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Partnering for Education & Optimizing Treatment in ImmunoScience

COVID-19

Infection, vaccination and thromboembolic events

Kristin Jochmans
Universitair Ziekenhuis Brussel

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Outline

1. Epidemiology and clinical presentation
2. Pathophysiology
3. Management
4. Summary & Take home messages

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Epidemiology and clinical presentation of thromboembolic events during COVID-19 infection

Coagulopathy in COVID-19

First reports

Received: 13 February 2020 | Accepted: 18 February 2020

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jth

BRIEF REPORT

Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang[1] | Dengju Li[2] | Xiong Wang[1] | Ziyong Sun[1]

Coagulopathy in COVID-19

Conventional coagulation parameters and outcomes

183 consecutive patients in Tongji hospital (Wuhan, China) with confirmed SARS-Coronavirus pneumonia

- Overall mortality: 11.5%
- 71.4% of non-survivors and 0.6% survivors met the ISTH-criteria of disseminated intravascular coagulation (DIC) during their hospital stay

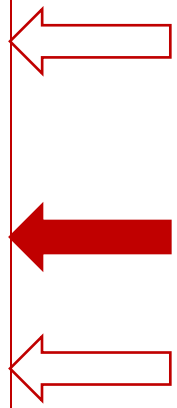
Tang N, et al. J Thromb Haemost 2020;18:844–847

Coagulopathy in COVID-19

DIC score* ≥ 5 = overt DIC

TABLE 2 The grade of DIC in non-survivors with NCP (n = 21)

	Number of patients (%)
Platelet counts ($\times 10^9$/L)	
50-100 (1 point)	7 (33.3)
<50 (2 points)	5 (23.8)
D-dimer (μg/mL)	
1.0-3.0 (2 points)	3 (14.3)
>3.0 (3 points)	18 (85.7)
Fibrinogen (g/L)	
<1.0 (1 point)	6 (28.6)
Prolongation of PT (sec)	
3-6 (1 point)	5 (23.8)
>6 (2 points)	10 (47.6)
Meeting the ISTH criteria of DIC (Total points ≥5)	15 (71.4)



* International Society on Thrombosis and Haemostasis (ISTH) - Diagnostic criteria for disseminated intravascular coagulation: Toh et al. J Thromb Haemost 2007;5:604–6
Tang N, et al. J Thromb Haemost 2020;18:844–847

Coagulopathy in COVID-19

Conventional coagulation parameters and outcomes

- Non-survivors ↔ survivors (parameters on admission):

  significantly higher D-dimer levels

- Elevated DIC score mainly driven by very high D-dimer (in 85,7%)

  while only 28,6% with low fibrinogen and 23,8% with platelets < $50x10^9$/L

► Thus, no classical presentation of DIC

Tang N, et al. J Thromb Haemost 2020;18:844–847

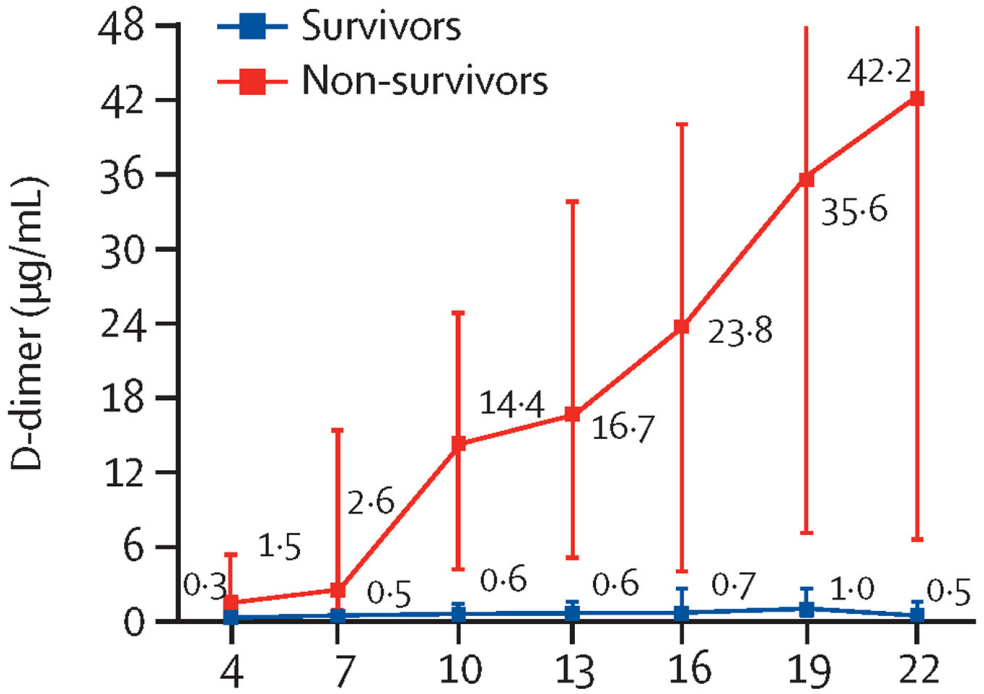
Coagulopathy in COVID-19

D-dimer levels (survivors vs non-survivors)

191 hospitalized COVID-19 patients

in Jinyintan Hospital and Wuhan

Pulmonary Hospital in Wuhan, China



Zhou F, et al. Lancet 2020;395:1054-1062

Thromboembolic complications in COVID-19

High incidence of thrombotic complications reported, if critically ill and hospitalized

- Major arterial and cardiovascular events (acute limb ischemia, mesenteric ischemia, myocardial infarction, acute cerebrovascular accident)
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)

Avila J, et al. Am J Emerg Med 2021;39:213–8; Poissy J, et al. Circulation 2020;142:184-6; Klok F, et al. Thromb Res 2020;191:148-50; Suh YJ, et al. Radiology 2021;298:E70-80, Middeldorp S, et al, J Thromb Haemost 2020;18:1995-2002,

