Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT)
Day +55

Mike Makris

Sheffield, UK

European countries ranked by total COVID-19 cases

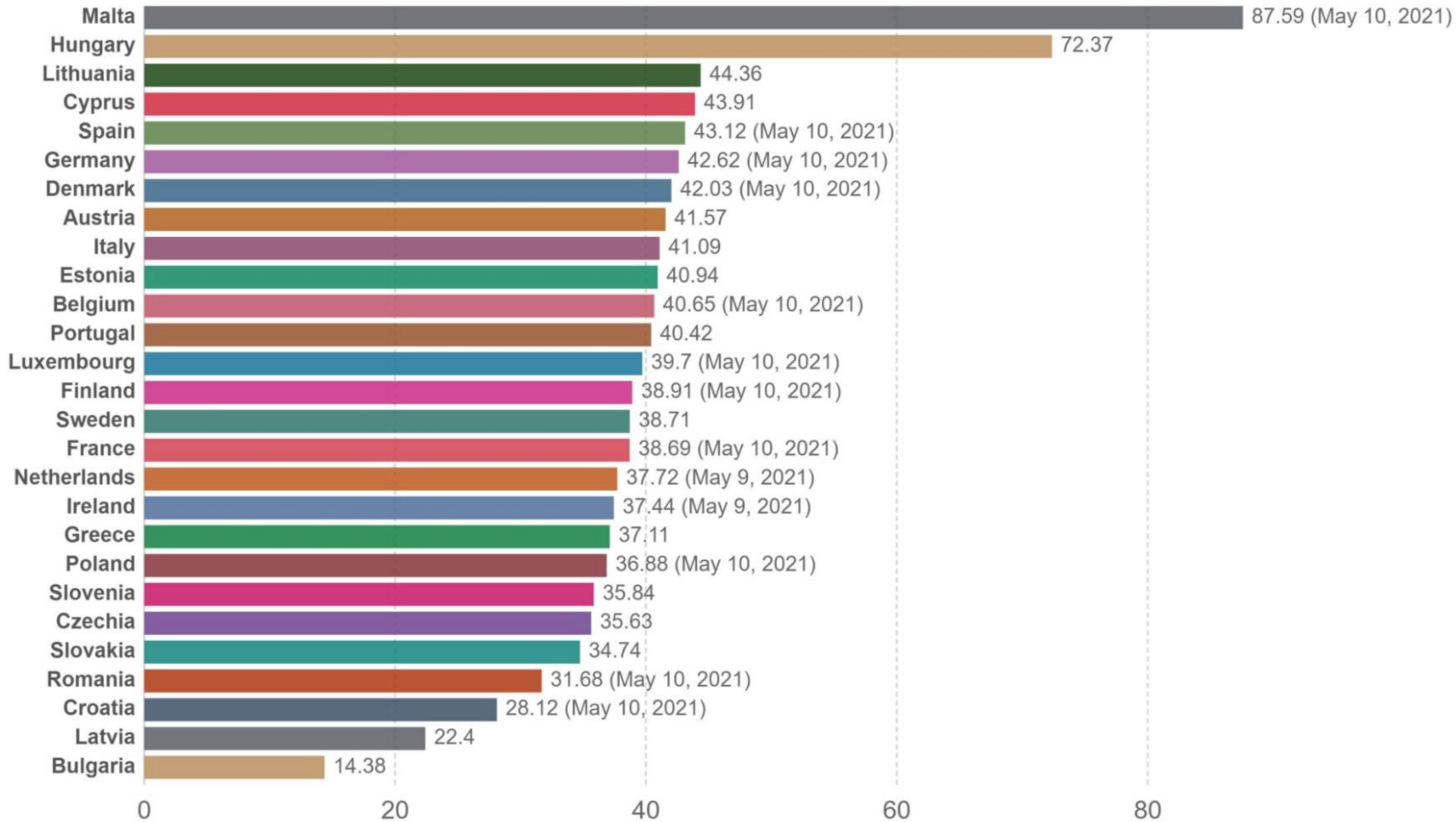
	Europe	45,758,341	+90,448	1,041,785	+2,344
1	France	5,821,668	+21,498	107,119	+184
2	Russia	4,905,059	+8,217	114,331	+355
3	UK	4,441,975	+2,284	127,640	+11
4	Italy	4,131,078	+7,852	123,544	+262
5	Spain	3,592,751	+6,418	79,208	+108
6	Germany	3,551,550	+7,235	85,921	+164
7	Poland	2,842,339	+4,255	70,679	+343
8	Ukraine	2,129,073	+4,538	46,987	+356
9	Czechia	1,648,667	+1,673	29,787	+15
10	Netherlands	1,577,754	+6,356	17,399	+16

Worldometer.info/coronavirus/ (accessed 12 May 2021)

COVID-19 vaccine doses administered per 100 people, May 11, 2021

Total number of vaccination doses administered per 100 people in the total population. This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).

