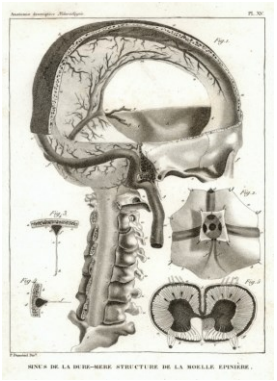
# Cerebral Venous and Sinus Thrombosis

*"past, present and future"*



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ECAT symposium 2022

# Faculty Disclosure

| *Company Name* | *Honoraria/ Expenses* | *Consulting/ Advisory Board* | *Funded Research* | *Royalties/ Patent* | *Stock Options* | *Ownership/ Equity Position* | *Employee* | *Other (please specify)* |
|---|---|---|---|---|---|---|---|---|
| Boehringer Ingelheim | | x | | | | | | |
| Bayer | | x | | | | | | |
| Portola | | x | | | | | | |

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Goede Doelen Fonds van de Landelijke Vereniging van Crematoria
NWO
Netherlands Organisation for Scientific Research

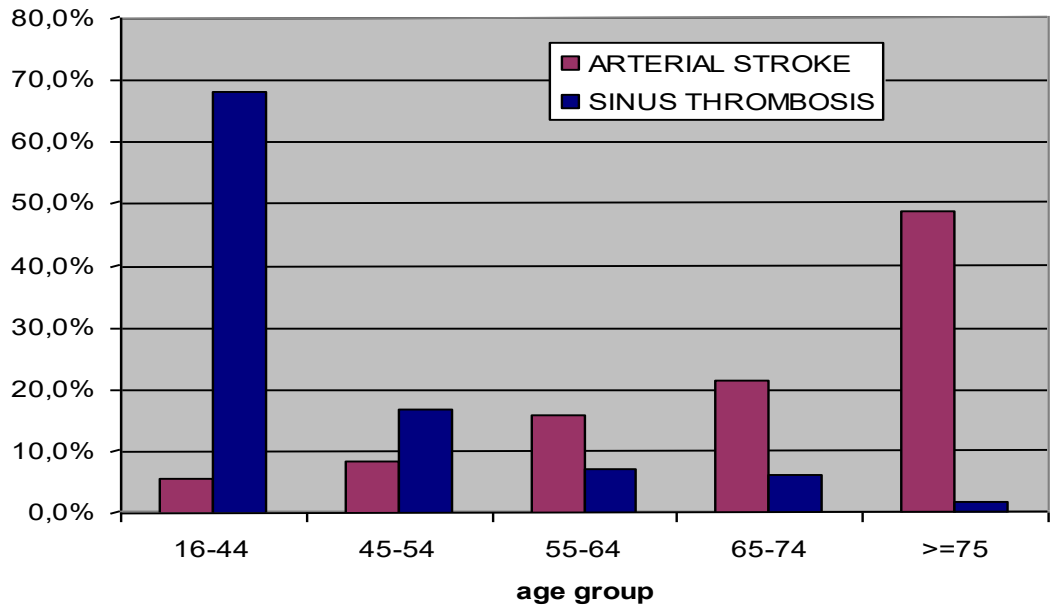
# Contents

- Background on cerebral venous thrombosis (past)
- CVT due to Vaccine induced Immune Thrombotic Thrombocytopenia (VITT; present)
- Unanswered research questions (future)

# Cerebral Venous and Sinus Thrombosis (CVT)

## Adults[1-2]

- Incidence approx. 12-20 per million / yr.
- Median age 37
- 75% women



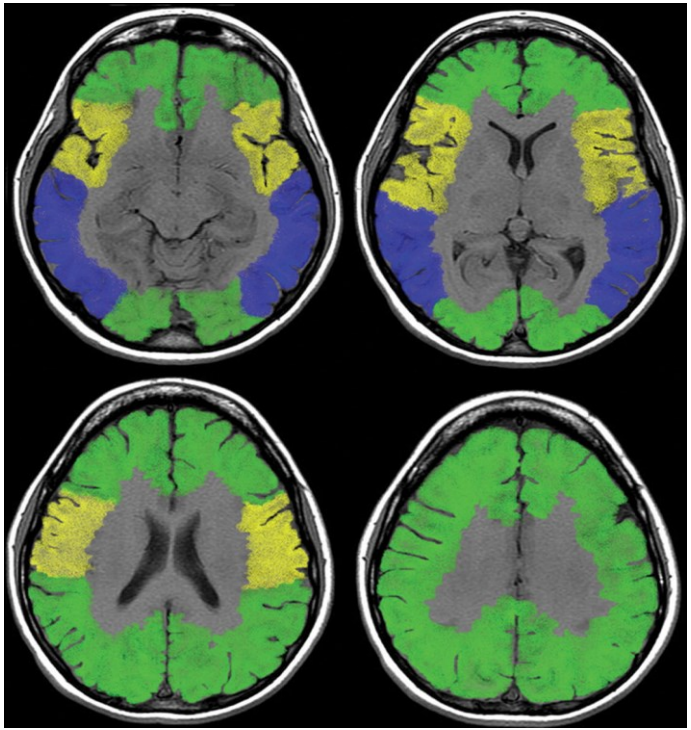

[1]Coutinho JM et al. Stroke 2012
[2]Devasagayam S et al. Stroke 2016
[3]Otite FO et al. Neurology 2020