Incidence of thromboembolic complications in COVID-19

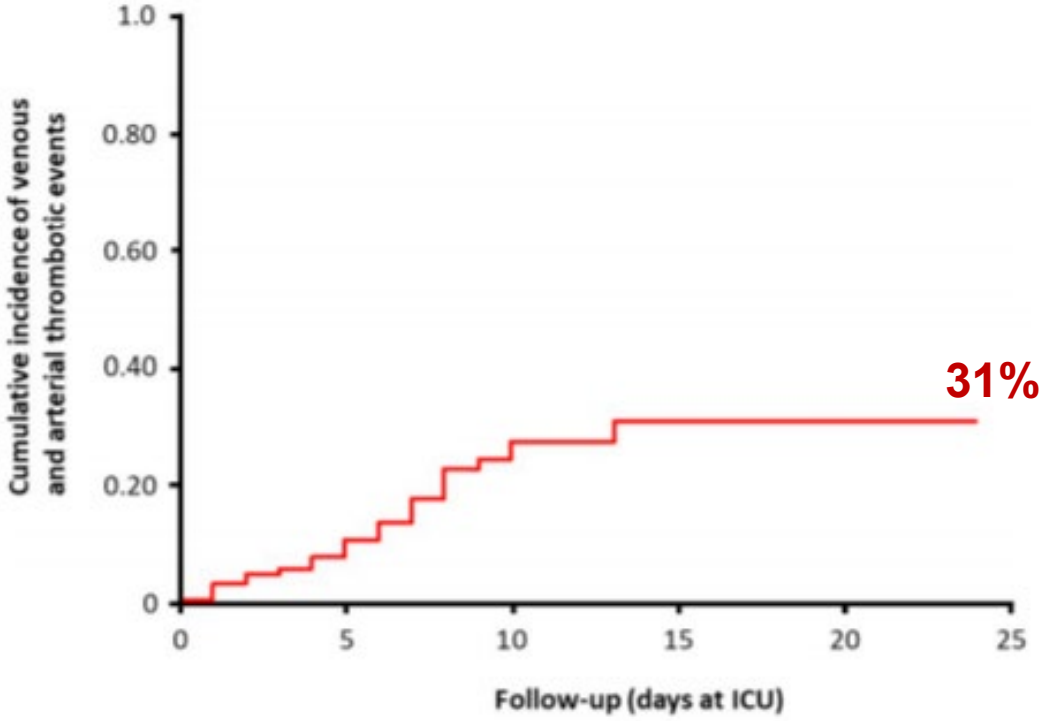
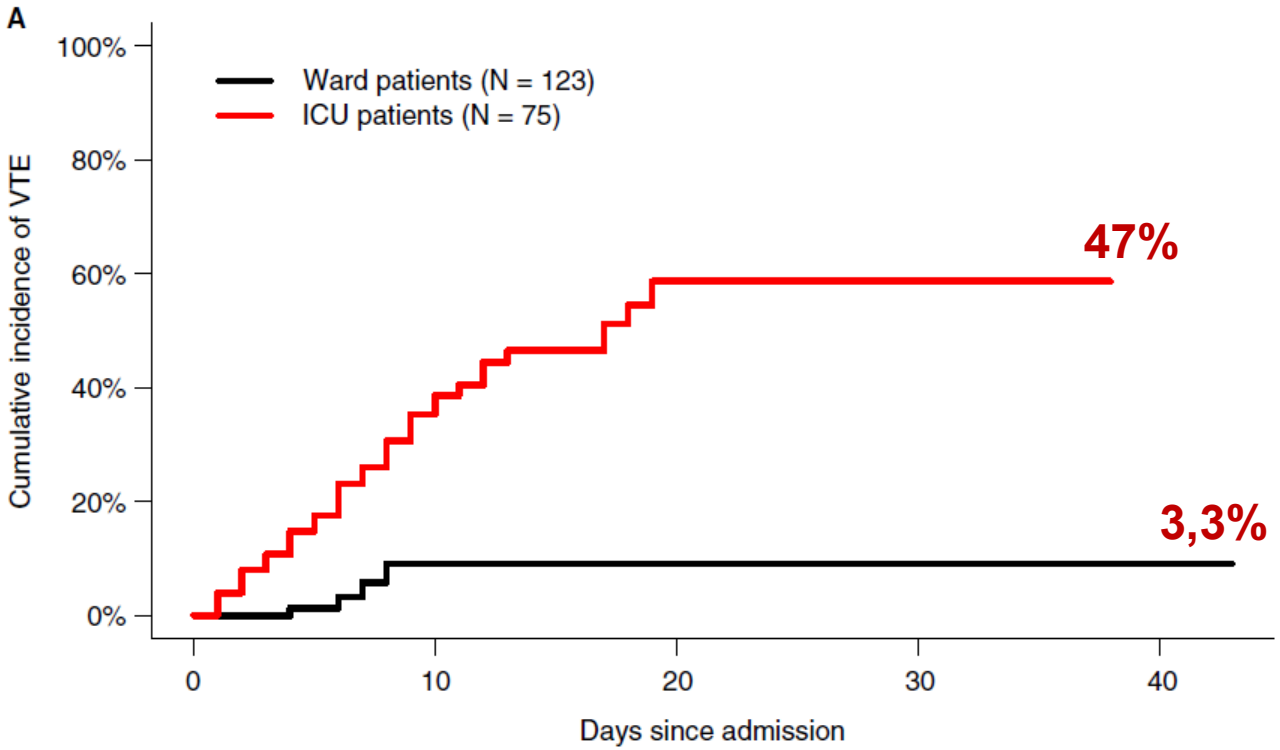


Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.



High incidence of **venous and arterial** complications among **ICU**-hospitalized COVID-19 patients, despite prophylaxis

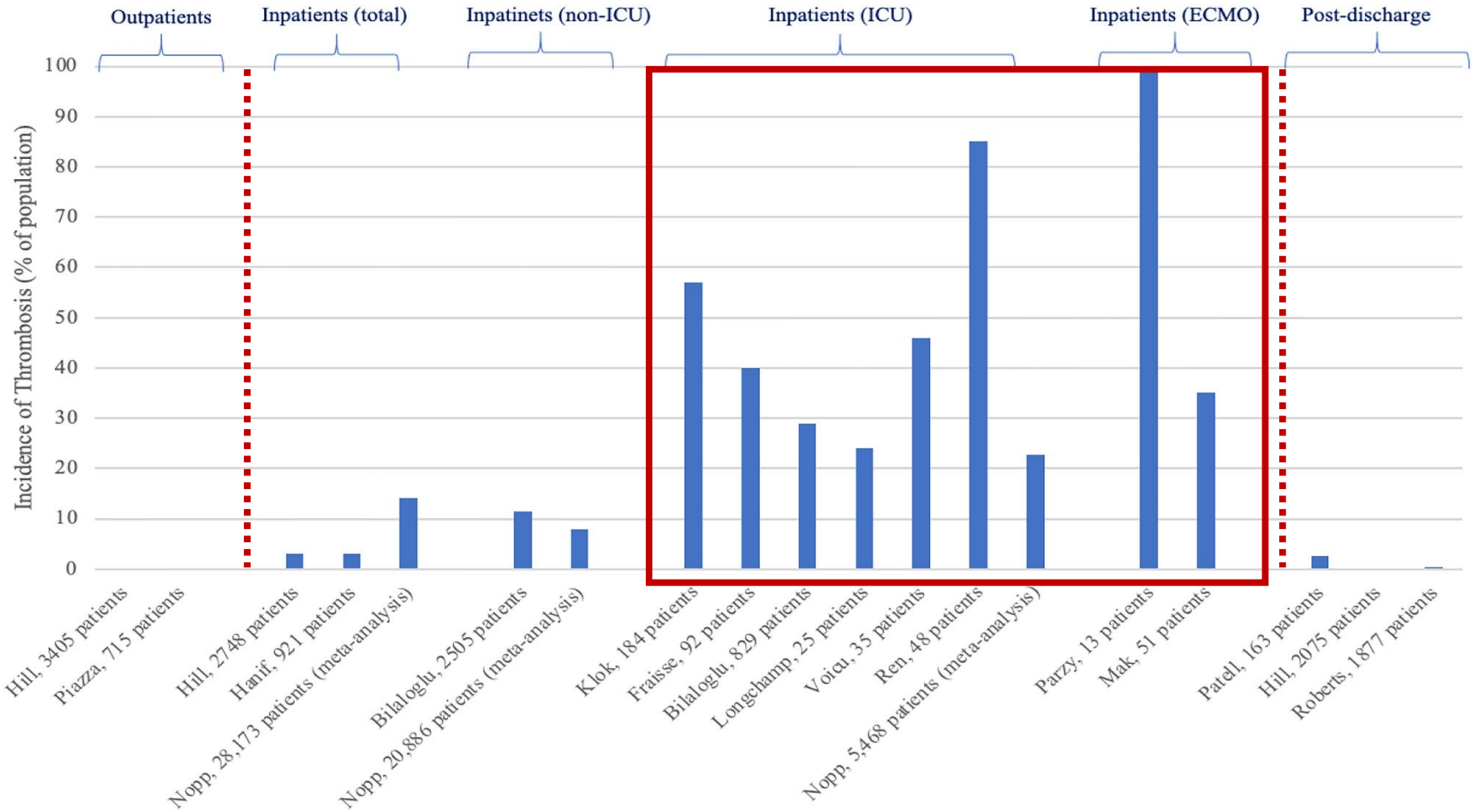
High incidence of **VTE** among **hospitalized** COVID-19 patients, despite prophylaxis

