

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

 Supplemental content

IMPORTANCE Thrombosis with thrombocytopenia syndrome (TTS) has been reported after vaccination with the SARS-CoV-2 vaccines ChAdOx1 nCov-19 (Oxford–AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson).

OBJECTIVE To describe the clinical characteristics and outcome of patients with cerebral venous sinus thrombosis (CVST) after SARS-CoV-2 vaccination with and without TTS.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from an international registry of consecutive patients with CVST within 28 days of SARS-CoV-2 vaccination included between March 29 and June 18, 2021, from 81 hospitals in 19 countries. For reference, data from patients with CVST between 2015 and 2018 were derived from an existing international registry. Clinical characteristics and mortality rate were described for adults with (1) CVST in the setting of SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia, (2) CVST after SARS-CoV-2 vaccination not fulfilling criteria for TTS, and (3) CVST unrelated to SARS-CoV-2 vaccination.

EXPOSURES Patients were classified as having TTS if they had new-onset thrombocytopenia without recent exposure to heparin, in accordance with the Brighton Collaboration interim criteria.

MAIN OUTCOMES AND MEASURES Clinical characteristics and mortality rate.

RESULTS Of 116 patients with postvaccination CVST, 78 (67.2%) had TTS, of whom 76 had been vaccinated with ChAdOx1 nCov-19; 38 (32.8%) had no indication of TTS. The control group included 207 patients with CVST before the COVID-19 pandemic. A total of 63 of 78 (81%), 30 of 38 (79%), and 145 of 207 (70.0%) patients, respectively, were female, and the mean (SD) age was 45 (14), 55 (20), and 42 (16) years, respectively. Concomitant thromboembolism occurred in 25 of 70 patients (36%) in the TTS group, 2 of 35 (6%) in the no TTS group, and 10 of 206 (4.9%) in the control group, and in-hospital mortality rates were 47% (36 of 76; 95% CI, 37–58), 5% (2 of 37; 95% CI, 1–18), and 3.9% (8 of 207; 95% CI, 2.0–7.4), respectively. The mortality rate was 61% (14 of 23) among patients in the TTS group diagnosed before the condition garnered attention in the scientific community and 42% (22 of 53) among patients diagnosed later.

CONCLUSIONS AND RELEVANCE In this cohort study of patients with CVST, a distinct clinical profile and high mortality rate was observed in patients meeting criteria for TTS after SARS-CoV-2 vaccination.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group members appear at the end of the article.

Corresponding Author: Jonathan M. Coutinho, MD, PhD, Department of Neurology, Amsterdam University Medical Center, Location AMC, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands (j.coutinho@amsterdamumc.nl).

JAMA Neurol. 2021;78(11):1314–1323. doi:[10.1001/jamaneurol.2021.3619](https://doi.org/10.1001/jamaneurol.2021.3619)
Published online September 28, 2021.

Reports of cerebral venous sinus thrombosis (CVST) and other thromboses at unusual sites in combination with thrombocytopenia occurring within 4 to 28 days of vaccination with the SARS-CoV-2 vaccines ChAdOx1 nCov-19 (Oxford–AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson) have prompted several countries to restrict the use of these vaccines, especially in younger patients.^{1–5} The similarities between the clinical syndrome reported in these patients and spontaneous heparin-induced thrombocytopenia⁶ led investigators to the identification of circulating platelet-activating platelet factor 4 (PF4) antibodies in many of these patients. The condition has been named *vaccine-induced immune thrombotic thrombocytopenia*.¹ To identify cases and promote research aimed at confirming whether this condition is indeed linked to vaccination, the Brighton Collaboration has proposed a definition of thrombosis with thrombocytopenia syndrome (TTS), which relies on evidence of thrombosis and new-onset thrombocytopenia without known recent exposure to heparin.⁷

To gain better insight into the clinical characteristics and outcomes of patients with CVST with TTS (CVST-TTS), we initiated an international registry of patients with CVST after SARS-CoV-2 vaccination. We hypothesized that patients with CVST-TTS would have distinct clinical features and a worse prognosis, while patients with postvaccination CVST without TTS would have a clinical profile resembling that of patients with CVST prior to the COVID-19 pandemic.

