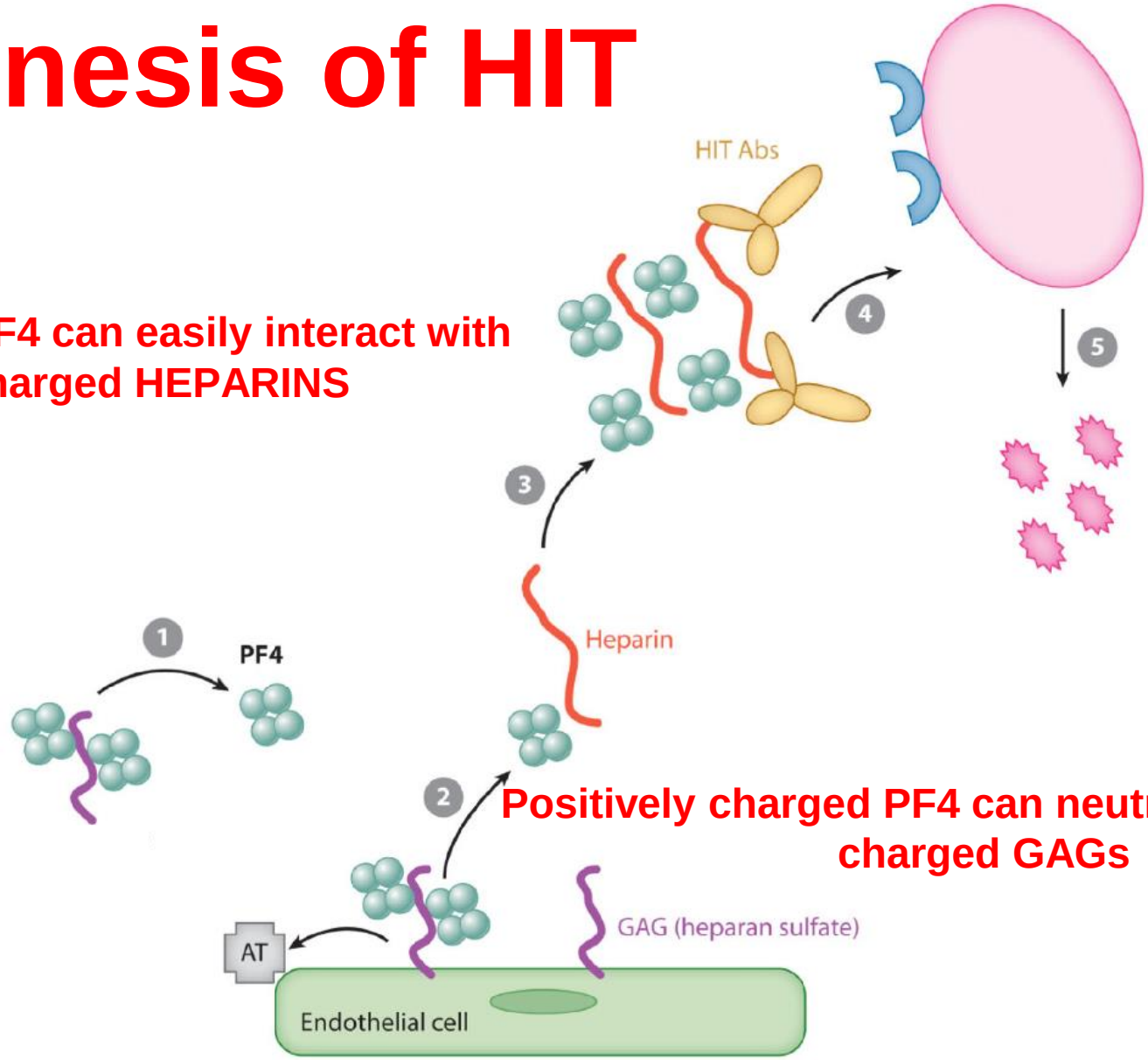




Adapted from Greinacher A, Drost W, Michels I, et al. *Ann Haematol.* 1992;64:40–42.

Pathogenesis of HIT

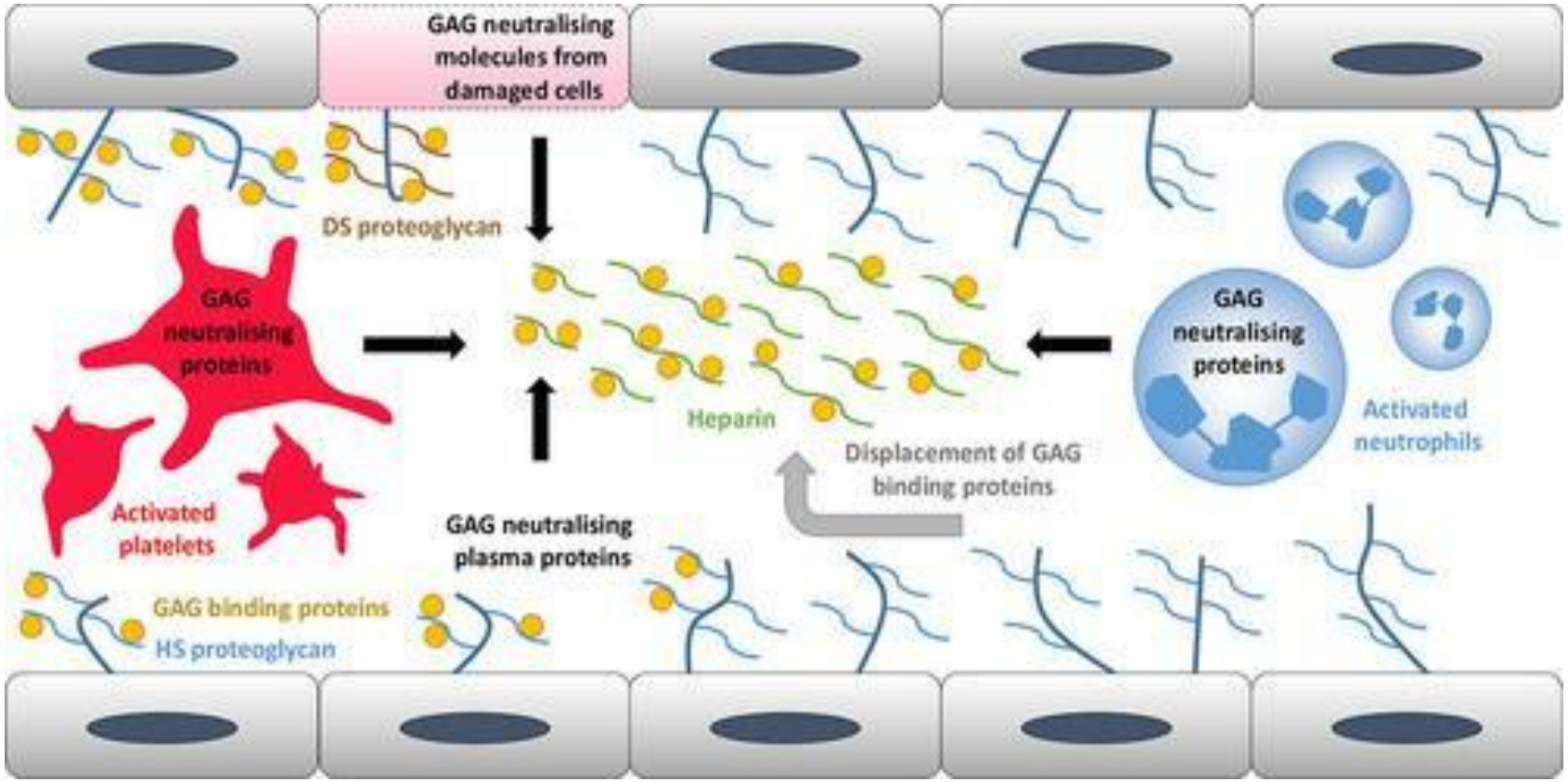
Positively charged PF4 can easily interact with negatively charged HEPARINS