# Predisposing conditions in CVT

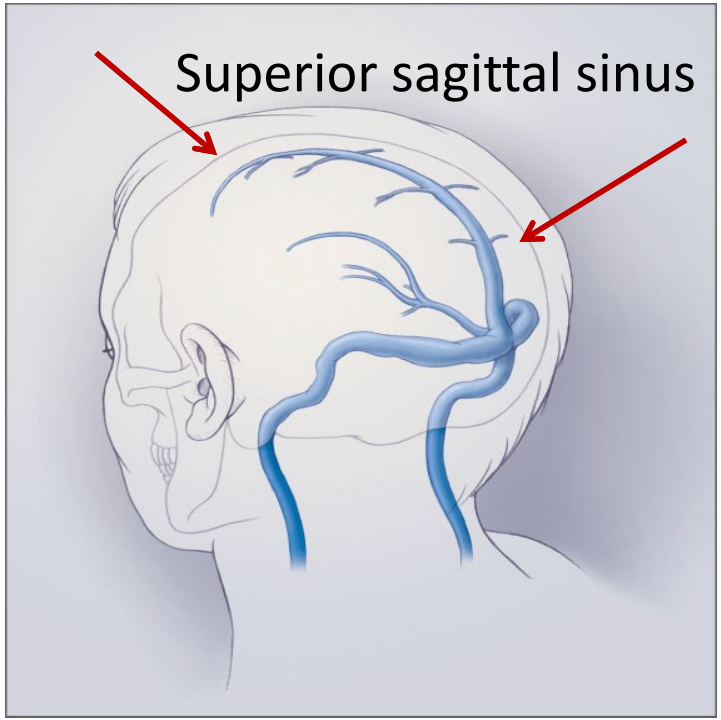
| Risk factor | Prevalence[a] | Risk factor for DVT/PE? | Strength of association | Type of studies |
|---|---|---|---|---|
| Sex-specific risk factors | | | | |
| Oral contraceptives | 54 to 71%[b] | Yes | OR = 5.59 | Case–control |
| Pregnancy and puerperium | 11 to 59%b | Yes | NA | Cohort |
| Hormone replacement therapy | 4%[b] | Yes | NA | Case reports |
| Hereditary thrombophilia | 34 to 41% | | | |
| Factor V Leiden | 9 to 13% | Yes | OR = 2.89 | Case–control |
| Prothrombin G20210A mutation | 9 to 21% | Yes | OR = 6.05 | Case–control |
| Antithrombin deficiency | 3% | Yes | OR = 3.75 | Case–control |
| Protein S deficiency | 2 to 3% | Yes | OR = 8.35 | Case–control |
| Protein C deficiency | 2 to 5% | Yes | OR = 6.45 | Case–control |
| Infections | 8 to 11% | No | NA | Cohort |
| Systemic diseases | | | | |
| Cancer | 7% | Yes | NA | Cohort |
| Myeloproliferative neoplasms | 2 to 3% | Yes | NA | Cohort |
| Inflammatory bowel disease | 2 to 3% | Yes | NA | Cohort |
| Behçet disease | 1% | Yes | NA | Cohort |
| Thyroid disease | 2% | Probably | NA | Case reports |
| Systemic lupus erythematosus | 1% | Yes | NA | Case series |
| Antiphospholipid antibodies | 6 to 17% | Yes | NA | Cohort |
| Nephrotic syndrome | 1% | Yes | NA | Case reports |
| Sarcoidosis | <1% | No | NA | Case reports |
| Wegener granulomatosis | NA | Yes | NA | Case reports |
| Hematologic conditions other than cancer | | | | |
| Anemia | 9 to 27% | No | OR = 4.4 | Case–control |
| Paroxysmal nocturnal hemoglobinuria | NA | Yes | NA | Case series |
| Miscellaneous | | | | |
| Iatrogenic | 4% | Yes | NA | Case reports |
| Obesity | 23% | Yes | OR = 2.63 | Case–control |
| Head trauma | 1 to 3% | No | NA | Cohort |
| Dural arteriovenous fistula | 2% | No | NA | Cohort |
| Spontaneous intracranial hypotension | NA | No | NA | Case reports |
| Dehydration | 2% | No | NA | Cohort |