Methods

Patient Selection

We report results of a registry-based study on adult patients diagnosed with CVST after vaccination with any SARS-CoV-2 vaccine. Patients with CVST with symptom onset within 28 days of SARS-CoV-2 vaccination were included. Through the existing International Cerebral Venous Thrombosis Consortium,^{8,9} we asked physicians to disseminate this research initiative within national and international stroke care networks. The study was endorsed by the European Academy of Neurology and European Stroke Organisation. Participating investigators were requested to report consecutive patients with postvaccination CVST from their hospital. The ethical review committee of the Amsterdam UMC gave a waiver of formal approval for this observational study. Each center was responsible for obtaining adequate permission from local authorities for study participation and for acquiring informed consent for the use of pseudonymized care data if required by national law and hospital regulation. We collected data from a total of 81 hospitals in 19 countries. Data were collected from March 29 to June 18, 2021, and included both prospectively and retrospectively enrolled patients. All included patients were diagnosed with CVST between January 30 and June 14, 2021.

In accordance with the Brighton Collaboration level 1 interim case definition of TTS (version 10.16.2; May 18, 2021),⁷ patients with CVST after SARS-CoV-2 vaccination were classified as having TTS if they met all of the following criteria:

Key Points

Question What are the clinical characteristics and outcomes of patients with cerebral venous sinus thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination?

Findings In this cohort study of 116 patients with cerebral venous sinus thrombosis after SARS-CoV-2 vaccination, 78 (67.2%) had thrombosis with thrombocytopenia syndrome. Patients with thrombosis with thrombocytopenia syndrome were frequently comatose at presentation (24%) and often had intracerebral hemorrhage (68%) and concomitant thromboembolism (36%), and 47% died during hospitalization.

Meaning Patients with cerebral venous sinus thrombosis after SARS-CoV-2 vaccination who met criteria for thrombosis with thrombocytopenia syndrome had a distinct clinical profile and high mortality rate.

(1) confirmed thrombosis, (2) new-onset thrombocytopenia, and (3) no known recent exposure to heparin. We refer to the group of patients classified as having TTS as the TTS group and patients with CVST after SARS-CoV-2 vaccination who were classified as not having TTS as the no TTS group.

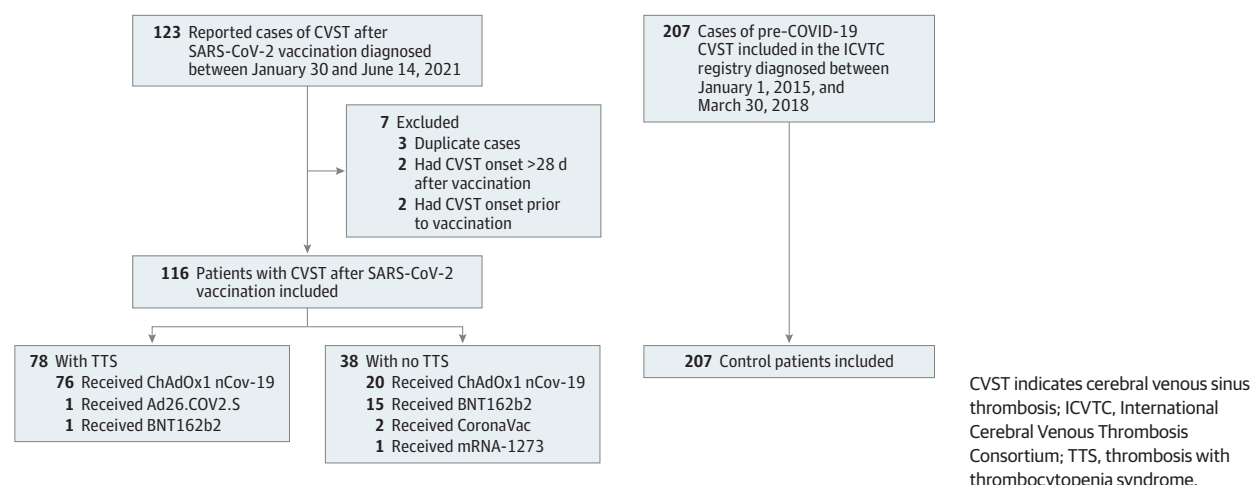
The control group consisted of adult patients diagnosed with CVST prior to the COVID-19 pandemic who were included in the International Cerebral Venous Thrombosis Consortium registry between January 2, 2015, and February 24, 2018, from 6 hospitals in Finland, the Netherlands, Switzerland, Mexico, Iran, and Costa Rica. All these centers are tertiary hospitals with experience in the management of patients with CVST. Each hospital had permission from their ethical review board for the collection of observational data and obtained written informed consent for the use of pseudonymized care data if required under applicable national laws. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection and Definitions