Positively charged PF4 can neutralize negatively charged GAGs

Annu Rev Med. 2010 ; 61: 77–90. doi:10.1146/annurev.med.042808.171814

Negatively charged Glycosaminoglycans contribute to the antithrombotic properties of the endothelium

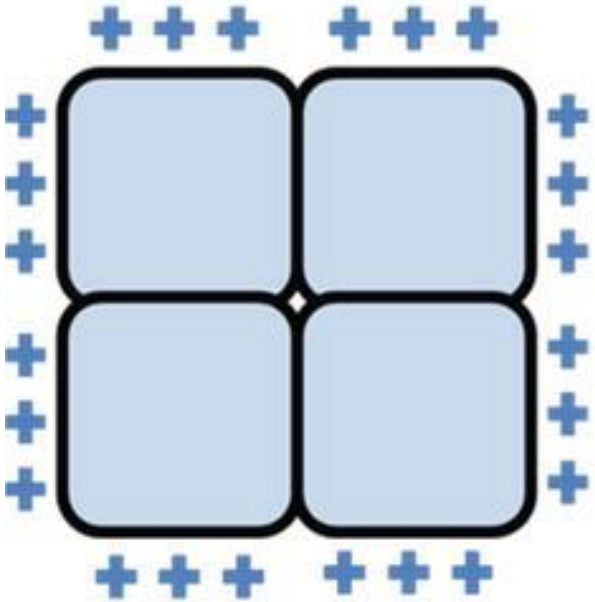


Amélie I.S. Sobczak. Arteriosclerosis, Thrombosis, and Vascular Biology. Glycosaminoglycan Neutralization in Coagulation Control, Volume: 38, Issue: 6, Pages: 1258-1270, DOI: (10.1161/ATVBAHA.118.311102)

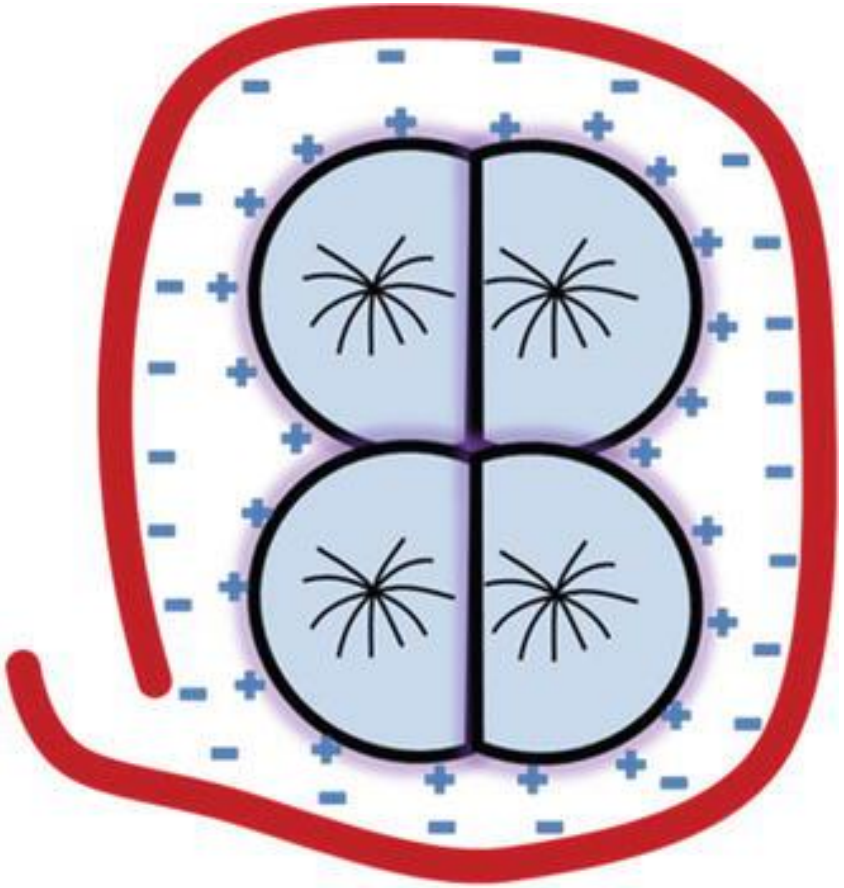
Heparin

PF4

- The mature size of PF4 is 70-amino-acid protein
- Its major physiological function is to promote blood coagulation
- Affinity for heparin and other glycosaminoglycans (GAGs)
- **By neutralizing the negatively charged heparan sulfate side chains of GAGs on the surface of platelets and endothelial cells, PF4 facilitates platelet aggregation to form a thrombus.**
- PF4 expression is elevated following trauma
- PF4 is also released by activated platelets in response to infection