Silvis et al. Sem Thromb Hem 2016

# Anatomy
## *superficial venous system*

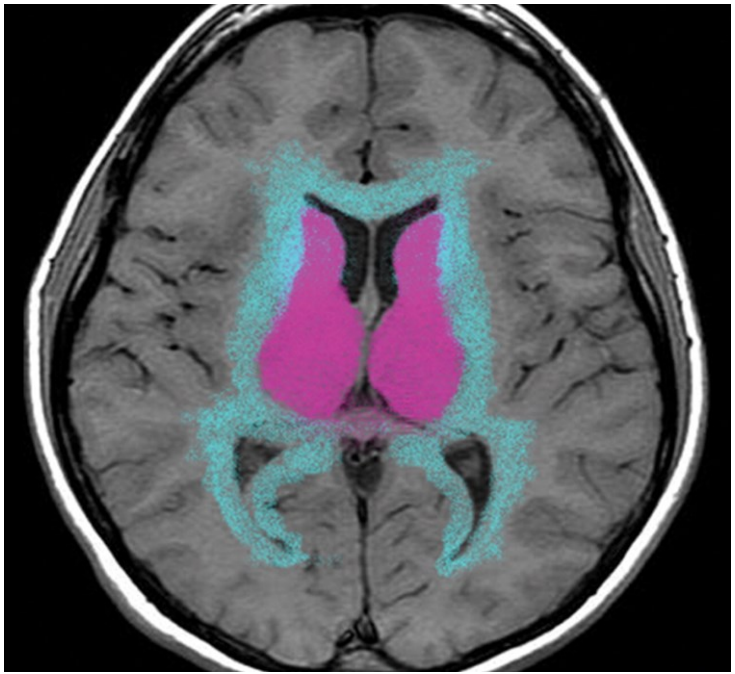


From: Leach JL et al. Radiographics 2006




From: Stam J. NEJM 2005

# Anatomy
## *deep venous system*



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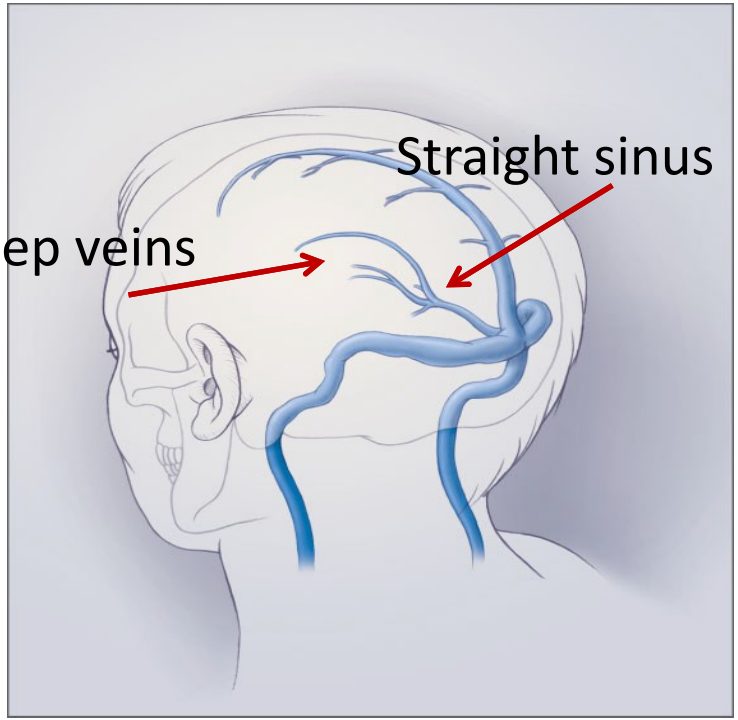



From: Stam J. NEJM 2005

# Clinical Manifestations

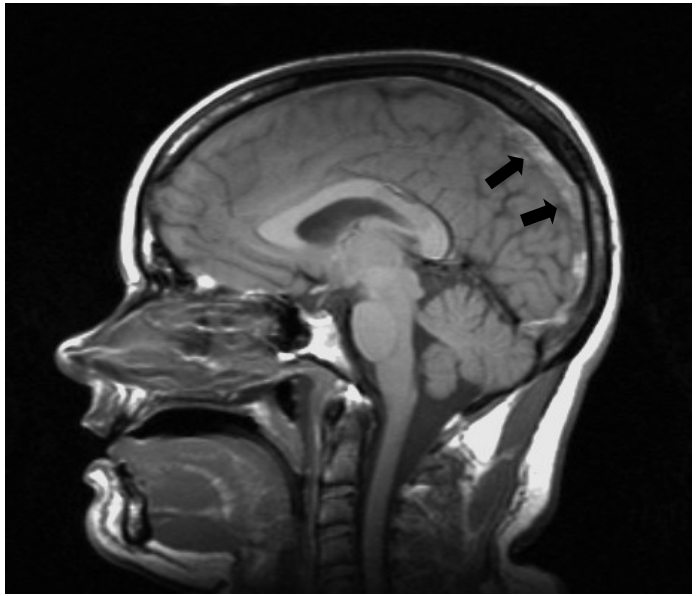
ISCVT, 624 patients, 21 countries

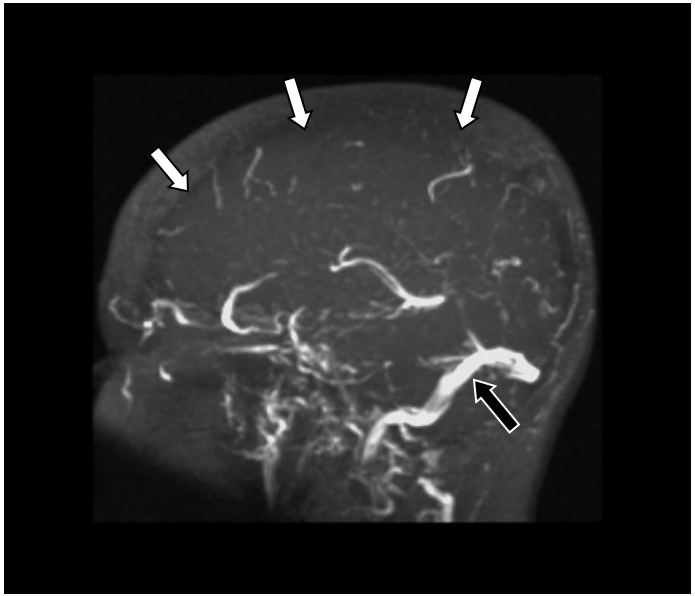
| | |
|---|---|
| • headache | 90 % |
| • paresis | 40 % |
| • aphasia | 20 % |
| • seizures | 40 % |
| • visual loss | 10 % |
| • comatose | 5 % |