Klok F, et al. Thromb Res 2020;191:148-50

Middeldorp S, et al, J Thromb Haemost 2020;18:1995-2002

Incidence of thromboembolic complications in COVID-19

Venous and arterial thrombotic complications (review, 14 studies)



ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Jenner W and Gorog DA. J Thromb Thrombolysis 2021;1-8. doi: 10.1007/s11239-021-02475-7 [Online ahead of print]On behalf of ICODE: The International COVID-19 Thrombosis Biomarkers Colloquium, UK

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Epidemiology and clinical presentation of thromboembolic events after COVID-19 vaccination

Vaccine-induced immune thrombotic thrombocytopenia (VITT)

Germany
Austria

The NEW ENGLAND JOURNAL of MEDICINE

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

Norway

The NEW ENGLAND JOURNAL of MEDICINE

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.

UK

The NEW ENGLAND JOURNAL of MEDICINE

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.

US

Original Investigation

April 30, 2021

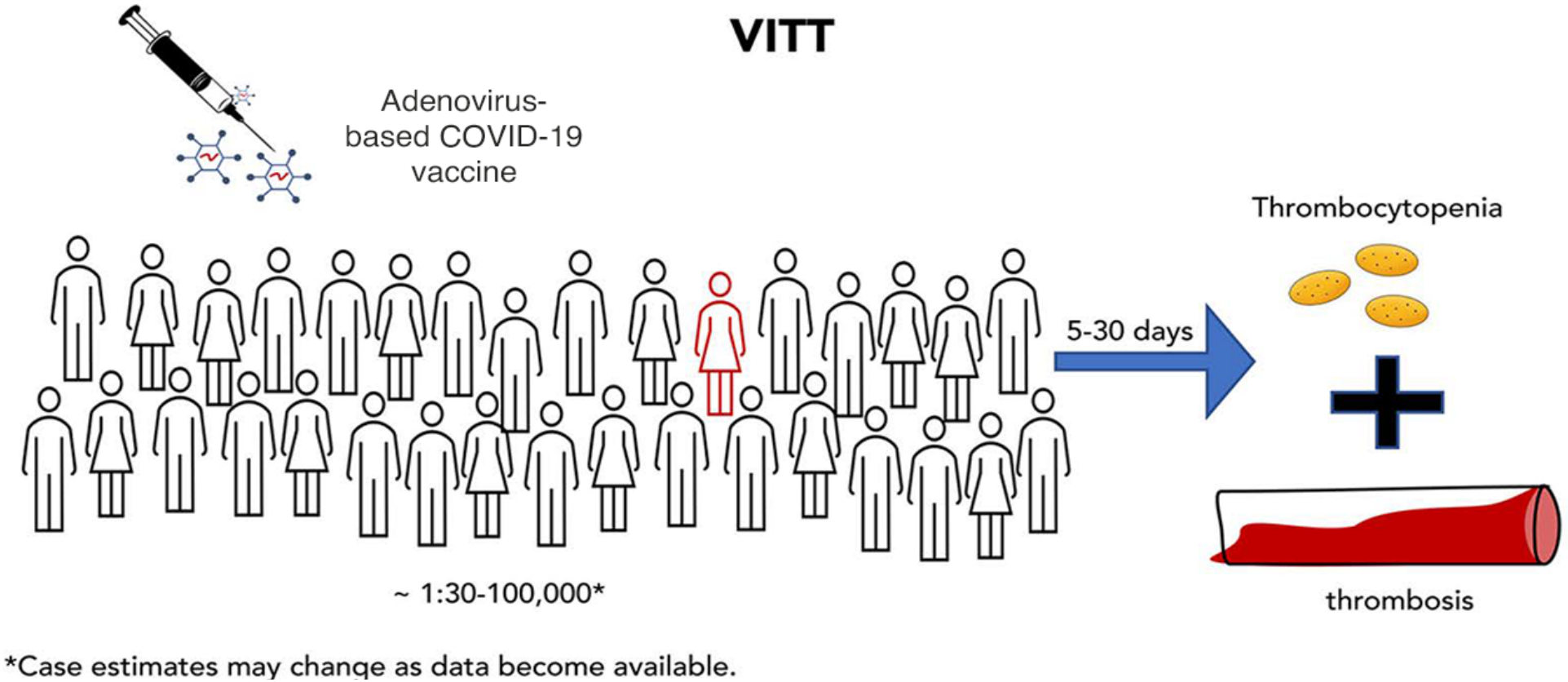
US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021

Isaac See, MD[1]; John R. Su, MD, PhD, MPH[1]; Allison Lale, MD, MPH[1]; et al

» Author Affiliations | Article Information

JAMA. 2021;325(24):2448-2456. doi:10.1001/jama.2021.7517

Incidence of VITT



VITT, vaccine-induced thrombotic thrombocytopenia.

Clinical presentation of VITT

- Age: median 48 years (range 18 - 79 years)
- Sex: 55 % female, 45 % male
- Time since vaccination: median 14 days (range 5 - 48 days)
- Thrombosis
- Platelet count: often < 150,000/µL
- D-dimer: very high

VITT, vaccine-induced thrombotic thrombocytopenia.
Pavord S, et al. N Engl J Med 2021; DOI: 10.1056/NEJMoa2109908
Arepally GM and Ortel TL. Blood 2021;138:293-298..