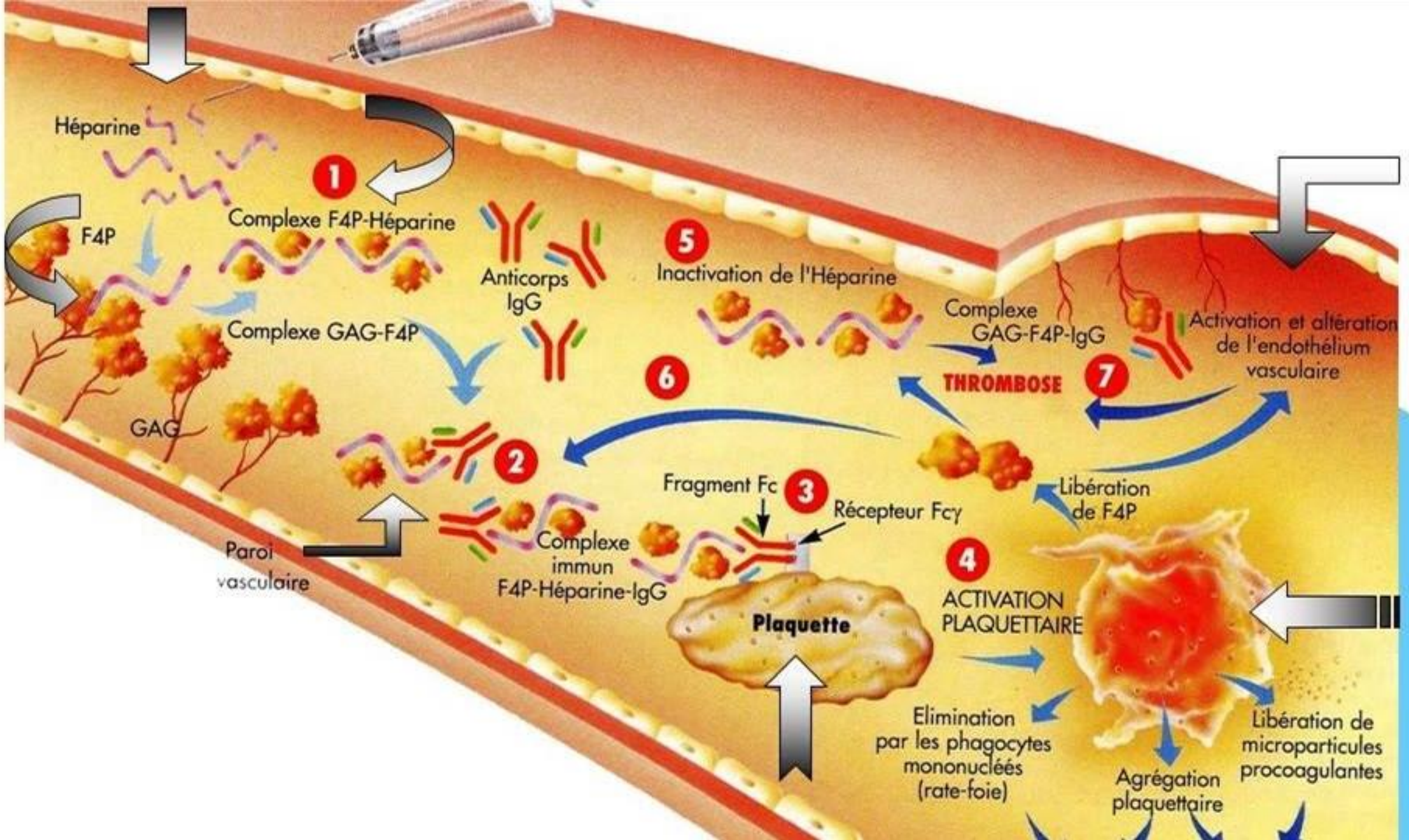
Native PF4 tetramer



Stochiometric

PF4-Heparin Complexes

PF4 (positively charged) + Heparin (negatively charged) = Neo-Antigen


Héparine
1
Complexe F4P-Héparine
F4P
Anticorps IgG
5
Inactivation de l'Héparine
Complexe GAG-F4P-IgG
Activation et altération de l'endothélium vasculaire
Complexe GAG-F4P
THROMBOSE
7
6
GAG
2
Fragment Fc
3
Récepteur Fcγ
Libération de F4P
Paroi vasculaire
Complexe immun F4P-Héparine-IgG
4
ACTIVATION PLAQUETTAIRE
Plaquette
Elimination par les phagocytes mononucléés (rate-foie)
Agrégation plaquettaire
Libération de microparticules procoagulantes

Spontaneous HIT (without heparin)

Patients with thrombosis after vaccination had anti-PF4 antibodies in the absence of heparin exposure

BRIEF OBSERVATION

THE AMERICAN JOURNAL of MEDICINE®

A Spontaneous Prothrombotic Disorder Resembling Heparin-induced Thrombocytopenia

Theodore E. Warkentin, MD,[a,b] Michael Makris, MD,[c] Richard M. Jay, MD,[d] John G. Kelton, MD[b]

[a]Department of Pathology and Molecular Medicine, [b]Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada; [c]Department of Haematology, Royal Hallamshire Hospital, Sheffield, United Kingdom; [d]Division of Medical Oncology and Clinical Haematology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada.

Journal of Thrombosis and Haemostasis, **15**: 2099–2114 DOI: 10.1111/jth.13813

REVIEW ARTICLE

Autoimmune heparin-induced thrombocytopenia

A. GREINACHER,* K. SELLENG* and T. E. WARKENTIN†

**Institut für Immunologie und Transfusionsmedizin, Universitätsmedizin Greifswald, Greifswald, Germany; and †Department of Pathology and Molecular Medicine, Department of Medicine, and McMaster Centre for Transfusion Research, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada*

To cite this article: Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost* 2017; **15**: 2099–114.

Warkentin T, et al. American Journal of Medicine 2008; 121:632-636

“spontaneous” heparin-induced thrombocytopenia syndrome

Polyanionic drugs

pentosan polysulfate

antiangiogenic agent

hypersulfated chondroitin sulfate

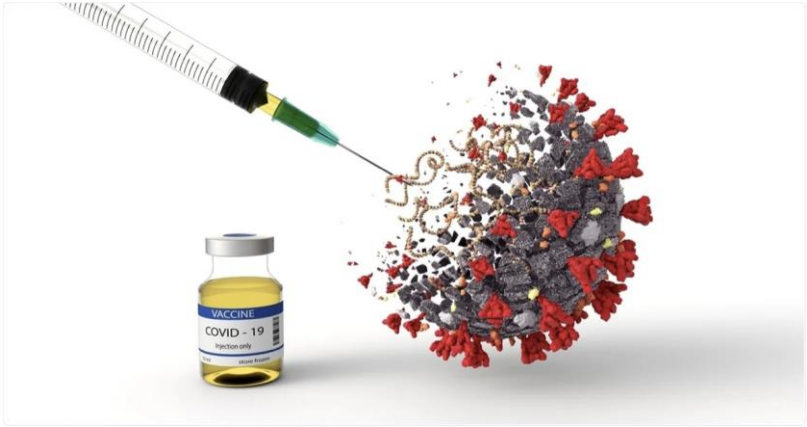
infections (viral, bacterial), or knee replacement surgery.

can rarely cause a disorder that strongly resembles heparin-induced thrombocytopenia on both clinical and serological grounds in patients who did not receive Heparins

WHICH COVID-19 VACCINES ARE ASSOCIATED WITH VITT ?

