

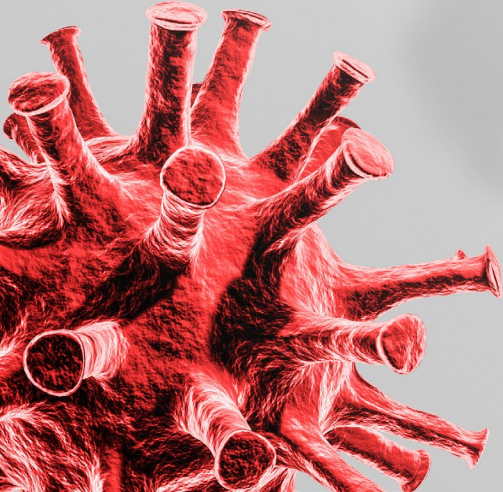
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# Thrombosis and COVID-19: vaccines

Professor Dr Saskia Middeldorp, internist  
Radboud umc,  
Nijmegen, Netherlands

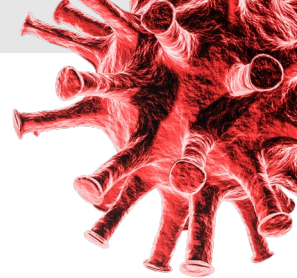
Radboudumc



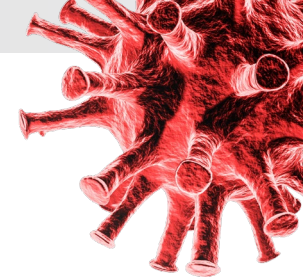
# Disclosures

Research support and lecture fees

- AbbVie
- Bayer
- BMS/Pfizer
- Boehringer Ingelheim
- Daiichi Sankyo
- GSK
- Portola
- Sanquin
- Sanofi



# Recent publicity



A man receives a dose of AstraZeneca's COVID-19 vaccine at a conference center in Rome on 24 March. Italy halted use of the vaccine on 15 March, but resumed immunizations 4 days later. ANTONIO MASELLO/GETTY IMAGES

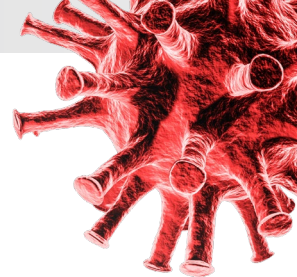
## A rare clotting disorder may cloud the world's hopes for AstraZeneca's COVID-19 vaccine

By Kai Kupferschmidt, Gretchen Vogel | Mar. 27, 2021, 10:20 AM

Kupferschmidt K and Vogel G. *Science*. 2021; <https://www.sciencemag.org/news/2021/03/rare-clotting-disorder-may-cloud-worlds-hopes-astrazenecas-covid-19-vaccine> [Last accessed May 2021]

# Outline

- Blood clots and COVID-19 vaccines
- VITT (aka VIPIT): vaccine-induced immune thrombotic thrombocytopenia
- Clinical presentation, mechanism and treatment





## AstraZeneca vaccine since December 2020 in UK and EU

- End of February > reports of unusual site thrombosis
- Enhanced pharmacovigilance by EMA > several pauses of AZ in several countries, Netherlands on 14 March
- No safety signal for classical VTE
- Mechanism for unusual site thrombosis described on 19 March (by 3 groups, independently)

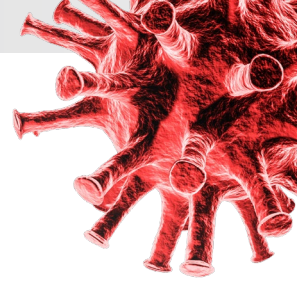
# Thrombocytopaenia, thrombosis and vaccines



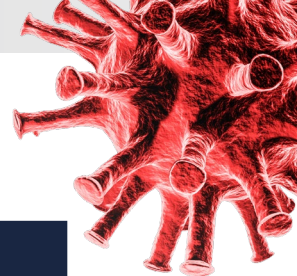
- Thrombocytopaenia combined with thrombosis, 4–28 days after vaccination
- Sometimes also accompanied by bleeding
- High death rate
- “Mainly in young women”

# Thrombocytopaenia

- ITP by antibodies against thrombocytes thrombocytin
- **Thrombocytopaenia, with or without thrombosis, by antibodies against PF4**
  - VIPIT
  - VITT