**Ferro JM, et al. Stroke 2004**

# Diagnosis

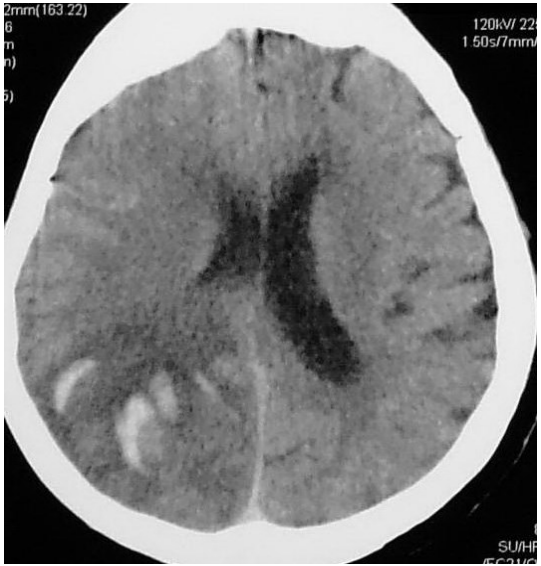
- MRI + MR-venography
- CT-venography





# Intracranial Lesions

- Intracerebral hemorrhage (30-40%)
- Cerebral edema (30-40%)
- Subarachnoid hemorrhage (10-15%)
- Subdural hemorrhage (<5%)



# Therapy for CVT

## Thrombosis

- Anticoagulation
- Endovascular treatment (EVT)

## Mass effect

- Decompressive hemicraniectomy

## Increased intracranial pressure

- Analgesics
- Acetazolamide
- Shunting procedure

## Seizures

- Anti-epileptic drugs

# Guidelines on heparin in CVT

**ESO guideline**

*Recommendation* We suggest treating patients with acute CVT with LMWH instead of UFH. This recommendation does not apply to patients with a contraindication for LMWH (e.g. renal insufficiency) or situations where fast reversal of the anticoagulant effect is required (e.g. patients who have to undergo neurosurgical intervention).

*Quality of evidence* Low.

*Strength of recommendation* Weak.

**AHA guideline**

**For patients with CVT, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by vitamin K antagonists, regardless of the presence of ICH[161,171,172,175,181,183] *(Class IIa; Level of Evidence B)*. (For further details, refer to "Acute Management and Treatment of CVT: Initial Anticoagulation.")**

# Oral anticoagulation

- Switch to oral anticoagulation when patient is clinically stable
- Optimal duration treatment unknown
- International guidelines[1,2]
  - Provoked cases: 3-6 months
  - Unprovoked cases: 6-12 months
  - Recurrent thrombosis or severe thrombophilia: indefinite
- Vitamin K antagonist routinely used
- Recent trial on use of DOACs in CVT

[1]Ferro et al. Eur J Neurol 2017
[2]Saposnik G et al. Stroke 2011

# RESPECT-CVT trial

JAMA Neurology | Original Investigation

Published online September 3, 2019.

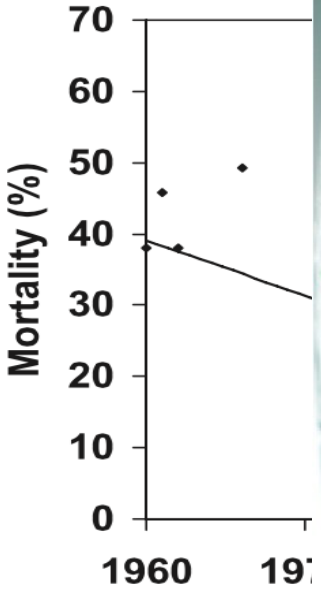
## Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis

### A Randomized Clinical Trial

José M. Ferro, MD, PhD; Jonathan M. Coutinho, MD, PhD; Francesco Dentali, MD; Adam Kobayashi, MD, PhD; Andrey Alasheev, MD, PhD; Patrícia Canhão, MD, PhD; Denis Karpov, MD, PhD; Simon Nagel, MD; Laura Posthuma, MD; José Mário Roriz, MD; Jorge Caria, MD; Mandy Frässdorf, PhD; Holger Huisman, MSc; Paul Reilly, PhD; Hans-Christoph Diener, MD, PhD; for the RE-SPECT CVT Study Group

| | Dabigatran (n=60) | Warfarin (n=60) |
|---|---|---|
| Major bleeding or VTE | 1 (1.7%; 95% CI 0.0–8.9)<br>Intestinal bleed | 2 (3.3%; 95% CI 0.4–11.5)<br>Intracranial bleeds |

# Prognosis (not applicable to VITT)





10%)

)

rating (75%)

to work (40-50%)