Reported cases

- Astra Zeneca Oxford – Chimpanzee adenovirus ChAdOx1
- Johnson & Johnson – Human adenovirus 26



No reported cases

- Pfizer –mRNA
- Moderna – mRNA
- Gamaleya Sputnik V – Human adenovirus 5 and 26
- CanSino Biologics Convidecia – Human adenovirus 5

A complex and not yet solved equation

PF4 + X (related to vaccination) >

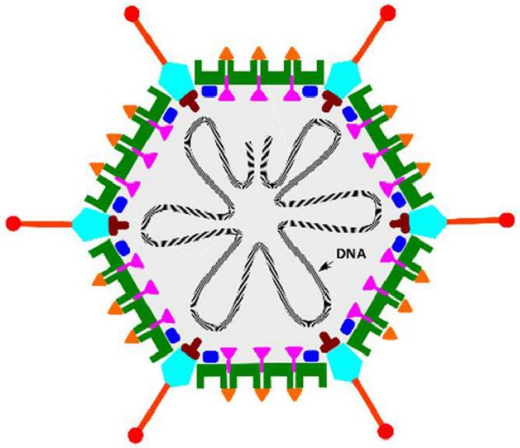
Unusual Thrombosis

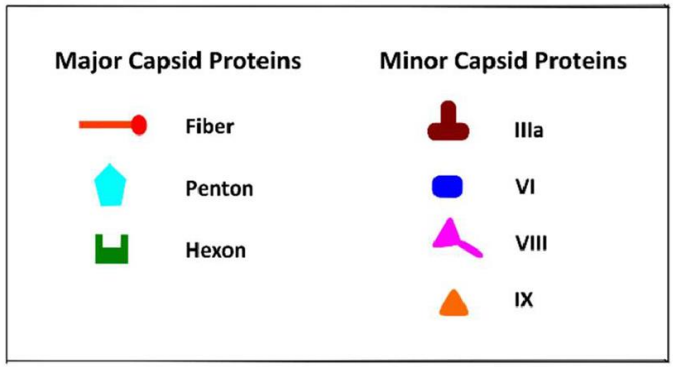
What is X ?

- Something in the adenoviral vaccines
- Something expressed by the infected cells
- Likely highly negatively charged (? free DNA ? other)
- Bind to platelet factor 4 (PF4) in plasma

- Patients make antibodies to a new epitope against PF4
- The anti-PF4 antibodies bind to platelets via the Fc gamma IIA receptors
- The antibodies bind to the receptor and activate the platelets

AZD1222:
Recombinant ChAdOX1 expressing the S protein of SARS-CoV-2





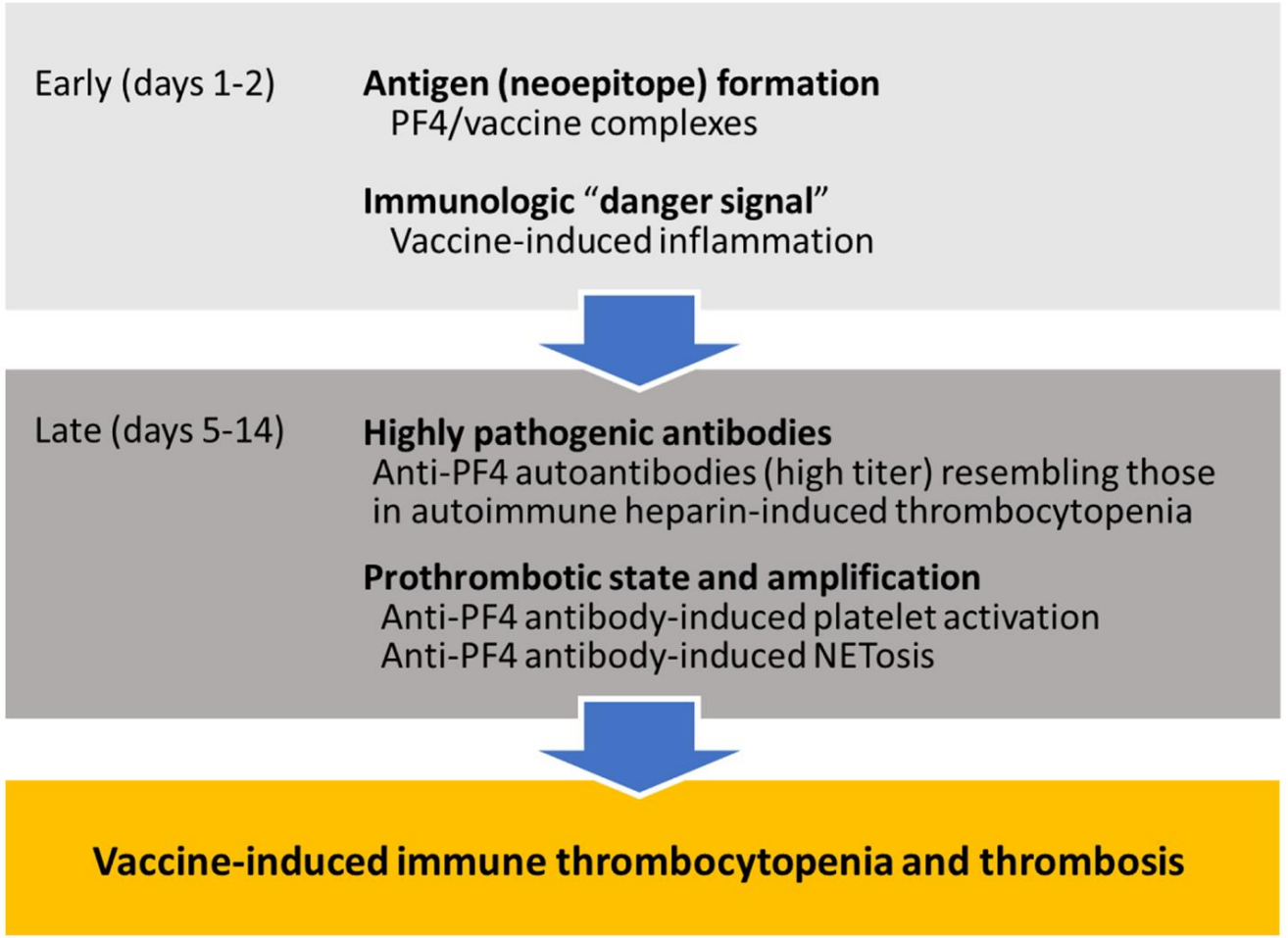
-Non-replicating, E1 and E3-deleted derived from the chimpanzee adenovirus Y25