Our World in Data



Source: Official data collated by Our World in Data – Last updated 12 May, 09:40 (London time)

February 2021

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

- Diagnoses considered
  - ITP with thrombosis
  - Thrombotic thrombocytopenic purpura (TTP)
  - Catastrophic antiphospholipid syndrome (CAPS)
  - Spontaneous Heparin Induced Thrombocytopenia (HIT)

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- Headache
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- Diagnoses considered
  - ITP with thrombosis
  - Thrombotic thrombocytopenic purpura (TTP) ADAMTS-13 Normal
  - Catastrophic antiphospholipid syndrome (CAPS) Antiphospholipid antibodies negative
  - Spontaneous Heparin Induced Thrombocytopenia (HIT) HIT test negative

VITT chronology

- 11 March 2021: MHRA & EMA – no increase in thrombotic risk
- 19 March 2021: 3 groups from Norway, Germany, UK report cases of CVST and thrombocytopenia with anti-PF4 antibodies
- 22 March 2021: Daily UK national MDT meetings started
- 7 April 2021: MHRA & EMA – Rare syndrome of atypical thrombosis and thrombocytopenia. In UK AZ restriction for <30 years

Vaccine-induced Immune Thrombocytopenia with Thrombosis (VITT)

Alternative names

- VATT – vaccine associated thrombosis with thrombocytopenia
- VIPIT – vaccine induced prothrombotic immune thrombocytopenia
- VITT – vaccine-induced immune thrombotic thrombocytopenia *

* Name used by New England Journal of Medicine for 3 papers in press but can be confused with immune thrombotic thrombocytopenic purpura (iTTP)

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 or PF4–heparin affinity purified antibodies in 2 patients 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.)

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.

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., Thomas 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 21 patients, negative in 1 patient, and equivocal 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.

From the Department of Haematology, University College London Hospitals NHS Foundation Trust (M.S., M.L.), National Institute for Health Research University College London Hospitals Biomedical Research Centre (M.S., M.L.), Special Coagulation, Health Services Laboratories (D.S.), Great Ormond Street Institute of Child Health, University College London (D.G.), and National Institute for Health Research Great Ormond Street Biomedical Research Centre (D.G.), London, the Department of Haematology, University Hospital Southampton, Southampton (R.L.), National Health Service Blood and Transplant, Bristol (A.P.), National Institute for Health Research Health Protection Research Unit, University of Liverpool, Liverpool (T.S.), the Department of Haematology, Mid Essex Hospitals, Chelmsford (P.K.), the Department of Haematology, Addenbrookes Hospital, Cambridge (W.T.), and the Department of Haematology, University Hospitals Birmingham, and Institute of Cardiovascular Sciences, University of Birmingham, Birmingham (W.L.) — all in the United Kingdom; and the Department of Vascular Medicine, Amsterdam University Medical Center, Amsterdam (M.L.). Address reprint requests to Prof. Scully at the Department of Haematology, University College London Hospitals NHS Foundation Trust, 250 Euston Rd., London NW1 2PG, United Kingdom, or at m.scully@ucl.ac.uk.

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Papers in press in New England Journal of Medicine

Reference	Vaccine	Country/Area	Number	Age mean (range) in years	Sex	Primary thrombosis type	Platelet count mean (range) X109/l	Outcome
Schultz	AZ	Norway	5	40.8 (32-54)	4 F, 1 M	4 CVST 1 Portal vein	27 (10-70)	Fatal 60%
Greinacher	AZ	Germany and Austria	11	36 (22-49)	9 F, 2 M	9 CVST 1 PE	35 (8-107)	Fatal 55%
Scully	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%
See	J&J	USA	12	<40 in 9	12 F	12 CVST	46 (9-127)	Fatal 25% Still in hospital 42%
Tiede	AZ	Germany	5	58.6 (41-67)	5F	1 CVST 3 Arterial strokes 1 Splanchnic	39 (12-105)	Fatal 0%

Types of thrombosis

- 60-70% Cerebral venous sinus thrombosis
- 10-20% Portal vein thrombosis

Others

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

Who gets VITT?