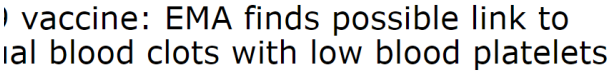
Coutinho JM et al. Stroke 2014

Koopman K et al. J Stroke Cerebrovasc Dis 2009
Hiltunen et al. J Neurol 2016

# CVT and COVID-19 vaccination





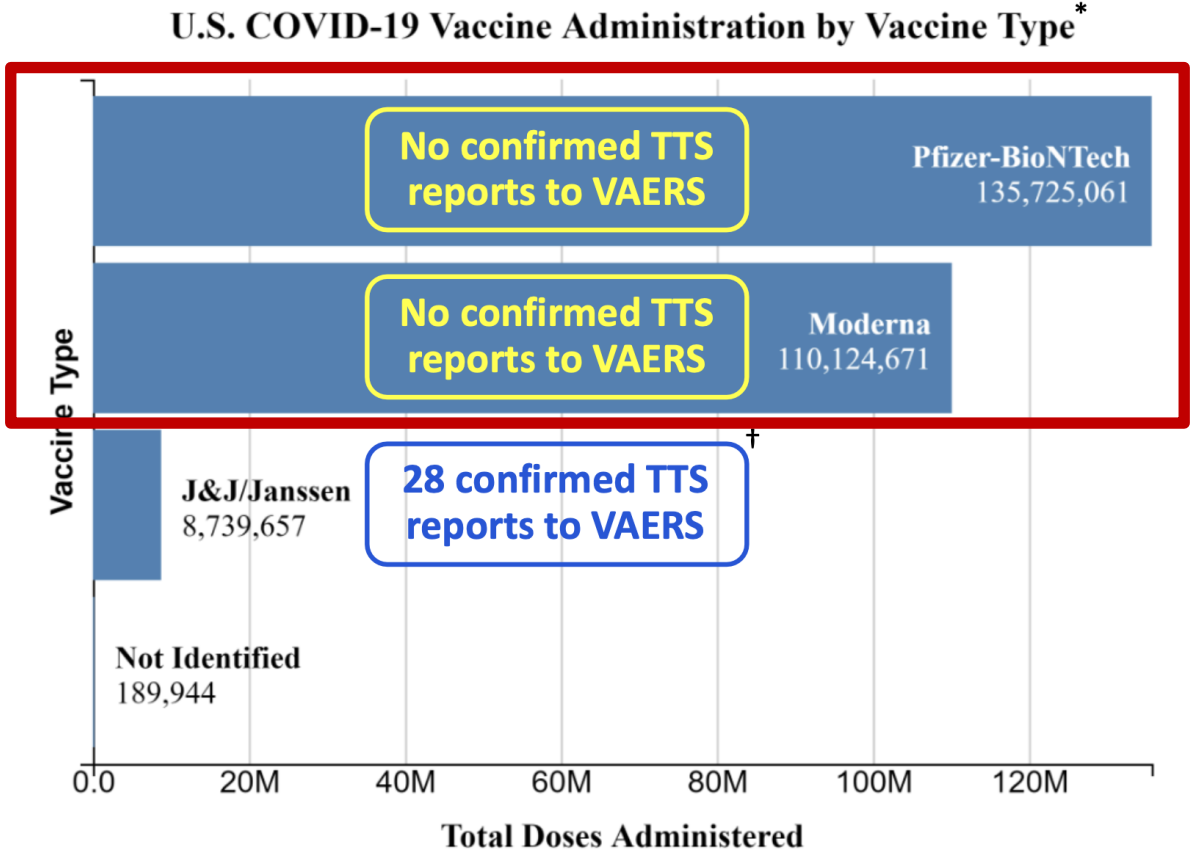

**Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine**

# Epidemiology VITT

- 4-28 days after vaccination with[1,2]
  - ChAdOx1 nCov-19 (AstraZeneca/Oxford)
  - Ad26.COV2.S (Janssen/Johnson and Johnson)
- Incidence
  - J&J: around 1:400.000[3]
  - AZ: around 1:40.000 – 1:130.000[4-7]
  - May be higher in (younger) women
  - May vary per country
- Clinical manifestations
  - Thrombosis
  - (Severe) thrombocytopenia


[1]Greinacher NEJM 2021
[2]Scully NEJM 2021
[3]www.cdc.gov
[4]Schulz et al. Ann Neurol 2021
[5]Pottegard et al. BMJ 2021
[6]Pavord et al. NEJM 2021
[7]Aguiar de Sousa, Coutinho et al. Neurology 2021;