Figure 2 **Structure of the nCov-19 Spike Protein Gene Expression Cassette (6,214 bp)**

-<u>Unmodified</u> S protein (i.e. no pre-fusion stabilized) with tPA leader seq

-Expressed on T-Rex-293 cells

Insights in ChAdOx1 nCov-19 Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)



Blood 2021 Sep 29;blood.2021013231. doi: 10.1182/blood.2021013231. Online ahead of print.

Received: 10 December 2020 | Accepted: 3 February 2021

DOI: 10.1111/jth.15262

BRIEF REPORT

Anti-PF4 antibodies also present in patients with COVID19

COVID-19 patients often show high-titer non-platelet-activating anti-PF4/heparin IgG antibodies

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[2]Division of Angiology and Haemostasis, University Hospitals of Geneva, Geneva,

Abstract

Background: Heparin-induced thrombocytopenia (HIT) is a severe adverse reaction to heparin caused by heparin-dependent, platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies. Heparin is a cornerstone of treatment in critically ill COVID-19

Conclusion: COVID-19 patients often present with strong reactivity in PF4/heparin antigen tests without the presence of platelet-activating antibodies. Diagnosis of HIT requires confirmation of heparin-dependent, platelets activating antibodies to avoid overdiagnosis and overtreatment with non-heparin anticoagulants

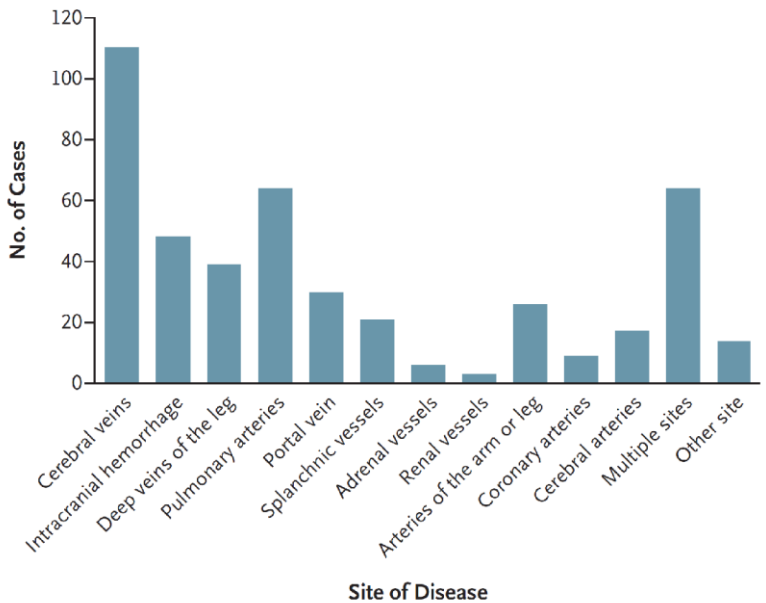
ORIGINAL ARTICLE

Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis

Sue Pavord, F.R.C.Path., Marie Scully, M.D., Beverley J. Hunt, M.D., William Lester, M.D., Catherine Bagot, M.D., Brian Craven, M.B., B.Ch., Alex Rampotas, M.R.C.P., Gareth Ambler, Ph.D., and Mike Makris, M.D.

Table 2. Baseline Clinicopathological Features of the Patients with VITT.*

Variable	Value
Age — yr	
Median (IQR)	48 (38–56)
Range	18–79
Sex — no./total no. (%)	
Female	119/217 (55)
Male	98/217 (45)
Race — no./total no. (%)	
White	90/99 (91)
Asian	9/99 (9)
Days since vaccination with ChAdOx1 nCoV-19	
Median (IQR)	14 (10–16)
Range	5–48
Platelet count — per mm^3	
Median (IQR)	47,000 (28,000–76,000)
Range	6,000–344,000
Prothrombin time — sec	
Median (IQR)	13 (10–14)
Range	10–30
Activated partial-thromboplastin time — sec	
Median (IQR)	29 (22–30)
Range	20–57
Fibrinogen level — g/liter	
Median (IQR)	2.2 (1.2–3.1)
Range	0.3–4.4
D-dimer level — FEU	
Median (IQR)	24,000 (8,000–37,000)
Range	5,000–80,000