- 4-21 days after Astra Zeneca vaccine
- Most previously healthy
- Ages 18-65 mostly
- Mean age in UK 48 years
- In UK M=F. In Germany M:F 1:9
- Most with 1st vaccine
- <5% had previous thrombosis.
- These are not people with comorbidities

Laboratory tests

- FBC – 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)

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

CASES of VITT reported to the MHRA, the UK regulator

Age range (years)	VITT cases	Fatal
18-29	24	6
30-39	31	8
40-49	38	7
50-59	68	15
60-69	36	8
70-79	25	4
80-89	5	1
90-99	1	0
Unknown	14	0
Total	**242**	**49 (20.2%)**

MHRA report 7 May 2021

Local VITT cases

Thrombosis type	Number
Cerebral venous sinus thrombosis	7
Splanchnic	1
PE	1
Aortic	1
VIT without thrombosis *	3

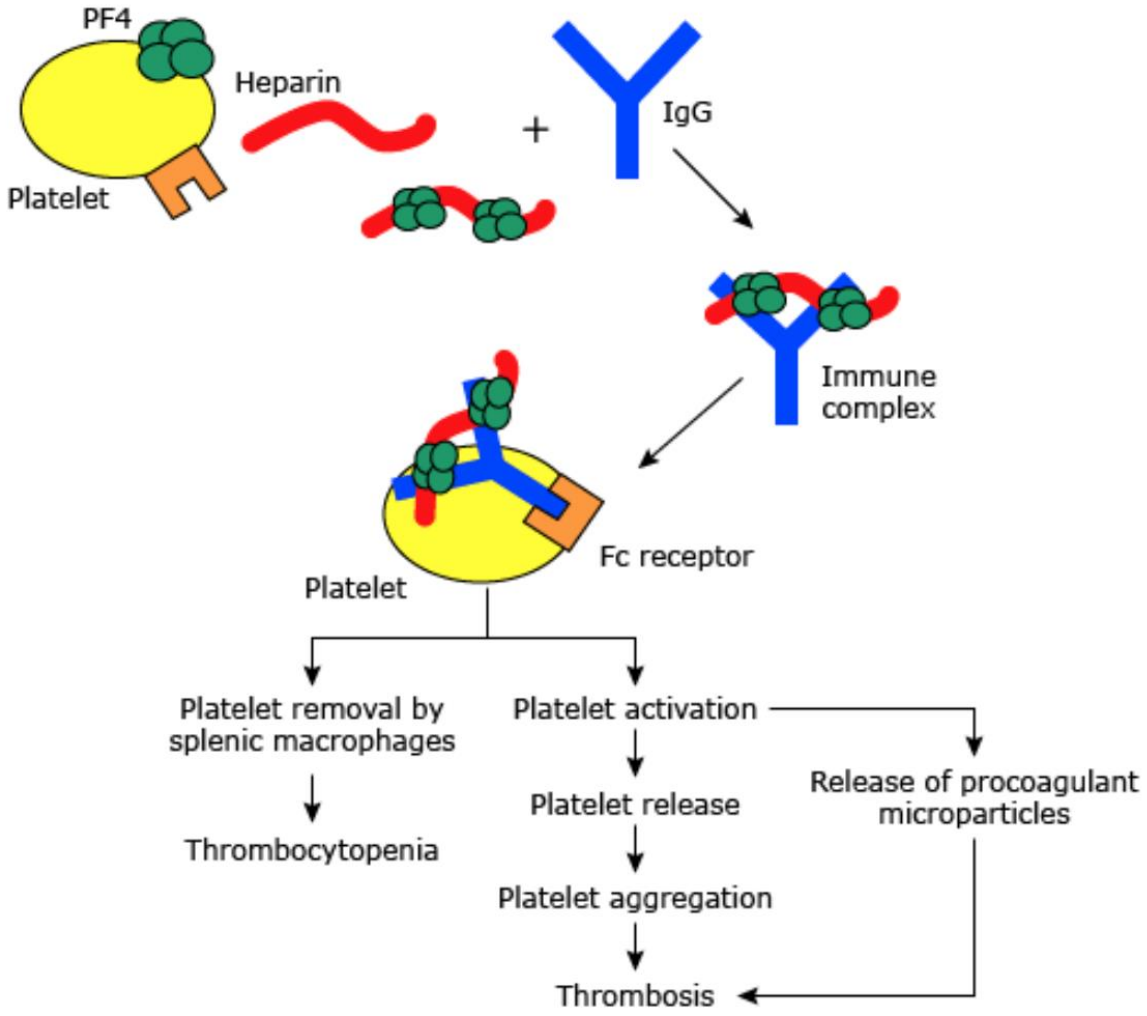
* VIT – thrombocytopenia, severe headaches with negative imaging, very high D-Dimer, very high anti-PF4