A standardized case report form was used to collect detailed information on demographic characteristics, CVST risk factors, clinical manifestations, laboratory and imaging characteristics, treatment, and outcome in both the post-SARS-CoV-2 vaccination and control groups. Vaccination details were collected for the post-SARS-CoV-2 vaccination CVST group. In both groups, CVST had to be confirmed with computed tomography venography, magnetic resonance imaging, magnetic resonance venography, catheter angiography, or autopsy, in accordance with international guidelines.^{10,11} Patients' sex and, for the post-SARS-CoV-2 vaccination registry, race were reported in the case report form by the local investigator. The race of the participants was observed by investigators. CVST risk factors included oral contraceptive use, hormone therapy use, pregnancy, recent delivery (up to 12 weeks prior to CVST diagnosis), cancer, concomitant infection, previous thromboembolism, and known thrombophilia.

Thrombocytopenia was defined as a platelet count of less than $150 \times 10^3/\mu\text{L}$ (to convert to $\times 10^9$ per liter, multiply by 1) and was further categorized into mild (100 to $150 \times 10^3/\mu\text{L}$),

Figure. Flowchart of Patient Selection



moderate (50 to $100 \times 10^3/\mu\text{L}$), or severe (less than $50 \times 10^3/\mu\text{L}$).¹² Intracerebral hemorrhage was defined as hemorrhagic infarction or intracerebral hematoma. Functional outcome at hospital discharge among patients after SARS-CoV-2 vaccination was assessed using the modified Rankin Scale.¹³

Statistical Analysis

We did not perform an a priori power calculation but used data of all patients included in the study up to June 18, 2021. For the primary analysis, we used descriptive statistics to describe characteristics of the 3 groups (TTS, no TTS, and control). The number of missing values for each variable is reported. In exploratory secondary analyses, we calculated 95% CIs using the Wilson method for the frequencies of concomitant venous thromboembolism, new major bleeding during admission, and mortality at hospital discharge in each of the 3 groups. To compare mortality at hospital discharge between patients in the TTS group and the control group, we calculated unadjusted and age- and sex-adjusted odds ratios (ORs) with 95% CIs using logistic regression. For this specific analysis, we excluded patients in the TTS group who were still admitted to the hospital at the time of analysis. Data on age, sex, and mortality at discharge were otherwise complete in both groups, and age had a linear association with log (odds[mortality]). In a descriptive secondary analysis, we report treatment details and outcome of patients with CVST-TTS diagnosed before and after March 19, 2021, which is the date when the scientific community first became aware of this new syndrome and suggestions for treatment were circulated.

Results

Of 123 reported patients with CVST after SARS-CoV-2 vaccination, 7 were excluded: 3 patients were reported in duplicate, 2 had CVST symptom onset more than 28 days after vaccination, and 2 had CVST symptom onset prior to vaccination

(Figure). Thus, we included 116 patients with postvaccination CVST, diagnosed between January 30 and June 14, 2021. In total, 96 patients (82.8%) were vaccinated with ChAdOx1 nCov-19, 16 (13.8%) with BNT162b2 (Pfizer/BioNTech), 2 (1.7%) with CoronaVac (Sinovac), 1 (0.9%) with Ad26.COV2.S, and 1 (0.9%) with mRNA-1273 (Moderna). The pre-COVID-19 control group consisted of 207 patients. The distribution of patients per country is provided in eTables 1 and 2 in the Supplement.

Among the 116 patients with CVST after SARS-CoV-2 vaccination, 78 (67.2%) met the Brighton criteria for TTS. In the control group, 2 patients (1.0%) had new-onset thrombocytopenia without recent exposure to heparin and would therefore have met criteria for TTS. In both of these patients, thrombocytopenia was due to infection.