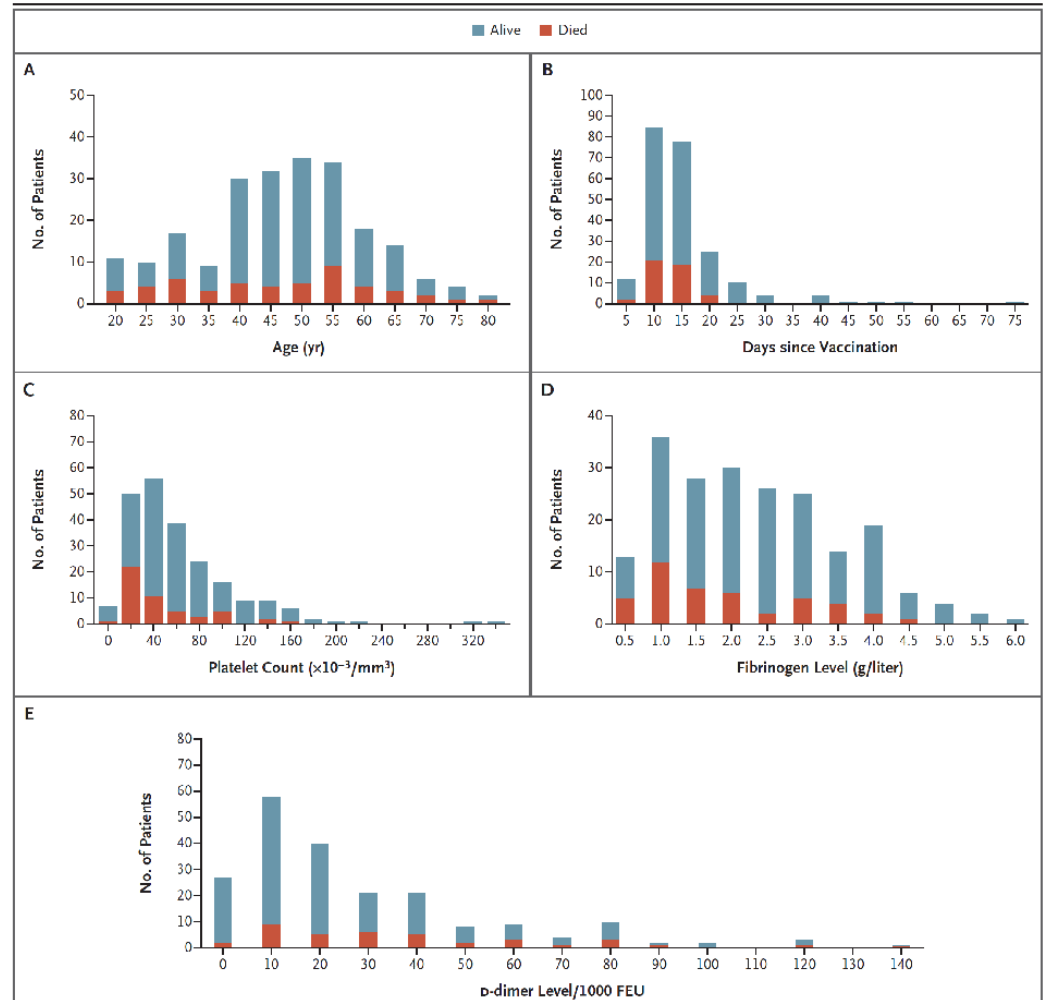


Figure 1. Baseline Distribution of Variables in Patients with Vaccine-Induced Immune Thrombocytopenia and Thrombosis (VITT).
Shown are the variables in patients with VITT, including those who did not survive.

VITT INCIDENCE

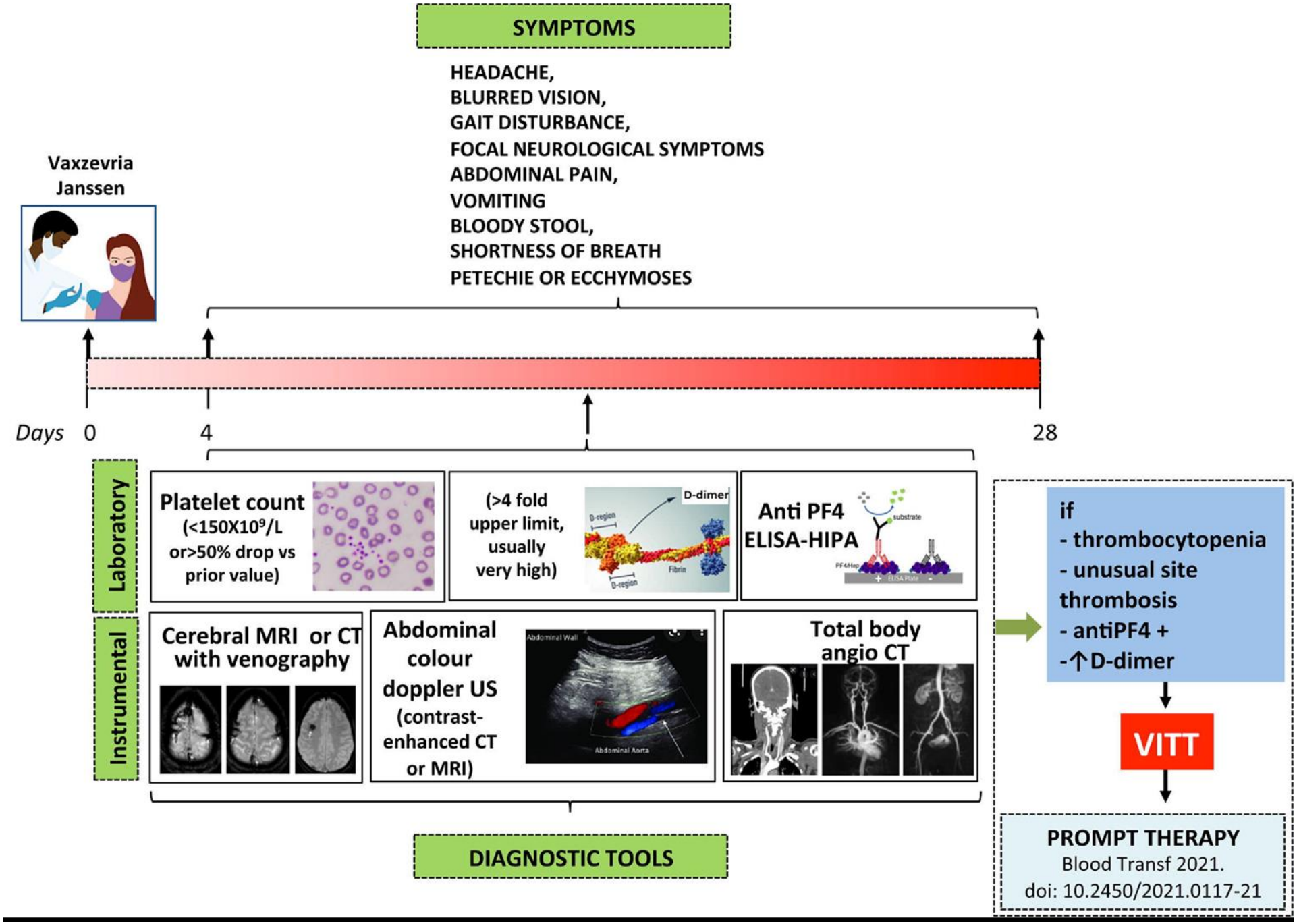
Country	Incidence among AZ vaccinated persons
Norway	1 per 25.000
Germany	1 per 100.000
UK	1 per 92.000
Australia	1 per 125.000
India	0 officially reported after 111 million vaccinated
Sri Lanka	1 per 154.000 (vaccine manufactured in India)

Types of thrombosis

- **60-70% Cerebral venous sinus thrombosis - CVST (WHY ?)**
- **10-20% Portal vein thrombosis (WHY ?)**