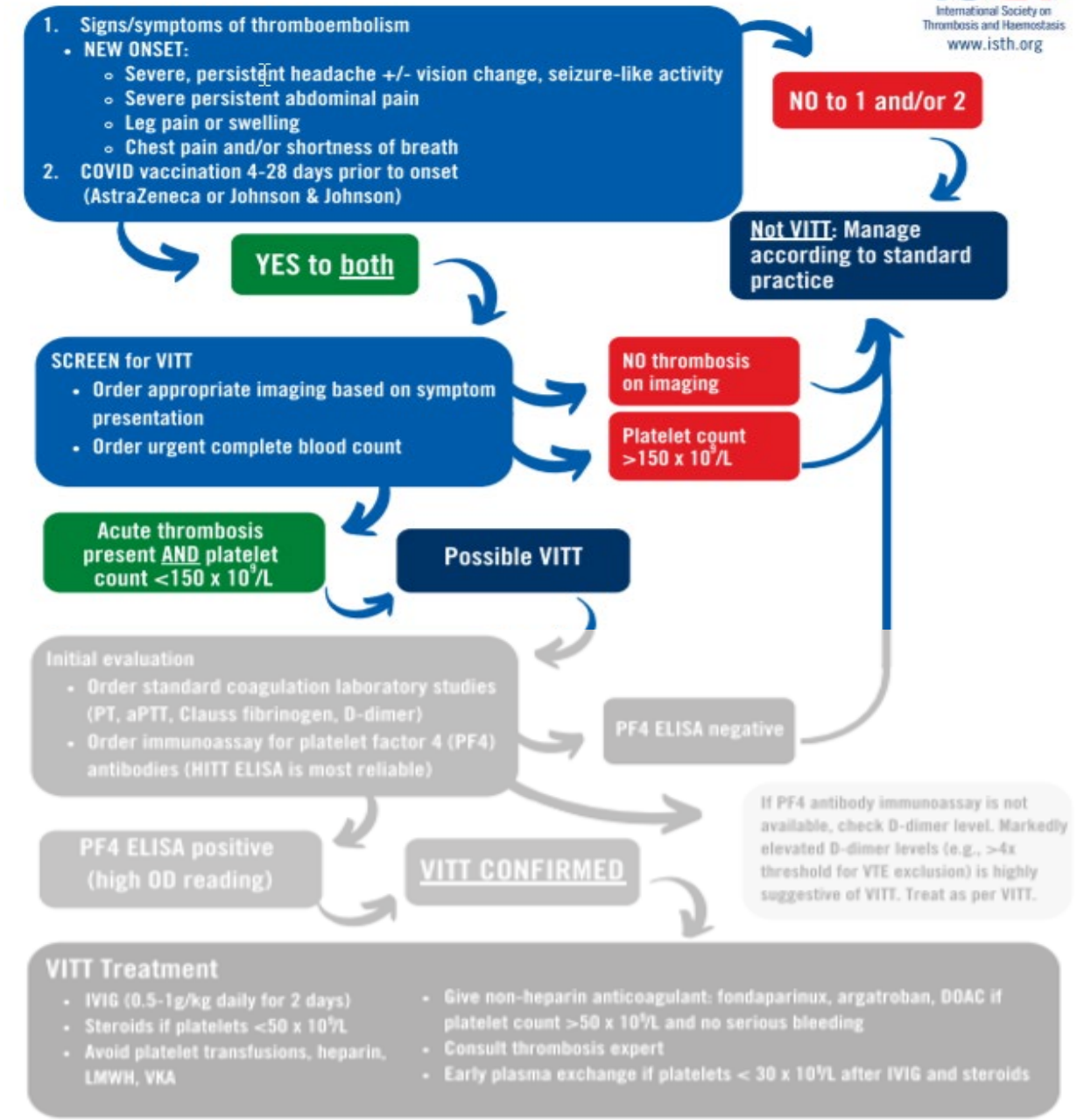
Clinical presentation of VITT

- Site(s) of thrombosis:
  - Cerebral veins (including intracranial hemorrhage),
  - Splanchnic veins (portal, splenic, mesenteric)
  - Deep veins of the leg, pulmonary embolism
  - Often thrombosis at multiple sites
- Symptoms
  - Severe headache, visual changes, nausea and vomiting
  - Abdominal pain, back pain
  - Leg pain or swelling, shortness of breath
  - Petechiae, easy bruising, or bleeding

VITT, vaccine-induced thrombotic thrombocytopenia.
Pavord S, et al. N Engl J Med 2021; DOI: 10.1056/NEJMoa2109908
Arepally GM and Ortel TL. Blood 2021;138:293-298..

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Diagnostic Flow Chart (Updated 20 April, 2021)

ISTH International Society on Thrombosis and Haemostasis www.isth.org



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Pathophysiology of thrombotic events

during COVID-19 infection

Coagulopathy in COVID-19

Pathogenesis not fully elucidated yet!

Clinical outcome determined by

- host reaction (= *damage-associated*)
- viral virulence (= *pathogen-associated*)

Coagulopathy in COVID-19

Host reaction = inflammation and cytokine storm

Activation of innate immunity → cytokine release (IL-6, IL-1b, TNF,…),

promoting hypercoagulable status

- Upregulation of tissue factor
- Increased synthesis of coagulation factors (FVIII, fibrinogen)
- Activation of endothelial cells – endothelial dysfunction
- Vascular permeability, leakage at endothelial layer
- Activation of platelets, lymphocytes, neutrophils (NETosis)
- …

Lazzaroni MG, et al. Blood Reviews 2021; 46; 100745
Libby P and Lüscher T. Eur Heart J 2020; 41:3038-3044