# VITT after mRNA vaccines? **No!**



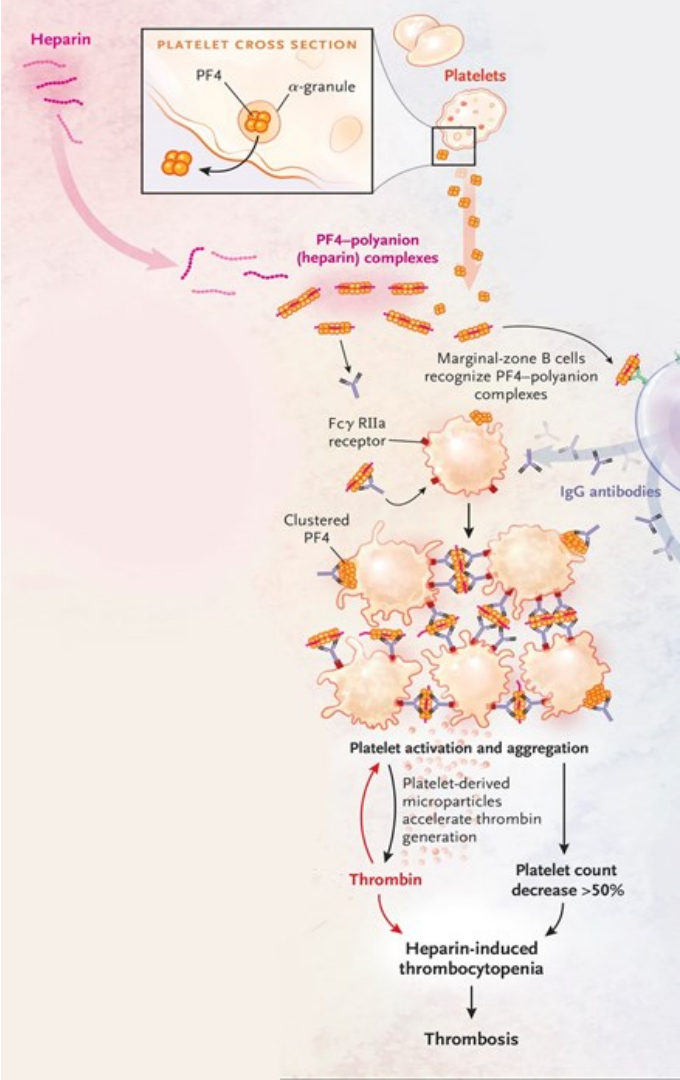

**Update: Thrombosis with thrombocytopenia syndrome (TTS) following U.S. COVID-19 vaccines**

**Advisory Committee on Immunization Practices (ACIP)**
**May 12, 2021**

**Tom Shimabukuro, MD, MPH, MBA**
**CDC COVID-19 Vaccine Task Force**
**Vaccine Safety Team**

# Pathophysiology

- Mechanism comparable to heparin induced thrombocytopenia (HIT)
- Antibodies against platelet factor 4 (PF4)
- Heparin-independent platelet activation
- Thrombosis and (severe) thrombocytopenia




From: Greinacher A. NEJM 2015

cerebralvenousthrombosis.com

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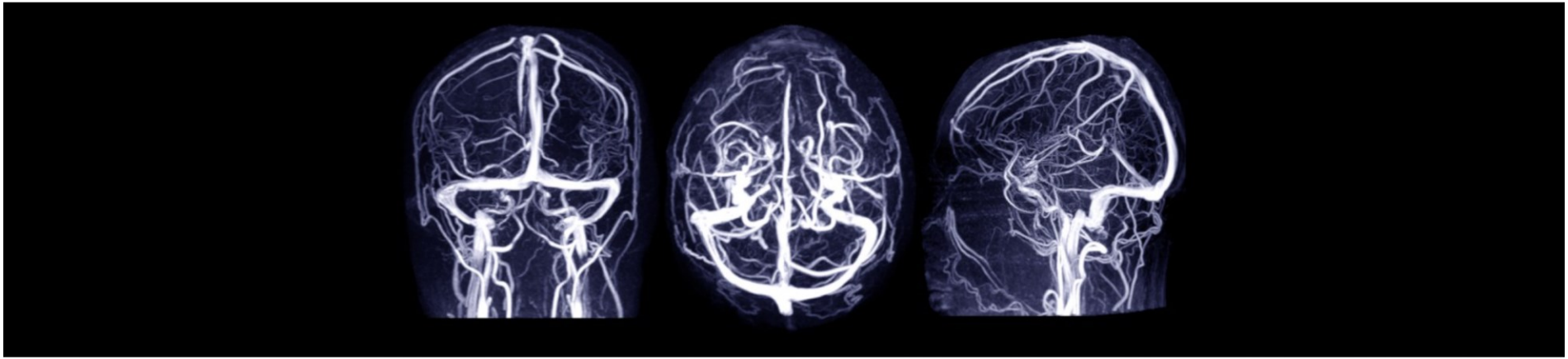

# CEREBRAL VENOUS THROMBOSIS CONSORTIUM

Welcome to the website of the International Cerebral Venous Thrombosis Consortium (ICVTC). ICVTC is an academic research collaboration between CVT experts, founded in 2015, and with the overarching aim to gain better insight into the epidemiology, clinical manifestations, treatment, and outcome of cerebral venous thrombosis



















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# Research question

- What are the clinical manifestations and prognosis of patients with VITT-associated CVT?