Of the 78 patients with TTS after SARS-CoV-2 vaccination, 76 (97%) had received ChAdOx1 nCov-19, 1 (1%) had received Ad26.COV2.S, and 1 (1%) had received BNT162b2. One patient developed CVST-TTS after the second ChAdOx1 nCov-19 vaccination. The patient who had received BNT162b2 presented with mild thrombocytopenia (platelet count of $148 \times 10^3/\mu\text{L}$) and had an alternative explanation for the thrombocytopenia (cyclosporine use). Two patients who received ChAdOx1 nCov-19 also had an alternative explanation for the thrombocytopenia (suspected Behçet disease [baseline platelet count of $90 \times 10^3/\mu\text{L}$] and suspected antiphospholipid antibody syndrome [baseline platelet count of $47 \times 10^3/\mu\text{L}$]).

The median (IQR) time from vaccination to CVST symptom onset was 9 (7-10) days in the TTS group and 7 (3-16) days in the no TTS group (Table 1). The median (IQR) platelet count at hospital admission among patients with postvaccination CVST-TTS was 45 (25 - 71) $\times 10^3/\mu\text{L}$. A total of 3 of 78 patients (4%) presented with a normal platelet count and developed thrombocytopenia during admission, 2 (3%) presented with mild thrombocytopenia, 30 (38%) with moderate thrombocytopenia, and 43 (55%) with severe thrombocytopenia. Details on the 5 patients with CVST-TTS with normal or mildly decreased platelet count at presentation are provided in eTable 3 in the Supplement. The median (IQR) platelet count nadir in

the TTS group was $30 (14-53) \times 10^3/\mu\text{L}$. PF4 antibodies were measured in 69 patients with TTS, of whom 63 (91%) tested positive (62 of 67 [93%] after ChAdOx1 nCov-19; 1 of 1 after Ad26.COV2.S; and 0 of 1 after BNT162b2). Of the 6 patients with negative PF4 antibody test findings, 3 were tested with an enzyme-linked immunosorbent assay (ELISA) and 3 with a rapid test. Findings of platelet activation assays were positive in all 36 tested patients (35 after ChAdOx1 nCov-19 and 1 after Ad26.COV2.S).

Baseline characteristics for those in the TTS, no TTS, and control groups are provided in **Table 2**. In the TTS, no TTS, and control groups, a conventional CVST risk factor was identified in 19 (24%), 16 (42%), and 110 (64.0%) patients, respectively. One patient in the TTS group and 1 in the no TTS group developed a COVID-19 infection after vaccination. In the TTS group, 7 patients (9%) presented with petechiae, 2 (3%) with purpura, and 4 (5%) with mucosal bleeding. Intracerebral hemorrhage at baseline was present in 53 patients (68%) in the TTS group.

Anticoagulant treatment was initiated in 67 patients with TTS (86%) (**Table 3**). Heparin treatment was initiated in 30 patients (38%) in the TTS group and 32 (84%) in the no TTS group, while nonheparin anticoagulants were started in 37 (47%) in the TTS group and in 6 (16%) in the no TTS group (eTable 4 in the **Supplement**). In the TTS group, 52 patients (67%) received immunomodulation therapy, most often intravenous immunoglobulins (47 [60%]). Of the patients with TTS, 60 (81%) were admitted to the intensive care unit, 16 (21%) underwent endovascular treatment, and 23 (30%) decompressive hemicraniectomy, compared with 8 (21%), 1 (3%), and 1 (3%), respectively, in the no TTS group, and 32 (17.9%), 1 (0.5%), and 10 (4.8%) in the control group.

A total of 25 patients (36%; 95% CI, 26-47) in the TTS group, 2 (6%; 95% CI, 2-19) in the no TTS group, and 10 (4.9%; 95% CI, 2.7-8.7) in the control group had concomitant thromboembolism in addition to CVST (**Table 3**). A new major bleeding complication during hospital admission occurred in 9 patients (12%; 95% CI, 6-21) in the TTS group, 3 (8%; 95% CI, 2-21) in the no TTS group, and 9 (4.4%; 95% CI, 2.3-8.1) in the control group. At the time of analysis, 76 patients (97%) in the TTS group and 37 (97%) in the no TTS group had been discharged from the hospital or had died. In-hospital mortality was 47% (36 of 76; 95% CI, 37-58) in the TTS group and 3.9% (8 of 207; 95% CI, 2.0-7.4) in the control group (unadjusted OR, 22; 95% CI, 10-52; age- and sex-adjusted OR, 46; 95% CI, 15-147). In-hospital mortality rate in the no TTS group was 5% (2 of 37; 95% CI, 1-18). All deaths in the TTS group were due to brain herniation. Within the TTS group, the mortality rate among patients receiving heparin as the first anticoagulant treatment was 41% (12 of 29). The mortality rate in patients with CVST-TTS treated with intravenous immunoglobulins was 28% (13 of 46). The median (IQR) time from hospital admission to death was 2 (1-4) days. The full range of the modified Rankin Scale scores at discharge among patients in the TTS and no TTS groups are depicted in the eFigure in the **Supplement**.