# Baseline characteristics

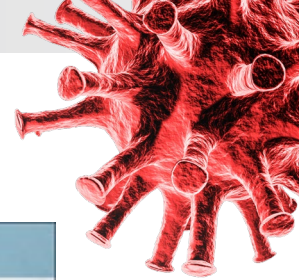
	Norway <sup>1</sup> n=5	Germany/Austria <sup>2</sup> n=11	UK <sup>3</sup> n=23
Age (years, range)	32–54	22–49	21–77
F:M	4:1	9:2	14:9
Time since vaccine (d, range)	7–10	5–16	6–12
Presents with bleeding	0	1	1
CVT/SVT/VTE/art	5/1/0/0	9/3/7/0	13/3/6/4
Thrombocytes, nadir	10–70	8–75	7–113
D-dimer peak (mg/L)	13→35	1.8→35	6–80
Fibrinogen (g/L)	0.8–2.3	0.4–5.7	<0.4–4.4
Died	3/5	6/10	7/23

art, arterial thrombosis; CVT, cerebral venous thrombosis; d, days; F:M, female to male ratio; SVT, superficial vein thrombosis; VTE, venous thromboembolism

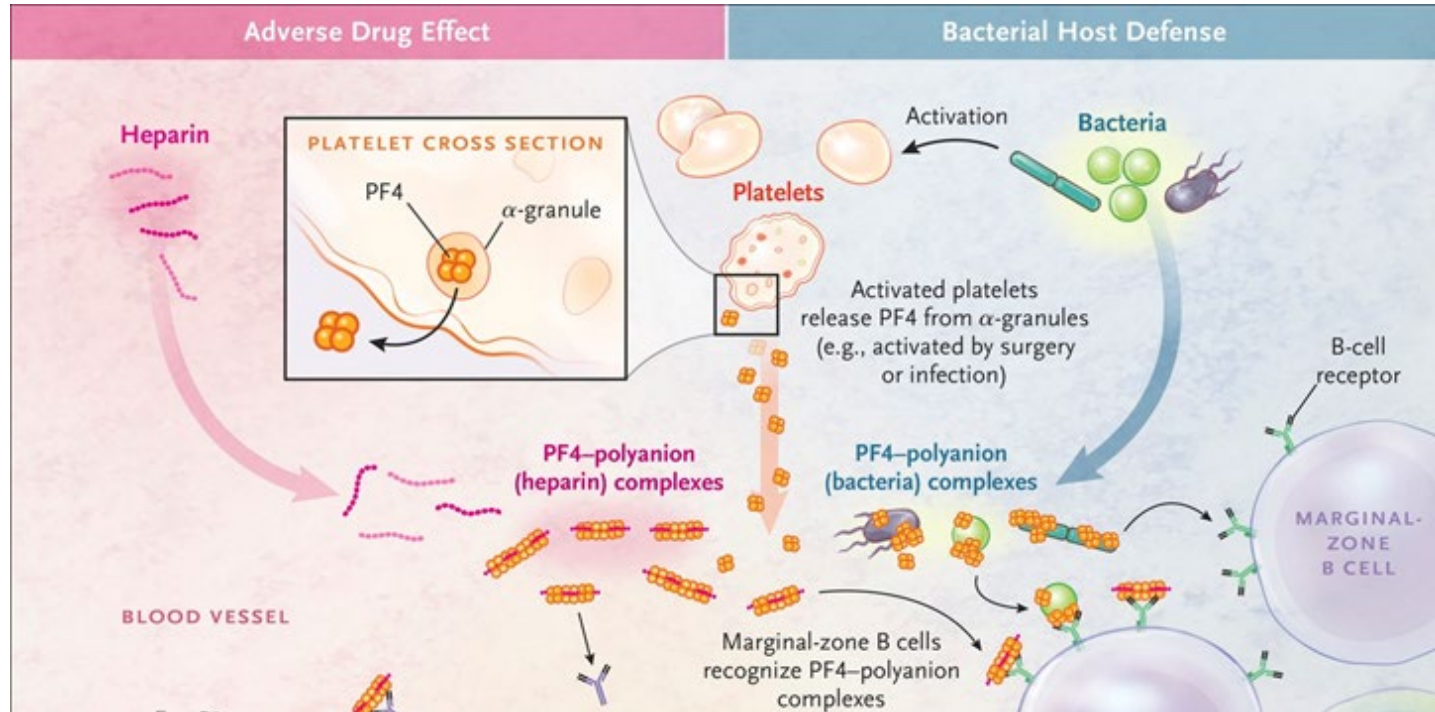
1. Schultz NH, et al. *N Engl J Med*. 2021; doi: 10.1056/NEJMoa2104882. Online ahead of print;