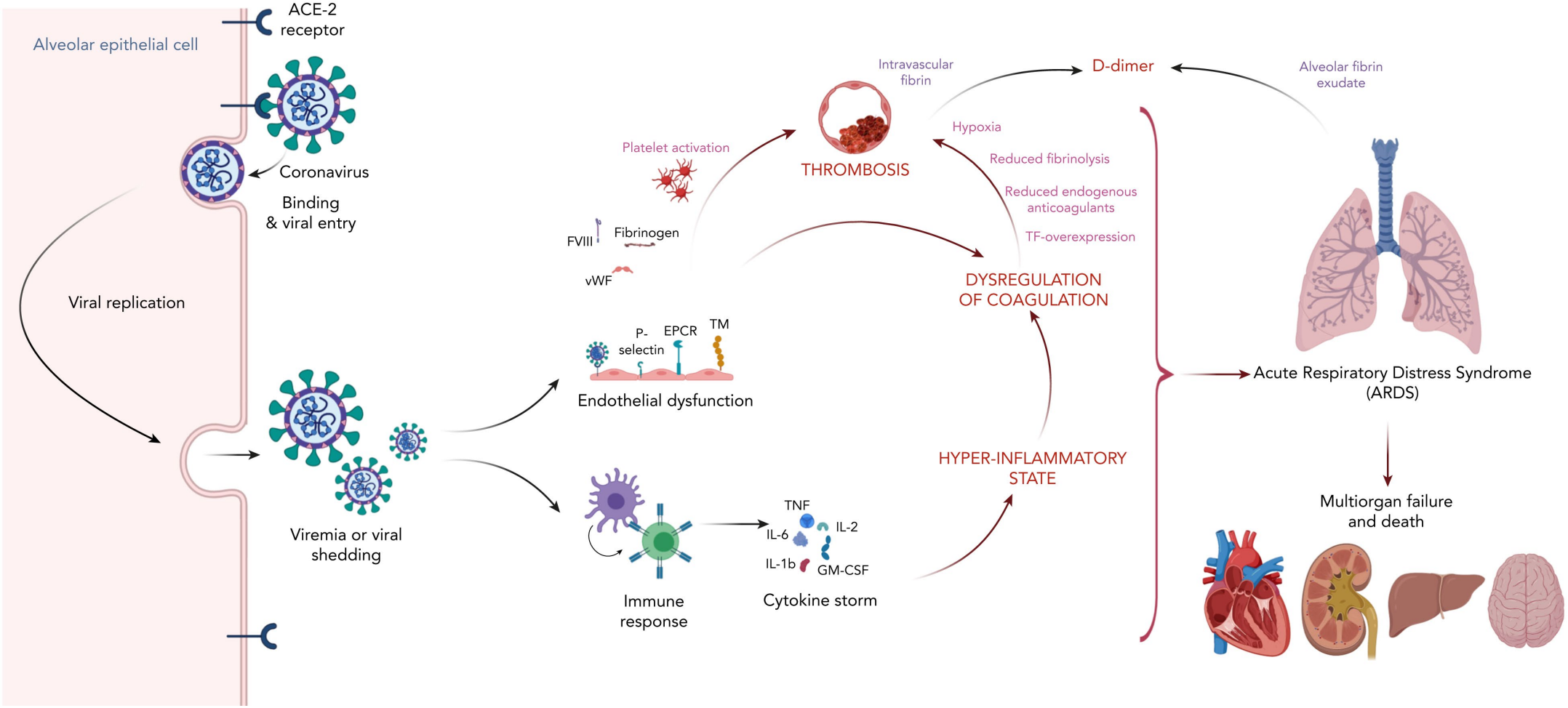
Coagulopathy in COVID-19

Virus-specific mechanisms

- Binding on Angiotensin Converting Enzyme II (ACE-2) receptor activating Renin-Angiotensin System: platelet adhesion and aggregation
- Direct infection of endothelial cells, myocytes
- Dysregulation of Plasminogen Activator/Inhibitor system: imbalance of fibrinolysis
- …

Lazzaroni MG, et al. Blood Reviews 2021; 46; 100745
Libby P and Lüscher T. Eur Heart J 2020; 41:3038-3044

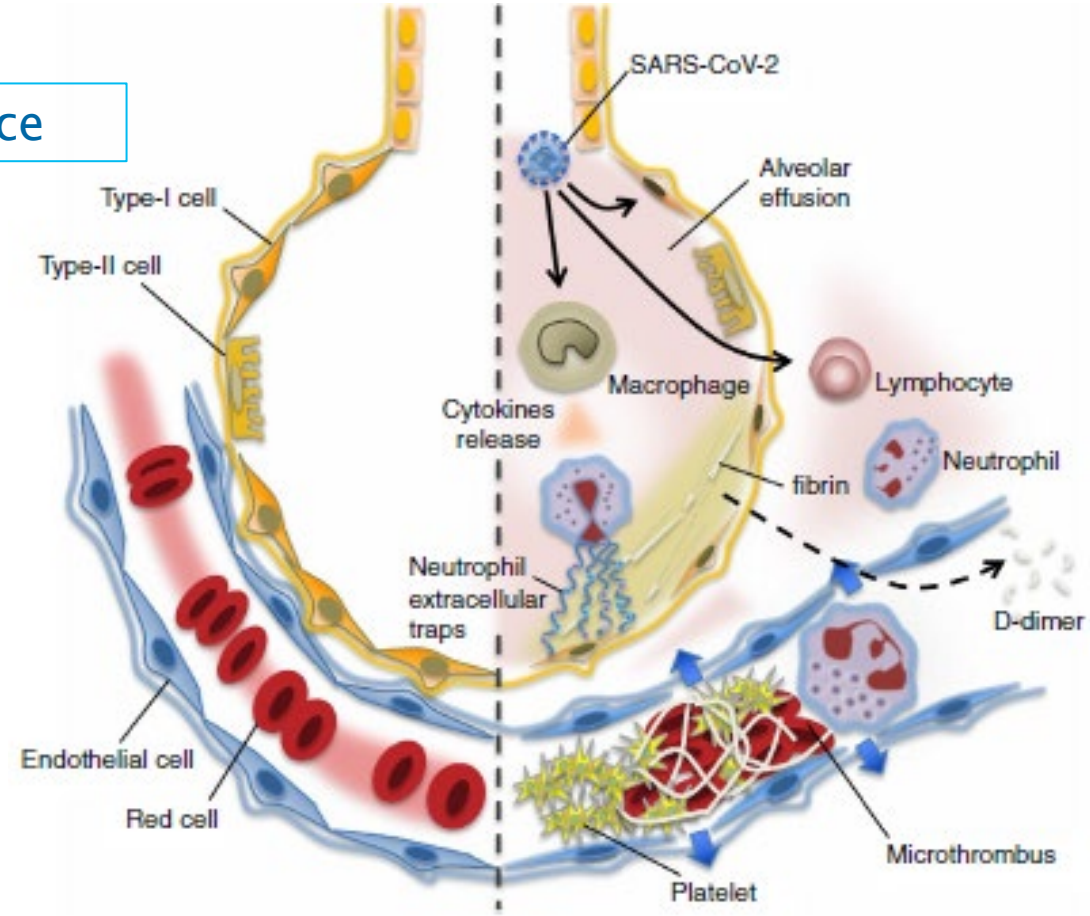
Coagulopathy in COVID-19



Chan N and Weitz J. Blood 2020;136:381–3.

Coagulopathy in COVID-19

Alveolar space



Iba T et al. J Thromb Haemost 2020;18:2103-2109

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Pathophysiology of thrombotic events