JAMA Neurology | Original Investigation

## Characteristics and Outcomes of Patients With Cerebral Venous Sinus Thrombosis in SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia

Mayte Sánchez van Kammen, MD; Diana Aguiar de Sousa, MD, PhD; Sven Poli, MD, MSc; Charlotte Cordonnier, MD, PhD; Mirjam R. Heldner, MD, MSc; Anita van de Munckhof, MD; Katarzyna Krzywicka, MD, MPhil; Thijs van Haaps, BSc; Alfonso Ciccone, MD, PhD; Saskia Middeldorp, MD, PhD; Marcel M. Levi, MD, PhD; Johanna A. Kremer Hovinga, MD; Suzanne Silvis, MD, PhD; Sini Hiltunen, MD, PhD; Maryam Mansour, MD; Antonio Arauz, MD, PhD; Miguel A. Barboza, MD, MSc; Thalia S. Field, MD, MHSc; Georgios Tsivgoulis, MD, PhD; Simon Nagel, MD; Erik Lindgren, MD; Turgut Tatlisumak, MD, PhD; Katarina Jood, MD, PhD; Jukka Putaala, MD, PhD; Jose M. Ferro, MD, PhD; Marcel Arnold, MD; Jonathan M. Coutinho, MD, PhD; and the Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group

ESO
EUROPEAN STROKE ORGANISATION

ean
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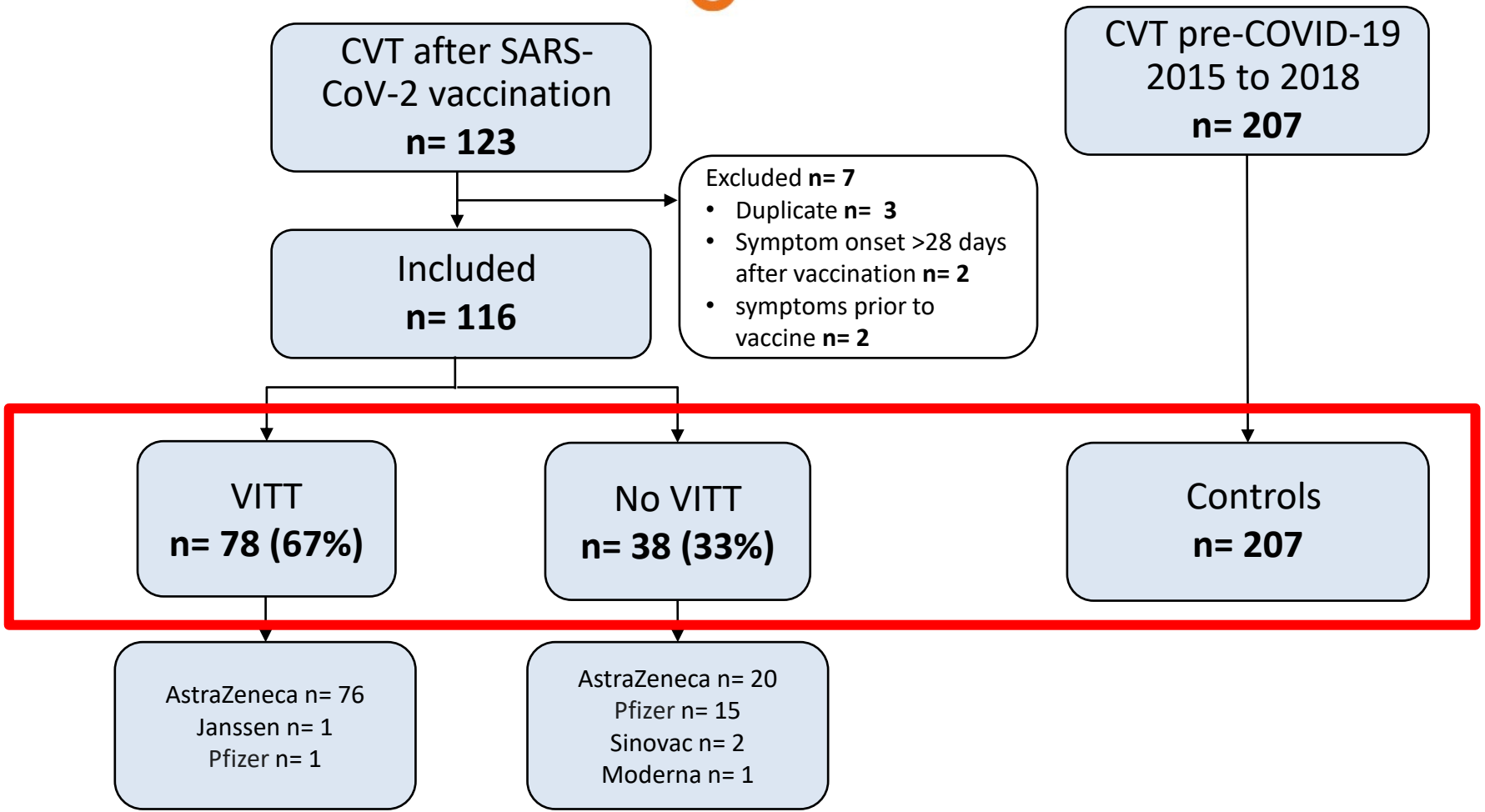
# Methods

- International registry, supported by ESO and EAN
- Adult patients with CVT<28 days after SARS-CoV-2 vaccination
- 81 hospitals in 19 countries
- March 29 – June 18 2021