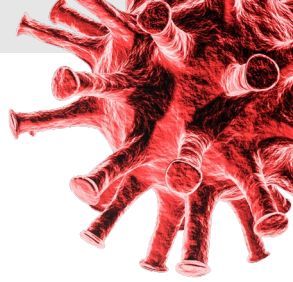
2. Greinacher A, et al. *N Engl J Med*. 2021; doi: 10.1056/NEJMoa2104840. Online ahead of print;

3. Scully M, et al. *N Engl J Med*. 2021; doi: 10.1056/NEJMoa2105385. Online ahead of print

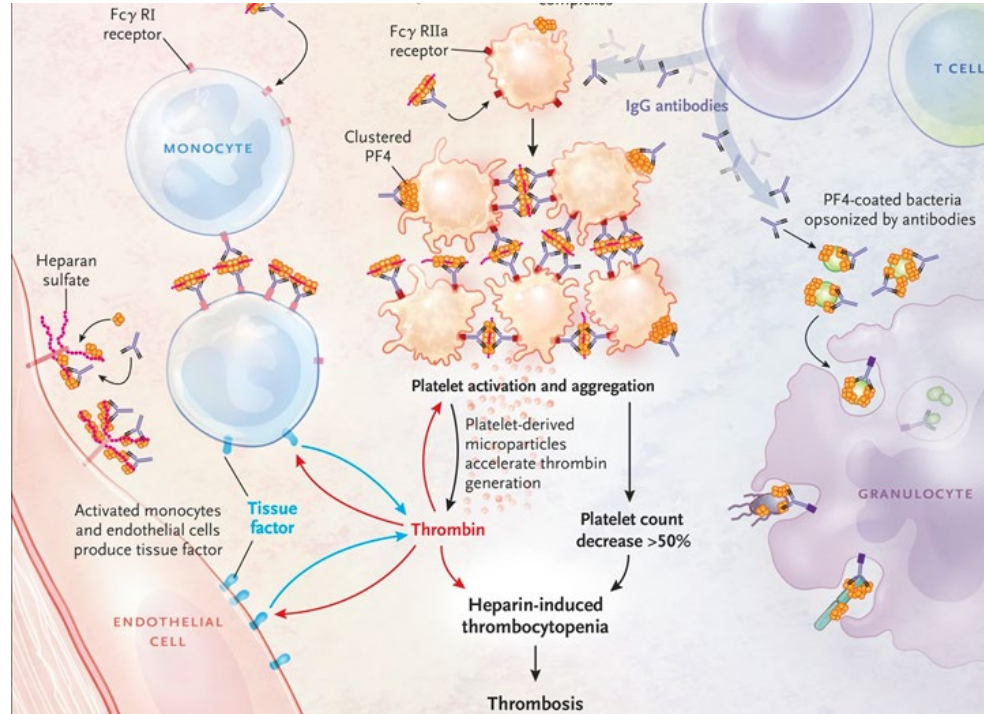


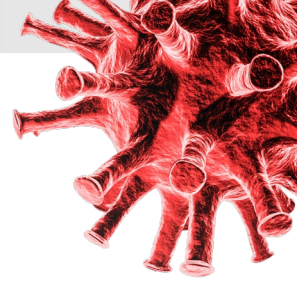
# Heparin-induced thrombocytopenia





# Heparin-induced thrombocytopenia

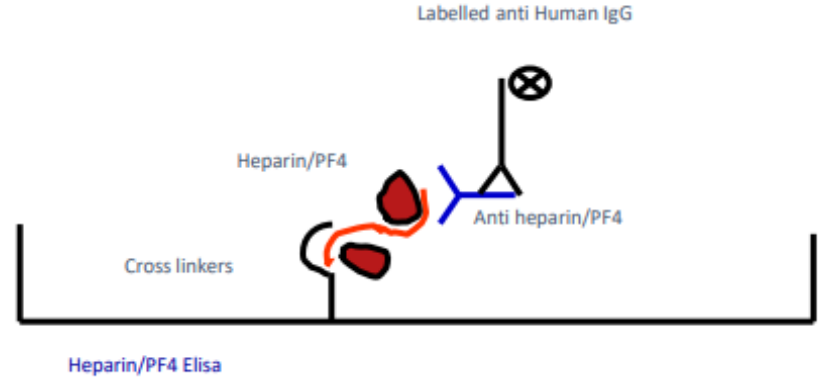


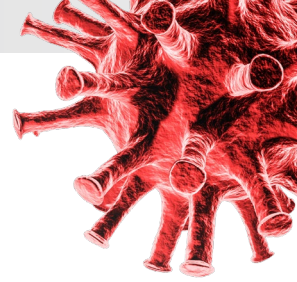