Heparin-induced thrombocytopenia (HIT)

- Thrombocytopenia 4-10 days after heparin exposure
- Unfractionated heparin > LMWH eg dalteparin
- Highly prothrombotic even with low platelets
- Bleeding is very infrequent even though most patients are post major surgery
- Antibodies against PF4-heparin complex

- Treated by avoiding platelets and heparin and giving argatroban
- Start warfarin when platelets >150 for at least 2 days

Mechanism of heparin induced thrombocytopenia (HIT)



Laura Ibsen slide from UptoDate

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]

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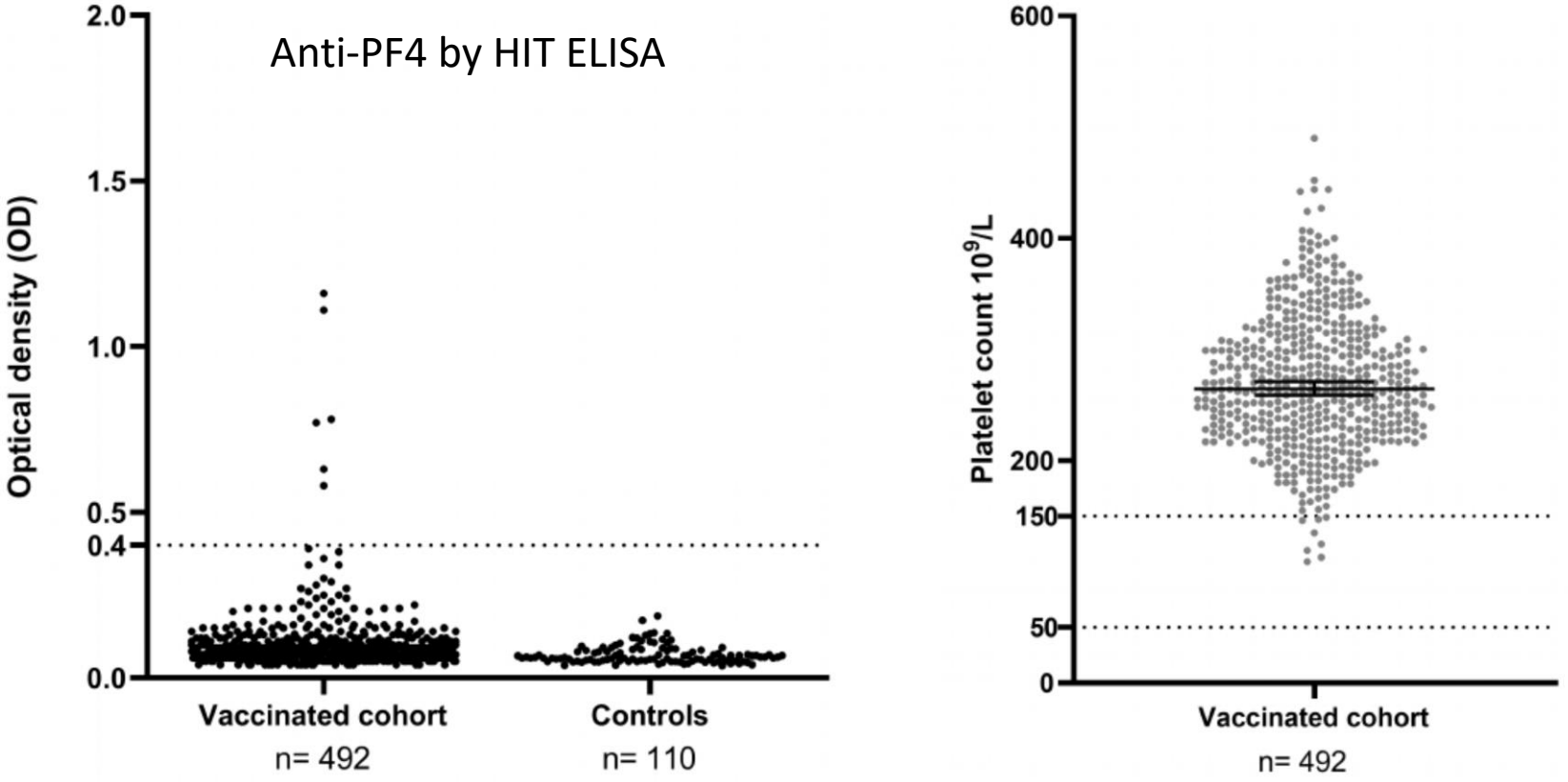
Warkentin T, et al. American Journal of Medicine 2008; 121:632-636

What causes VITT?