after COVID-19 vaccination

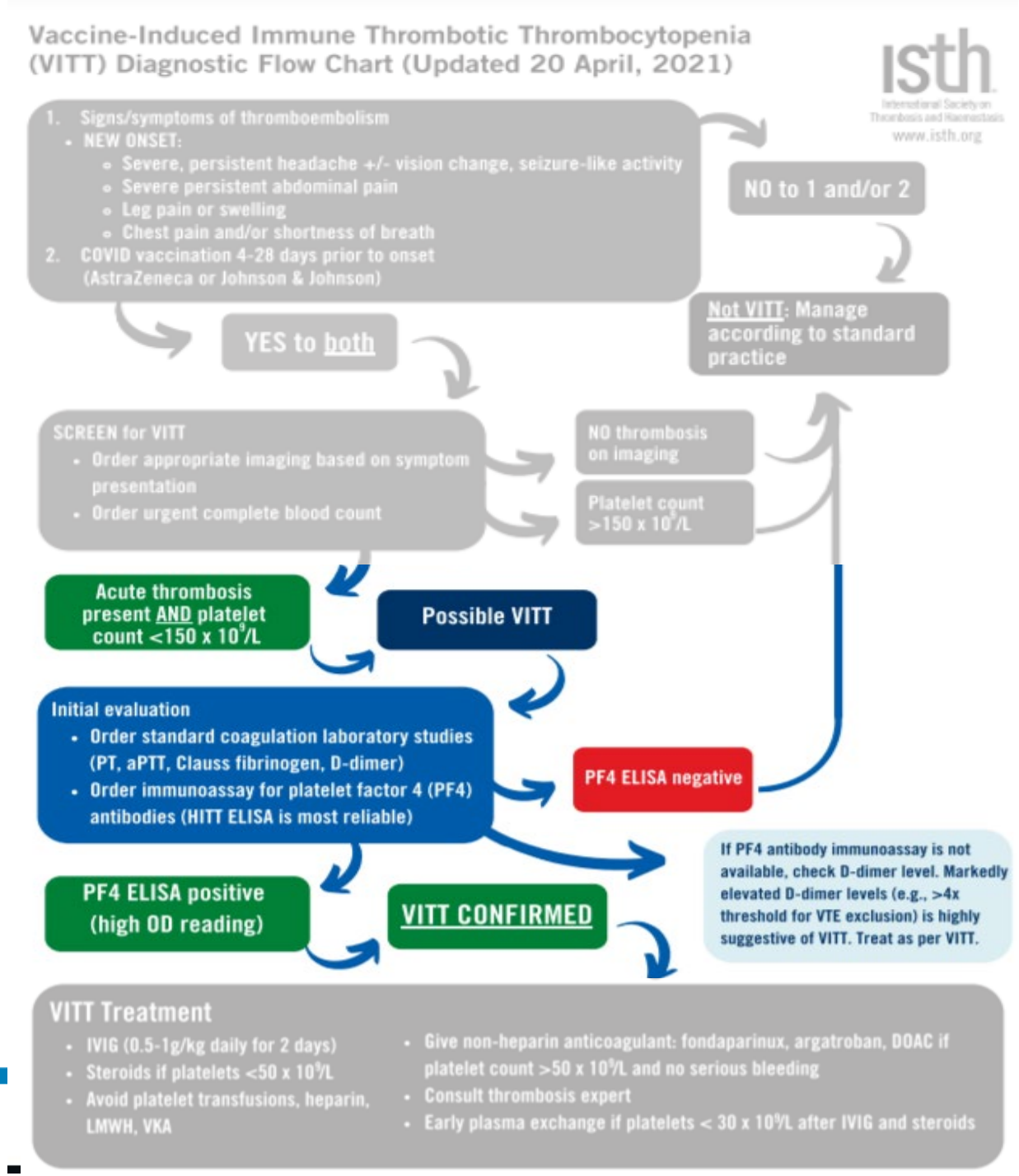
VITT: suggested pathogenesis

- Immune complication resembling variant of autoimmune heparin-induced thrombocytopenia (aHIT):
  - Circulating IgG anti-platelet factor 4 (PF4) antibodies
  - Thrombocytopenia
  - Thrombosis
  - But… no previous exposure to heparin

- Pathogenic anti-PF4/heparin antibodies cross-link FcγRIIA on platelets, monocytes and neutrophils

→ procoagulant cellular responses leading to severe hypercoagulable state

Arepally GM and Ortel TL. Blood 2021;138:293-298; Greinacher A, et al. N Engl J Med 2021;384:2092-101; Schultz N, et al. N Engl J Med 2021; 384:2124-30; Scully M, et al. N Engl J Med 2021; 384:2202-2211; Arepally GM and Padmanabhan A. Arterioscler Thromb Vasc Biol 2021;41:141-152


Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Diagnostic Flow Chart (Updated 20 April, 2021)
isth
International Society on Thrombosis and Haemostasis
www.isth.org
1. Signs/symptoms of thromboembolism
• NEW ONSET:
◦ Severe, persistent headache +/- vision change, seizure-like activity
◦ Severe persistent abdominal pain
◦ Leg pain or swelling
◦ Chest pain and/or shortness of breath
2. COVID vaccination 4-28 days prior to onset (AstraZeneca or Johnson & Johnson)
NO to 1 and/or 2
Not VITT: Manage according to standard practice
YES to both
SCREEN for VITT
• Order appropriate imaging based on symptom presentation
• Order urgent complete blood count
NO thrombosis on imaging
Platelet count >150 x 10⁹/L
Acute thrombosis present AND platelet count <150 x 10⁹/L
Possible VITT
Initial evaluation
• Order standard coagulation laboratory studies (PT, aPTT, Clauss fibrinogen, D-dimer)
• Order immunoassay for platelet factor 4 (PF4) antibodies (HITT ELISA is most reliable)
PF4 ELISA negative
If PF4 antibody immunoassay is not available, check D-dimer level. Markedly elevated D-dimer levels (e.g., >4x threshold for VTE exclusion) is highly suggestive of VITT. Treat as per VITT.
PF4 ELISA positive (high OD reading)
VITT CONFIRMED
VITT Treatment
• IVIG (0.5-1g/kg daily for 2 days)
• Steroids if platelets <50 x 10⁹/L
• Avoid platelet transfusions, heparin, LMWH, VKA
• Give non-heparin anticoagulant: fondaparinux, argatroban, DOAC if platelet count >50 x 10⁹/L and no serious bleeding
• Consult thrombosis expert
• Early plasma exchange if platelets < 30 x 10⁹/L after IVIG and steroids

VITT: suggested pathogenesis

Triggers of VITT: only hypothetic until now…

- Constituents of the vaccine, including the adenoviral vector?
- Unique biological characteristics of patient?
  - Pathological inflammatory responses in humoral or cellular immune pathways
  - Excessive innate immune response: cytokines, endothelial damage, neutrophil activation (neutrophil extra cellular traps or NETs detected in clots)

Allow a normally minor response to vaccination to evolve into full-blown VITT

Connors J. Eur Heart J 2021;ehab585: doi: 10.1093/eurheartj/ehab585; Holm S, et al. Eur Heart J 2021; doi:10.1093/eurheartj/ehab506