Others

- *DVT and PE*
- *Thrombotic strokes, MCA (middle cerebral artery) thrombosis*
- *Acute coronary syndrome with normal coronary arteries*
- *DIC, skin necrosis*
- *Ovarian vein thrombosis*
- *Arterial – aorta, femoral arteries*


SYMPTOMS
HEADACHE,
BLURRED VISION,
GAIT DISTURBANCE,
FOCAL NEUROLOGICAL SYMPTOMS
ABDOMINAL PAIN,
VOMITING
BLOODY STOOL,
SHORTNESS OF BREATH
PETECHIE OR ECCHYMOSES
Vaxzevria
Janssen
Days 0
4
28
Laboratory
Platelet count
(<150X10⁹/L
or>50% drop vs
prior value)
(>4 fold
upper limit,
usually
very high)
D-dimer
D-region
Fibrin
D-region
Anti PF4
ELISA-HIPA
substrate
PF4/Hep
ELISA Plate
Instrumental
Cerebral MRI or CT
with venography
Abdominal
colour
doppler US
(contrast-
enhanced CT
or MRI)
Abdominal Wall
Abdominal Aorta
Total body
angio CT
if
- thrombocytopenia
- unusual site
thrombosis
- antiPF4 +
-↑D-dimer
VITT
PROMPT THERAPY
Blood Transf 2021.
doi: 10.2450/2021.0117-21
DIAGNOSTIC TOOLS

LABORATORY TESTS

- Full blood count – platelets mostly 10-150 (normal range 150-400)
- Fibrinogen – often 1.0-2.0g/l (normal range 2.0-4.0)
- D-Dimer – 4.000-60.000 (normal <500) ng/ml

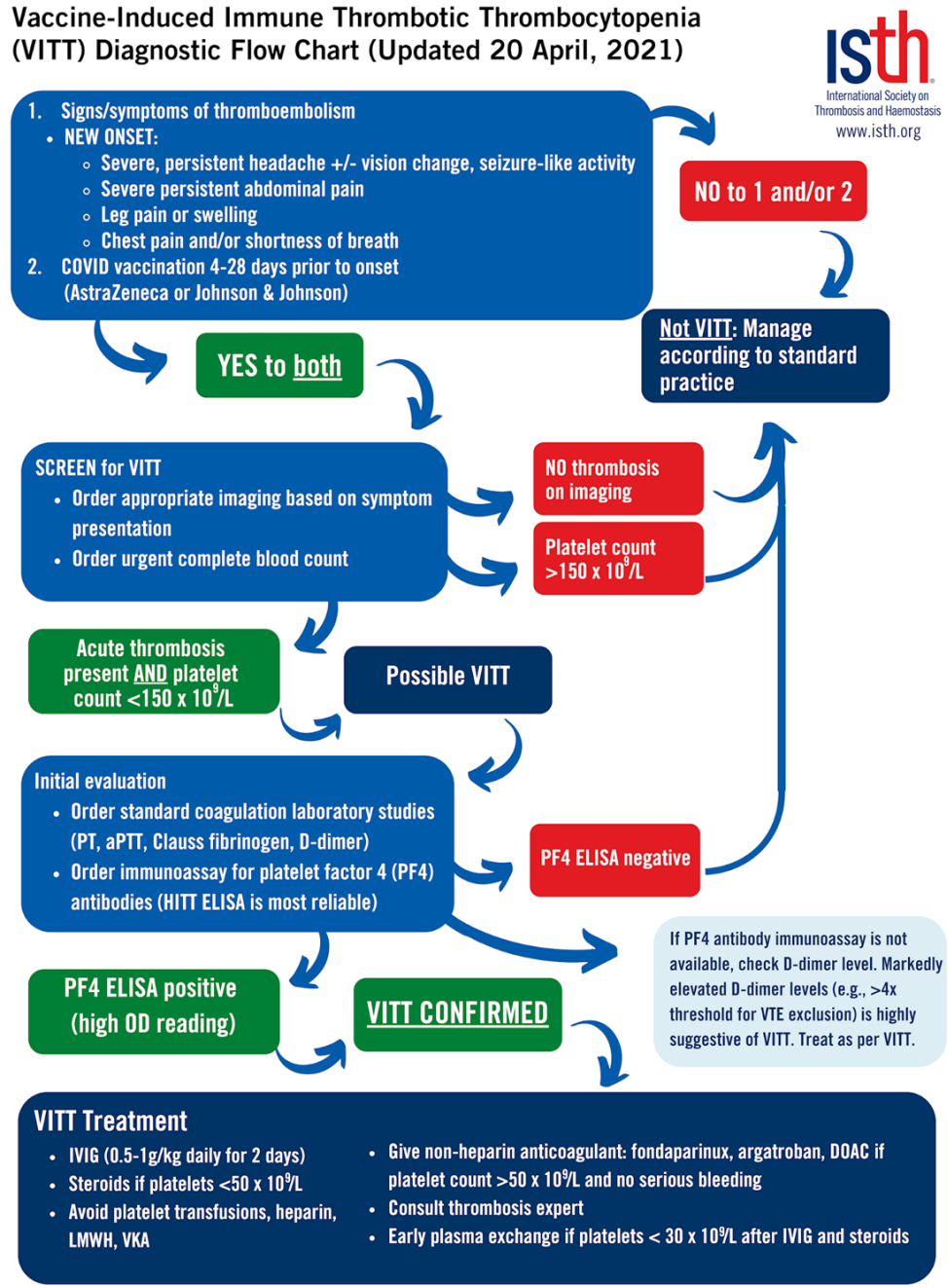
- Anti-PF4 antibodies
  - Only positive with HIT Elisa assays
  - The more widely used Acustar assay is negative

  - **Functional test required to demonstrate the ability of anti-PF4 antibodies to activate platelets**

VITT adapted 4T scoring system

VITT-adapted 4Ts scoring system

Parameter	Point(s)
Thrombocytopenia	
▪ Platelet count 10,000 to 99,000/microL	2
▪ Platelet count <10,000/microL or 100,000 to 149,000/microL	1
▪ Platelet count ≥150,000/microL	0
Timing*	
▪ 5 to 14 days post vaccine	2
▪ 15 to 30 days post vaccine	1
▪ 0 to 4 days or ≥30 days post vaccine	0
Thrombosis	
▪ Definite thrombosis **or** D-dimer >10 mg/L (>10,000 ng/mL)	2
▪ Suspected (not documented) thrombosis **or** D-dimer 2.00 to 9.99 mg/L (2000 to 9990 ng/mL)	1
▪ No thrombosis **and** D-dimer <2 mg/L (<2000 ng/mL)	0
Other cause of thrombosis or thrombocytopenia	
▪ None apparent	2
▪ Possible	1
▪ Definite	0
Interpretation	**Total**
▪ 0 to 3 points – Low probability	
▪ 4 to 5 points – Intermediate probability	
▪ 6 to 8 points – High probability	