# Detection of PF4 antibodies; ELISA

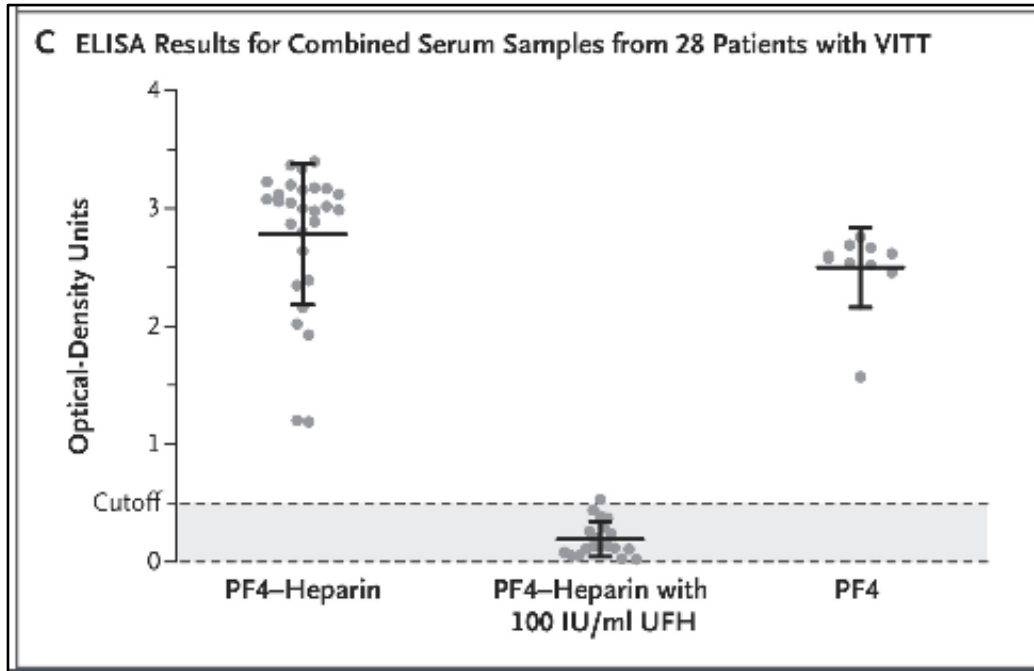
## HIT laboratory diagnostics

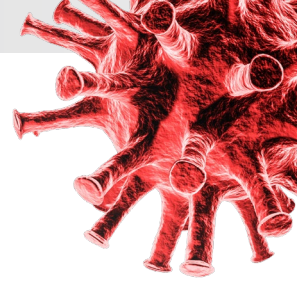
- Enzyme immunoassays:
  - High sensitivity
  - Do not differentiate between pathogenic antibodies and clinically irrelevant antibodies (low specificity)
  - IgG-specific methods are more specific than IgTotal methods
    - Only 50% of anti-PF4/heparin IgG antibodies are capable of platelet activation