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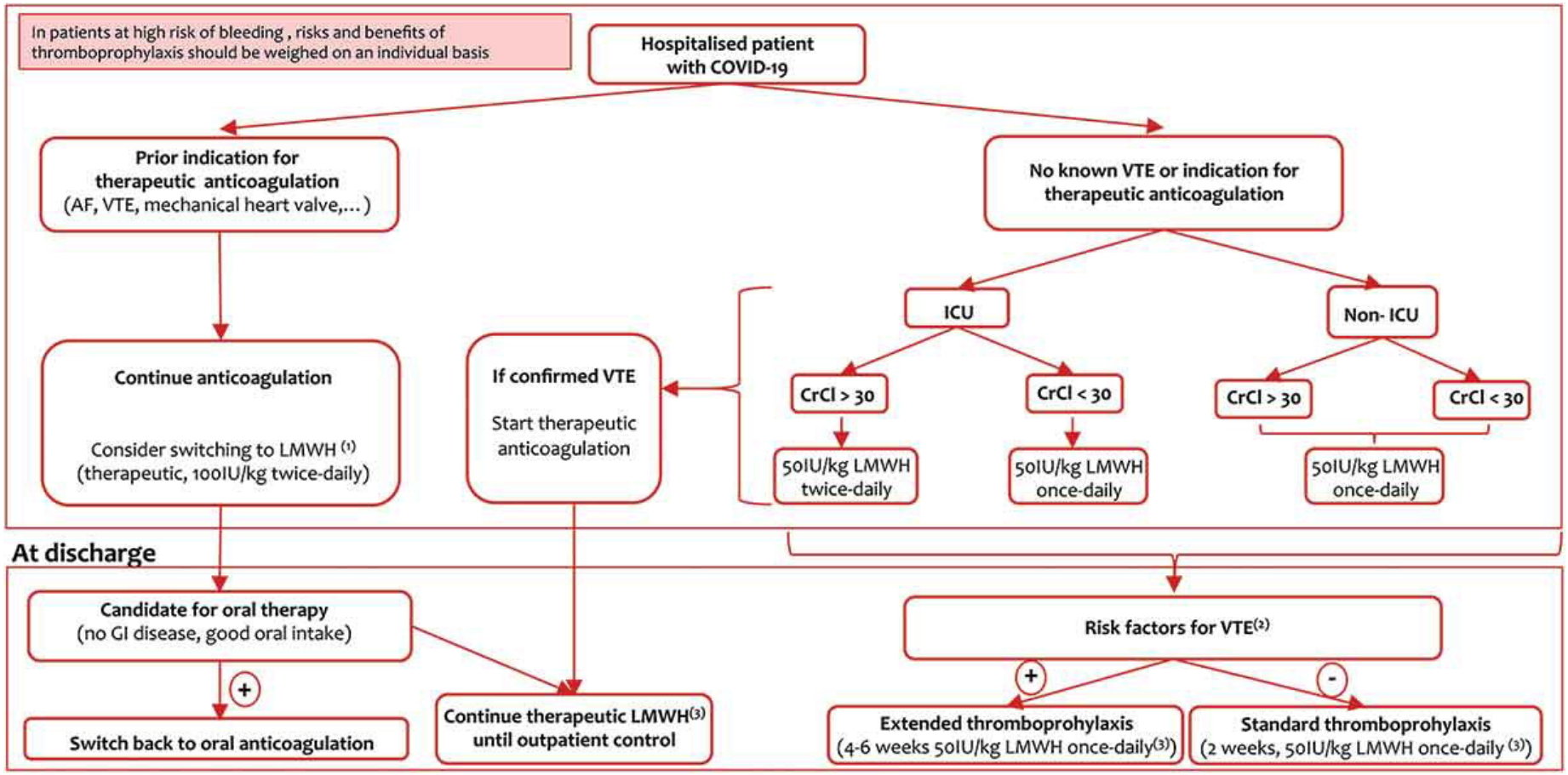
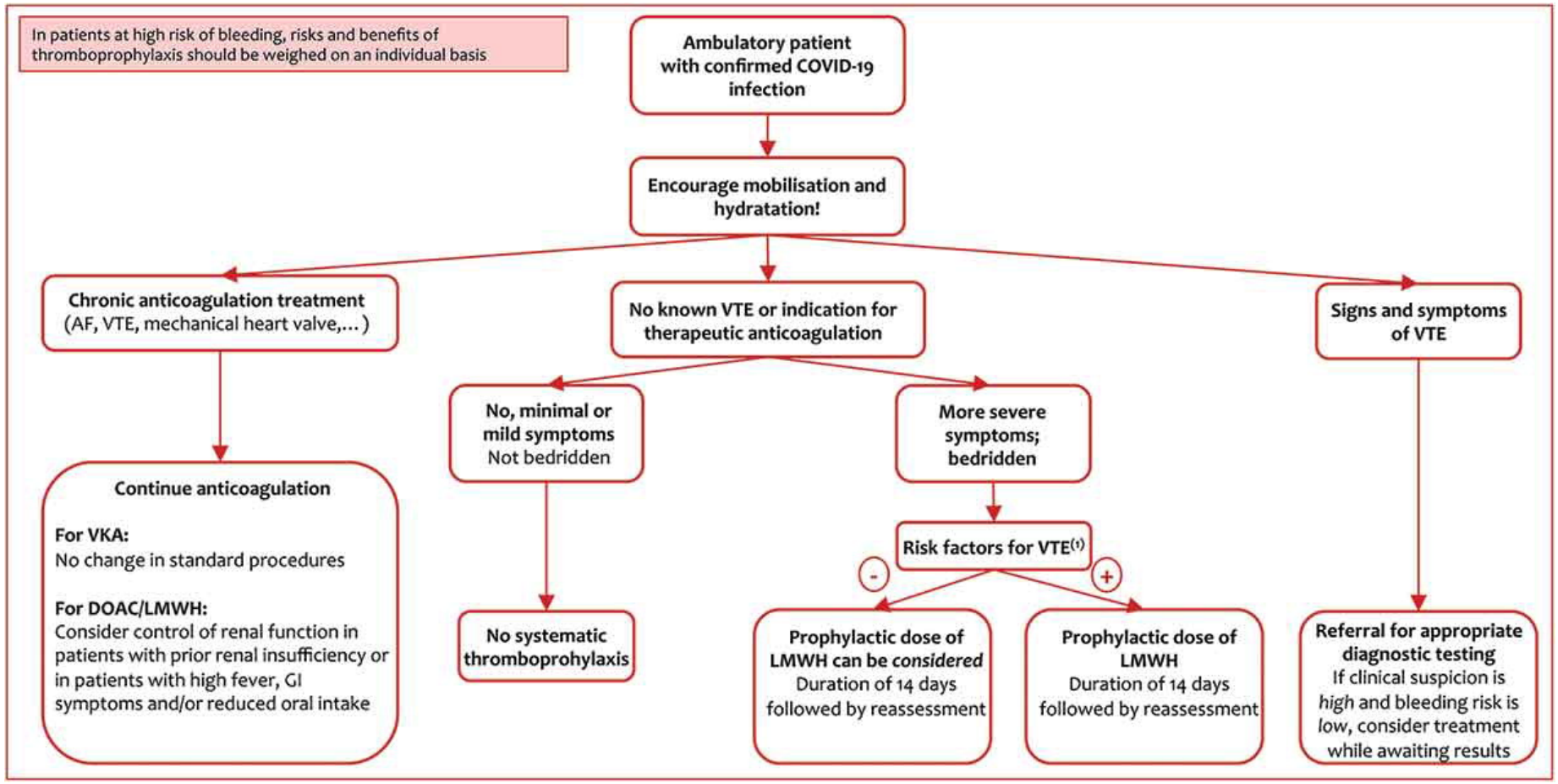
Management of COVID-19 thrombotic events & VITT

Anticoagulation management in hospitalised COVID-19 patients and after discharge: Belgian clinical guidance