- Something in the adenoviral vaccines or something expressed by the infected cells
- Likely highly negatively charged (?free DNA)
- 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 bound to the receptor activate the platelets

Norway: 492 post AZ and 110 controls. No thrombosis



Sorvoll IH et al. RPTH 2021 (in press)

Management of acute VITT

- Avoid platelets
- Give intravenous immunoglobulin (IVIG)
- Avoid heparin and LMWH
- Give non-heparin anticoagulation
  - Argatroban, Fondaparinux, Apixaban, Rivaroxaban, Dabigatran
- Sometimes
  - Steroids
  - Plasma exchange
  - Rituximab

CVST themes

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

VITT incidence

Country	Incidence among AZ vaccinated persons
Norway	1 per 25,000
Germany	1 per 100,000
UK	1 per 95,000
Australia	1 per 125,000
India	0 officially reported after 111 million vaccinated
Sri Lanka	1 per 154,000 (vaccine manufactured in India)

Incidence of VITT in the UK

Date	VITT cases	Vaccinated with first AZ dose (in millions)	Rate
April 28	242	22.6	1 in 95,000
April 21	209	22.0	1 in 105,000
April 14	168	21.2	1 in 125,000
April 7	100	20.5	1 in 200,000
March 31	79	19.5	1 in 250,000
March 24	30	18.1	1 in 600,000

Data from the weekly MHRA adverse event reports

Ages for avoiding AZ vaccine in different countries

< 40 years	<50 years	<55 years	<60 years	<65 years
UK	Australia	Canada France	Germany Ireland Netherlands Spain	Finland Sweden

Norway and Denmark have stopped using AZ vaccine altogether

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

				Vaccine doses given in the UK (in millions)		
	VITT	**Neutropenia**	**ITP/ Thrombocytopenia**	**1st dose**	**2nd dose**	**Total**
Pfizer	0	27	106	11.4	8.1	19.5
AstraZeneca	242*	71	629	22.6	5.9	28.5
Moderna	0	0	0	0.1	0	0.1

Data from UK MHRA reports released 6th May 2021, covering period up to 28th April 2021

* 236 after 1st dose and 6 after 2nd dose

		Vaccine doses given in the UK (in millions)		
	Headache	**1st dose**	**2nd dose**	**Total**
Pfizer	12,916	11.4	8.1	19.5
AstraZeneca	63,393	22.6	5.9	28.5
Moderna	115	0.1	0	0.1

Data from UK MHRA reports released 6th May 2021, covering period up to 28th April 2021

Post vaccination headache

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

The Royal College of Emergency Medicine

sam THE SOCIETY FOR ACUTE MEDICINE

Royal College of Physicians

Guidance agreed with Expert Haematology Panel (EHP) April 10th 2021
Guidance agreed with British Society of Neuroradiologists (BSNR) and RCR April 11th 2021

Management of patients presenting to the Emergency Department/ Acute Medicine with symptoms

The condition of concern is **Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT)**

Post discharge following a VITT diagnosis

- Avoid 2nd dose of AZ vaccine
- Natural history unknown
- Antibodies persist for weeks/months
- No new thrombosis so far
- Thrombocytopenia and high D-Dimer have recurred in some
- Close observation with FBC and D-Dimer monitoring

Atypical VITT

- Outside the day 5-28 post vaccine window
- No proven thrombosis
- No thrombocytopenia, at least on admission
- Normal D-Dimer
- No anti-PF4 antibodies detected

Uncertainties

- What is the best treatment?
- Will early presentation reduce mortality?
- Role of anticoagulation when CVST and platelets <20
- Can we define a high risk group?
- Role of plasma exchange
- How long do the anti-PF4 antibodies last in VITT?
- Will this be a chronic disorder if the antibodies persist?
- Role of thrombectomy for CVST
- Role of neurosurgery for large bleeds post CVST

Twitter handle: @ProfMakris