ISTH released 19th April 2021

Clinical management of patients with confirmed, probable or possible VITT

TREATMENT OF VITT

1. **IVIG 1g/kg/day for 2 days**

Cave at new clots post IVIG – start anticoagulation concomitantly

2. **Non-heparin anticoagulation** (based on clinical status and organ function)

- IV direct thrombin inhibitors (Bivalirudin, Argatroban)
- Fondaparinux
- DOAC (Apixaban-Rivaroxaban-Dabigatran)
- Danaparoid

Anticoagulation at least 3 months

Before stopping anticoagulation, ensure normalisation of platelets and

absence of anti-PF4 antibodies.

No guidelines on prophylactic anticoagulation after VITT

Covid-ressources ASH version 1.6, updated Aug 2021
WHO interim guidance 19 July 2021

TREATMENT OF VITT

3. Avoid platelet transfusion. However, assess individual bleeding and need for invasive procedures.

4. Consider replacement with Fibrinogen

5. Corticosteroids: no consensus or data on their role

6. Avoid aspirin as either treatment or prophylaxis for VITT.
Cave at increased risk of bleeding with aspirin.

7. Plasma exchange in patients with severe disease.
To be considered if thrombosis continues despite IVIG and non-heparin anticoagulation.

8. No second dose of non-replicant adenovirus vector-based vaccine

Covid-ressources ASH version 1.6, updated Aug 2021
WHO interim guidance 19 July 2021

Case definition criteria		
Likelihood of VITT	**Clinical and laboratory features**	**Recommended management**
	- Onset of symptoms 5-30 days post Covid 19 vaccine (or up to 42 days if isolated DVT/PE) - documented thrombosis or severe and persistent headache - thrombocytopenia (platelet count < 150,000/µL) - D-dimer >4000 µg/mL (and >8x upper limit of normal (ULN)) - positive anti-PF4/heparin IgG ELISA assay	
Definite VITT	**Meets all five criteria**	**anticoagulation, IVIG**
Probable VITT	D-dimer > 4000 µg/mL (and > 8x ULN), but one criteria not fulfilled (timing, thrombosis, thrombocytopenia, anti-PF4/heparin antibodies) or D-dimer unknown or 2000-4000 µg/mL (4 - 8 x ULN) with all other criteria present	anticoagulation, IVIG
Possible VITT	D-dimer unknown or 2000-4000 µg/mL (4 - 8 x ULN) with one other criteria not fulfilled or two criteria not fulfilled (timing, thrombosis, thrombocytopenia, anti-PF4/heparin antibodies)	anticoagulation, close clinical monitoring
Unlikely	Platelet count < 150,000/µL without thromboses, D-dimer <2000 µg/mL (<4 x ULN), regardless of anti-PF4/heparin antibody result, and/or alternative diagnosis more likely	Anticoagulation only if thrombosis is present. Consider if ITP treatment is needed

FOLLOW-UP AND MONITORING

ALL PATIENTS WITH CONFIRMED VITT	
Patients should be kept under the care of the haematology department. Close monitoring is required after discharge	
1-2 weeks	Check D-dimer and platelet count every 2 to 3 days
1-4 weeks	Perform anti-PF4 ELISA weekly
4 weeks-6 months	Perform anti-PF4 ELISA monthly
6 months onwards	Perform anti PF4-ELISA every 3 months
Patients with confirmed venous thrombosis	
At least 3 months after discharge and until anti-PF4 antibodies are no longer detected	Continue anticoagulation
For patients with coronary artery thrombosis or arterial thrombosis in vessels without atherosclerosis	
At least 1 month	Continue anticoagulation and consider adding antiplatelet agents

CEREBRAL VENOUS SINUS THROMBOSIS

- Much more severe bleeding than classical CVST
- Patients can quickly deteriorate and die
  - Recommended to be managed in hospitals with neurosurgery onsite
  - At least 30% mortality
- Low dose anticoagulation when platelets are low
- Once major cerebral bleeding, medical therapy unlikely to help
  - Go for neurosurgery with platelet support
- Thrombectomy should be attempted in a deteriorating patient

LOW PLATELET COUNT AFTER VACCINATION

	VITT	Neutropenia	ITP / thrombocytopenia	1st dose	2nd dose	Total
Pfizer	0	28	123	11.4	8.7	20.1
AstraZeneca	262[1]	71	682	23.4	7.5	30.9
Moderna	0	0	0	0.1	0	0.1

Data from UK MHRA reports released 13th May 2021, covering period up to 5th May 2021

[1] 254 after 1th dose and 8 after 2nd dose

POST VACCINATION HEADACHE

- Common immediately post vaccination
- VITT cases are 5-24 days post vaccination
- Headache after 4 days could be significant
- Use Full Blood Count measurement as screening test
- D-Dimer can help but not advised unless platelets low

NOT ALL TROMBOSES POST-VACCINATION ARE VITT

- Many patients post-vaccination develop venous thrombo-embolic events
- Incidence not established
- Consequence of systemic inflammatory syndrome post-vaccination
- With all COVID-19 vaccines
- Most of these patients have predisposing risk factors for VTED
- Classical location (lower limbs ..)
- No thrombocytopenia
- Increase of DDs in expected ranges
- Treatment : short course of LMWH/VKA/DOACs

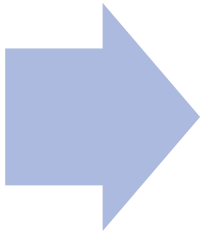
Personal views

Vaccine-associated autoimmune thrombocytopenia thrombosis syndrome

- Very rare entity
- Mainly seen with adenovirus vector-based vaccines
- Pathophysiology much better understood
- Diagnostic work-ups have been developed
- Treatment approaches have been defined
- The benefit of vaccination clearly outweigh the potential risks
- No evidence of particular predisposing factors

COVID-19 : A major thrombotic disease

COVID-19



Coagulopathy and thrombosis in up to 20 % of patients

J Am Heart Assoc. 2021;10:e019650. DOI: 10.1161/JAHA.120.019650

Thank you for your attention