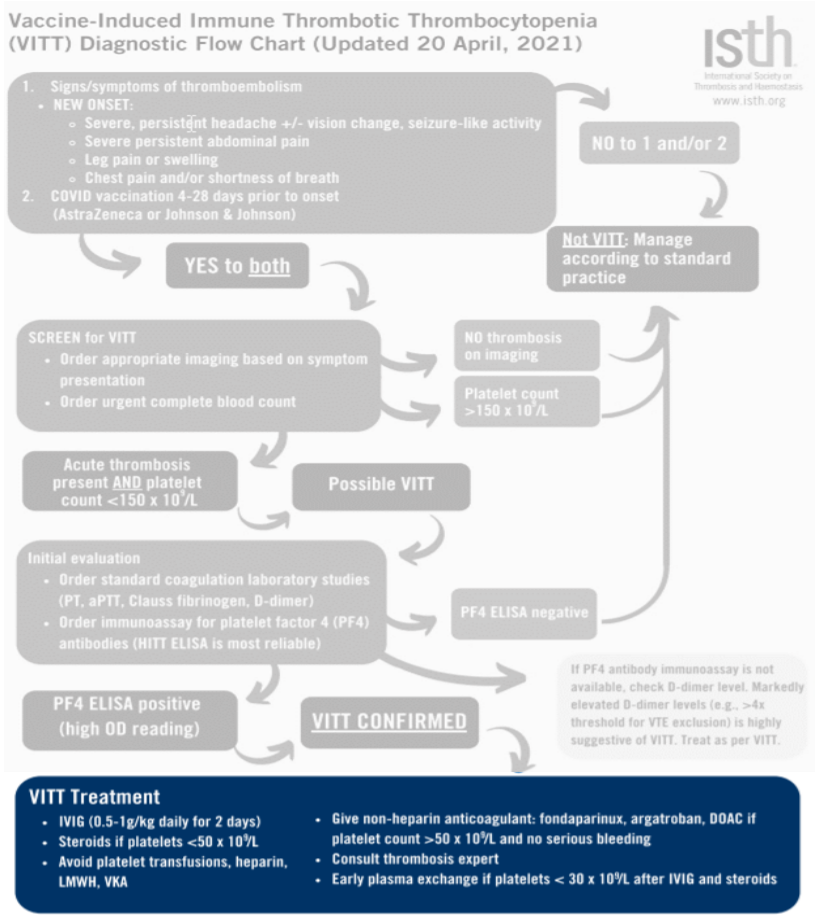
Vanassche T, et al. Acta Clin Belg 2020;1-6. doi: ahea10.1080/17843286.2020.1829252. Epub d of print

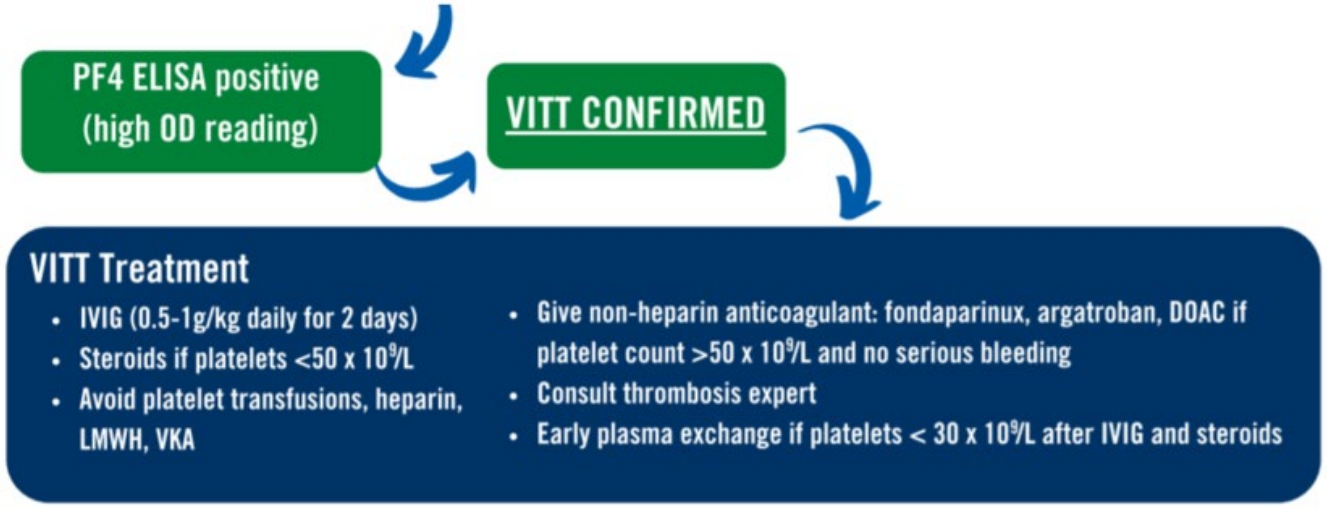
Anticoagulation management in non-hospitalised COVID-19: Belgian clinical guidance



Vanassche T, et al. Acta Clin Belg 2020;1-6. doi: ahea10.1080/17843286.2020.1829252. Epub d of print

VITT management





SHORT COMMUNICATION

european journal of neurology

Declining mortality of cerebral venous sinus thrombosis with thrombocytopenia after SARS-CoV-2 vaccination

Anita van de Munckhof[1] | Katarzyna Krzywicka[1] | Diana Aguiar de Sousa[2] | Mayte Sánchez van Kammen[1] | Mirjam R. Heldner[3] | Katarina Jood[4,5] | Erik Lindgren[4,5] | Turgut Tatlisumak[4,5] | Jukka Putaala[6] | Johanna A. Kremer Hovinga[7] | Saskia Middeldorp[8] | Marcel Levi[9,10] | Marcel Arnold[3] | José M. Ferro[2] | Jonathan M. Coutinho[1]

	Patients with CVST after adenoviral vector vaccination $N = 266$	
	Until 28 March $N = 99$	After 28 March $N = 167$
Age, median (IQR), years	46 (33–57)[†]	46 (37–55)[‡]
Female sex, *n/N* (%)	83/99 (84)	108/167 (65)
Intracranial haemorrhage at baseline, *n/N* (%)[a]	28/79 (35)	43/144 (30)
Confirmed COVID-19 infection, *n/N* (%)[b]	1/99 (1)	2/167 (1)
Lowest reported platelet count, median (IQR) $\times 10^9$/L	27 (14–60)[††]	42 (20–65)[‡‡]
Mortality, *n/N* (%)	47/99 (47)[c]	36/167 (22)[c]

Note: Number of missing values: [†]18; [‡]29; [††]17; [‡‡]46.

Abbreviations: COVID-19, coronavirus disease 2019; CVST, cerebral venous sinus thrombosis; IQR, interquartile range.

[a]Missing cases ($N = 43$) had an intracranial haemorrhage with an unknown onset date.

[b]One patient had a COVID-19 infection prior to CVST onset; the date of COVID-19 infection onset was unknown in the other two patients.

[c]$p < 0.001$.

van de Munckhof A, et al. Eur J Neurol 2021; doi:10.1111/ene.15113

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Summary & Take home messages

Thrombosis in COVID-19 and VITT: different or similar?

	COVID-19	VITT
Sites of thrombosis	Mainly DVT/PE	Cerebral, visceral veins
Incidence	High in hospitalized patients	Very rare
Direct trigger	SARS-CoV-2	?
Impact of other thrombotic risk factors for VTE	✓	-
Treatment	Conventional anticoagulation	Specific guidance (IV Ig, cortico, no heparin)
Cross-talk between innate inflammatory responses and activation of coagulation	✓	✓
Excessive thrombo-inflammatory reaction (‘immunothrombosis’)	✓	✓
Role of complement	?	?

Key take home messages

- High incidence of arterial and venous thromboembolic events in COVID-19
- Highest incidence in severely ill patients (ICU), low in non-hospitalized patients
- Hypercoagulable state induced by virus- and host-related processes
- Adapted thromboprophylaxis improves outcome

- VITT is a very rare but potentially life-threatening complication post-COVID-19 vaccination
- Accurate diagnosis and management leads to lower morbidity/mortality