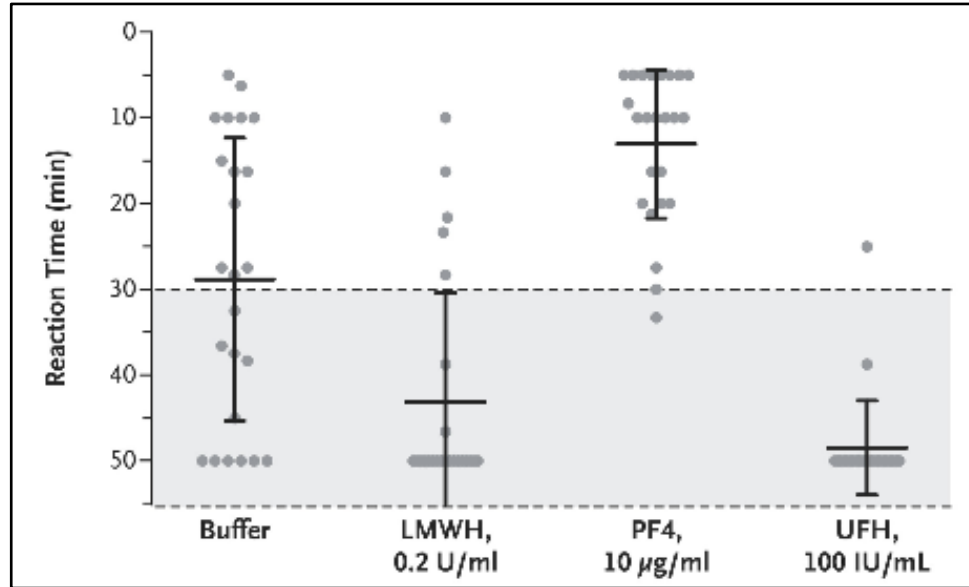


# ELISA results in patients with VITT

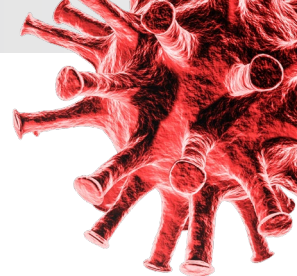




# HIPAA results in patients with clinical VITT



# Are HIT tests always positive?



The NEW ENGLAND JOURNAL of MEDICINE

- 23 patients
- 1 with negative test
- 1 with equivocal test

ORIGINAL ARTICLE

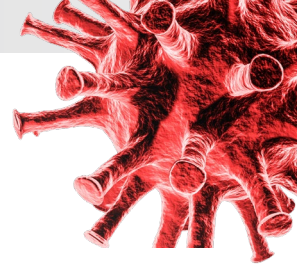
## Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

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.

MAT-GLB-2101946(V1.0) June 2021



# Can we expect the same with the Janssen vaccine?



*The NEW ENGLAND JOURNAL of MEDICINE*

Our case suggests that the rare occurrence of vaccine-induced immune thrombotic thrombocytopenia could be related to adenoviral vector vaccines.

Kate-Lynn Muir, D.O.  
Avyakta Kallam, M.B., B.S.  
Scott A. Koepsell, M.D., Ph.D.  
Krishna Gundabolu, M.B., B.S.  
University of Nebraska Medical Center  
Omaha, NE

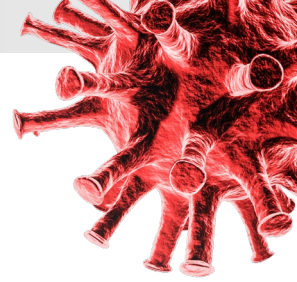
**Thrombotic T**

**US Vaccination**



# To put some risks into perspective

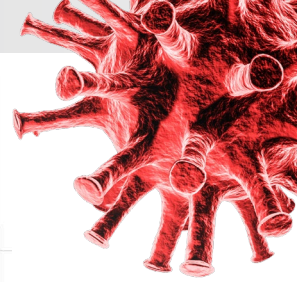
- Thrombosis and pulmonary embolism: 2 per 1000 per year<sup>1</sup>
- Cerebral venous thrombosis: 2 to 3 per 100,000 per year<sup>2</sup>
- Oral contraceptives: 5 per 10,000 young women (aged 20–30) per year<sup>3</sup>
- Pregnancy: 1 to 2 per 1000<sup>3</sup>
- Air travel: 1 per 4600 flights (>4 hours)<sup>4</sup>



# Recent COVID-19 Vaccination with the last 20 days

## Laboratory Investigations:

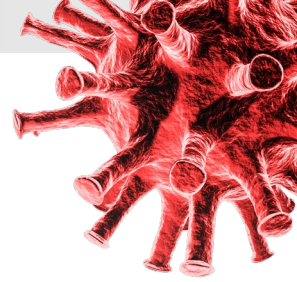
Platelet count, activated partial prothrombin time, partial thromboplastin time, fibrinogen, D-Dimer