**Sanchez van Kammen, Coutinho et al, JAMA Neurology 2021**


CVT after SARS-CoV-2 vaccination
n= 123
CVT pre-COVID-19
2015 to 2018
n= 207
Excluded n= 7
• Duplicate n= 3
• Symptom onset >28 days after vaccination n= 2
• symptoms prior to vaccine n= 2
Included
n= 116
VITT
n= 78 (67%)
No VITT
n= 38 (33%)
Controls
n= 207
AstraZeneca n= 76
Janssen n= 1
Pfizer n= 1
AstraZeneca n= 20
Pfizer n= 15
Sinovac n= 2
Moderna n= 1

| Baseline table | VITT N=78 | No VITT N=38 | Pre-COVID-19 controls N=207 |
|---|---|---|---|
| **Demographics** | | | |
| Age– mean (SD) | 45 (14) | 55 (20) | 42 (16) |
| Women | 81% | 79% | 70% |
| **Risk factors** | | | |
| Previous COVID-19 infection | 1% | 11% | - |
| Conventional CVT risk factor | 24% | 42% | 64% |
| **Clinical manifestations** | | | |
| Days from vaccination to symptom onset– median (IQR) | 9 (7–10) | 7 (3–16) | - |
| Coma | 24% | 3% | 5% |
| **Imaging** | | | |
| Intracerebral hemorrhage | 68% | 26% | 35% |

# Complications and outcome

| | VITT N=78 | No VITT N=38 | Pre-COVID-19 control group N=207 |
|---|---|---|---|
| Concomitant thromboembolism | 36% | 6% | 5% |
| Major bleeding complication* | 12% | 8% | 4% |
| Mortality (in-hospital) | 47%<br>95% CI 37-58 | 5%<br>95%CI 1-18 | 4%<br>95%CI 2-7 |

* ISTH major bleeding criteria:
Schulman et al, JTH 2005

# If you want to read more..

JAMA Neurology | Original Investigation

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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]

## Cerebral venous thrombosis due to vaccine-induced immune thrombotic thrombocytopenia after a second ChAdOx1 nCoV-19 dose

blood® 28 APRIL 2022 | VOLUME 139, NUMBER

Katarzyna Krzywicka,[1] Anita van de Munckhof,[1] Julian Zimmermann, Felix J. Bode, Giovanni Frisullo, Theodoros Karapanayiotides, Bernd Pötzsch,[5] Mayte Sánchez van Kammen,[1] Mirjam R. Heldner,[6] Marcel Arnold,[6] Johanna A. Kremer Hovinga,[7] José M. Ferro,[8] Diana Aguiar de Sousa,[9,*] and Jonathan M. Coutinho,[1,*] for the Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group

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February 15, 2022; 98 (7) RESEARCH ARTICLE

## Age-Stratified Risk of Cerebral Venous Sinus Thrombosis After SARS-CoV-2 Vaccination

Katarzyna Krzywicka, Anita van de Munckhof, Mayte Sánchez van Kammen, Mirjam R. Heldner, Katarina Jood, Erik Lindgren, Turgut Tatlisumak, Jukka Putaala, Johanna A. Kremer Hovinga, Saskia Middeldorp, Marcel M. Levi, Charlotte Cordonnier, Marcel Arnold, Aeilko H. Zwinderman, José M. Ferro, Jonathan M. Coutinho, Diana Aguiar de Sousa

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ORIGINAL ARTICLE

of neurology

## Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency

Katarzyna Krzywicka[1] | Mirjam R. Heldner[2] | Mayte Sánchez van Kammen[1] | Thijs van Haaps[3] | Sini Hiltunen[4] | Suzanne M. Silvis[5] | Marcel Levi[3,6] | Johanna A. Kremer Hovinga[7] | Katarina Jood[8,9] | Erik Lindgren[8,9] | Turgut Tatlisumak[8,9] | Jukka Putaala[4] | Diana Aguiar de Sousa[10] | Saskia Middeldorp[11] | Marcel Arnold[2] | Jonathan M. Coutinho[1] | José M. Ferro[10]

JAMA | Original Investigation

## Frequency of Thrombocytopenia and Platelet Factor 4/Heparin Antibodies in Patients With Cerebral Venous Sinus Thrombosis Prior to the COVID-19 Pandemic

Mayte Sánchez van Kammen, MD; Mirjam R. Heldner, MD, MSc; Justine Brodard, MSc; Adrian Scutelnic, MD; Suzanne Silvis, MD, PhD; Verena Schroeder, PhD; Johanna A. Kremer Hovinga, MD; Saskia Middeldorp, MD, PhD; Marcel Levi, MD, PhD; Sini Hiltunen, MD, PhD; Erik Lindgren, MD; Maryam Mansour, MD; Antonio Arauz, MD, PhD; Miguel A. Barboza, MD, PhD; Susanna M. Zuurbier, MD, PhD; Diana Aguiar de Sousa, MD, PhD; Jose M. Ferro, MD, PhD; Urs Fischer, MD, MSc; Thalia S. Field, MD, MHSc; Katarina Jood, MD, PhD; Turgut Tatlisumak, MD, PhD; Jukka Putaala, MD, PhD; Marcel Arnold, MD; Jonathan M. Coutinho, MD, PhD

# Unanswered research questions


General CVT

- Can we safely use DOACs for CVT in routine practice?
- Is there a role for endovascular treatment of CVT?

CVT due to VITT

- Why does VITT have a preference for thrombosis of the cerebral venous system?
- Is there a genetic predisposition to develop VITT?

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