Low platelet count, Abnormal coagulation, with thrombosis	Low platelet count, Abnormal coagulation, No bleeding or thrombosis	Low platelet count; Normal coagulation parameters, with bleeding	Low platelet count, Normal coagulation parameters, No bleeding or thrombosis																		
VITT-Testing		Autoantibody testing	Monitoring																		
Blood collection before therapy																					
<p><b>Recommended laboratory methods:</b></p> <ol style="list-style-type: none"> <li>Antigen-binding assay (ELISA) for PF4/heparin antibodies: ELISA testing</li> <li><b>NOTE: rapid immunoassay (RIA), Chemiluminescence Immunoassay (CLIA) may reveal false-negative results</b></li> <li>Functional platelet activation assay (SRA, HIPA, PAT, HIMEA, PEA, PF4-SRA, PF4-HIPA and PF4/heparin-SRA)</li> </ol> <p style="text-align: center;">↓ <b>Anti-PF4/heparin-ELISA testing</b></p> <table border="0" style="width: 100%;"> <tr> <td style="width: 50%; text-align: center; background-color: #e0ffe0;">negative</td> <td style="width: 50%; text-align: center; background-color: #ffe0e0;">positive</td> </tr> <tr> <td style="text-align: center;">↓ <b>VITT unlikely</b></td> <td style="text-align: center;">↓ <b>VITT likely</b></td> </tr> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>➤ Rule out false-negative results</li> <li>➤ Anticoagulation with heparin possible</li> <li>➤ Re-evaluation of clinical symptoms</li> </ul> </td> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>➤ Functional platelet activation testing</li> <li>➤ Avoid anticoagulation with heparin</li> </ul> </td> </tr> </table> <p style="text-align: center;">↓ <b>Functional platelet activation testing</b></p> <table border="0" style="width: 100%;"> <tr> <td style="width: 50%; text-align: center; background-color: #e0ffe0;">negative</td> <td style="width: 50%; text-align: center; background-color: #ffe0e0;">positive</td> </tr> <tr> <td style="text-align: center;">↓ <b>VITT unlikely</b></td> <td style="text-align: center;">↓ <b>VITT confirmed</b></td> </tr> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>➤ Re-evaluation of clinical symptoms</li> </ul> </td> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>➤ Non-heparin anticoagulation</li> <li>➤ Consider high dose IVIG</li> </ul> </td> </tr> </table>		negative	positive	↓ <b>VITT unlikely</b>	↓ <b>VITT likely</b>	<ul style="list-style-type: none"> <li>➤ Rule out false-negative results</li> <li>➤ Anticoagulation with heparin possible</li> <li>➤ Re-evaluation of clinical symptoms</li> </ul>	<ul style="list-style-type: none"> <li>➤ Functional platelet activation testing</li> <li>➤ Avoid anticoagulation with heparin</li> </ul>	negative	positive	↓ <b>VITT unlikely</b>	↓ <b>VITT confirmed</b>	<ul style="list-style-type: none"> <li>➤ Re-evaluation of clinical symptoms</li> </ul>	<ul style="list-style-type: none"> <li>➤ Non-heparin anticoagulation</li> <li>➤ Consider high dose IVIG</li> </ul>	<p><b>Recommended laboratory methods:</b></p> <ol style="list-style-type: none"> <li>MAIPA, MAPA, PABA, flow cytometry</li> <li>If available: with and without vaccine in the tests</li> </ol> <table border="0" style="width: 100%;"> <tr> <td style="width: 50%; text-align: center; background-color: #e0ffe0;">negative</td> <td style="width: 50%; text-align: center; background-color: #ffe0e0;">positive</td> </tr> <tr> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> </tr> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>➤ consider other diagnoses</li> <li>➤ Rule out false negative results</li> </ul> </td> <td style="vertical-align: top;"> <ul style="list-style-type: none"> <li>➤ consider IVIG</li> <li>➤ Check coagulation during treatment</li> </ul> </td> </tr> </table>	negative	positive	↓	↓	<ul style="list-style-type: none"> <li>➤ consider other diagnoses</li> <li>➤ Rule out false negative results</li> </ul>	<ul style="list-style-type: none"> <li>➤ consider IVIG</li> <li>➤ Check coagulation during treatment</li> </ul>	<p>Continue monitoring of clinical and laboratory parameters and manage according to the local guidelines for thrombocytopenia</p>
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# Treatment

- Avoid heparin
- Treat thrombosis with alternative anticoagulants
  - Fondaparinux, argatroban, bivalirudin
  - DOACs
- Immunoglobulines (IVIG); consider prednisone?
- Avoid platelet transfusions, unless severe bleeding and after IVIG



# What's next?

- More epidemiology
  - EMA database for CSVT currently scrutinised
  - Age and sex-stratification
  - Risk factors
- More insights into mechanisms > vaccine development
- Improving prognosis by earlier recognition