Prior to March 19, 2021, when the scientific community first became aware of this new syndrome, 8 of 23 patients

Table 1. Details of SARS-CoV-2 Vaccination, Previous COVID-19 Infection, and Thrombocytopenia

Variable	Group, No./total No. (%)	
	TTS (n = 78)	No TTS (n = 38)
SARS-CoV-2 vaccine ^a		
ChAdOx1 nCov-19	76/78 (97) ^b	20/38 (53)
Ad26.COV2.S	1/78 (1)	0
BNT162b2	1/78 (1)	15/38 (40) ^c
mRNA-1273	0	1/38 (3)
CoronaVac	0	2/38 (5)
Time from vaccination to CVST symptom onset, median (IQR), d ^d	9 (7-10)	7 (3-16)
Previous COVID-19 infection		
Confirmed ^e	0	4/36 (11)
Suspected	1/72 (1)	0
Thrombocytopenia details		
Platelet count at admission, median (IQR), $\times 10^3/\mu\text{L}$	45 (25-71)	272 (224-319)
Platelet count nadir, median (IQR), $\times 10^3/\mu\text{L}$	30 (14-53) ^f	NA
Positive for PF4 antibodies	63/69 (91) ^g	NA
Positive findings on platelet activation assays	36/36 (100)	NA
Positive for antiphospholipid antibodies	8/56 (14) ^h	0 ⁱ

Abbreviations: CVST, cerebral venous sinus thrombosis; NA, not applicable; TTS, thrombosis with thrombocytopenia syndrome.

SI conversion factor: To convert platelet count to $\times 10^9$ per liter, multiply by 1.

^a In the ChAdOx1 nCov-19 group, 29 different vaccine batch numbers could be identified among 53 patients; in the BNT162b2 group, 9 different batch numbers among 10 patients; and in the CoronaVac group, 1 batch number in 1 patient.

^b One patient developed CVST with TTS after the second ChAdOx1 nCov-19 vaccination; PF4 antibodies were not tested in this patient.

^c Nine patients developed CVST without TTS after the second BNT162b2 vaccination.

^d Data for 1 patient was missing in each group.

^e Positive findings on nucleic acid amplification test.

^f Data missing for 11 patients.

^g Of the 6 patients who tested negative for PF4 antibodies, 3 were tested with an enzyme-linked immunosorbent assay and 3 with a rapid test.

^h Not performed in 22 patients.

ⁱ Not performed in 9 patients.

with CVST-TTS (35%) were treated with intravenous immunoglobulins and 17 of 23 (74%) with heparin (**Table 4**). After March 19, 2021, 39 of 55 patients (71%) and 13 of 55 (24%) were treated with intravenous immunoglobulins and heparin, respectively. In-hospital mortality rate of patients with CVST-TTS before and after March 19, 2021, were 14 of 23 (61%) and 22 of 53 (42%), respectively.

Discussion

In this study, patients with CVST after recent SARS-CoV-2 vaccination who fulfilled the criteria for TTS had a severe clinical profile, with high rates of coma and intracerebral hemorrhage at presentation, high rates of concomitant thromboembolism, and death due to brain herniation occurring in ap-

Table 2. Baseline Characteristics of Patients With Cerebral Venous Sinus Thrombosis (CVST) After SARS-CoV-2 Vaccination With and Without Thrombocytopenia Syndrome (TTS)

Characteristic	Group, No./total No. (%)		
	TTS (n = 78)	No TTS (n = 38)	Control (n = 207)
Demographic characteristics			
Age, mean (SD), y	45 (14)	55 (20)	42 (16)
Sex			
Female	63/78 (81)	30/38 (79)	145/207 (70.0)
Male	15/78 (19)	8/38 (21)	62/207 (30.0)
Race			
Asian	4/77 (5)	2/38 (5)	ND
Black	0	1/38 (3)	ND
White	73/77 (95)	35/38 (92)	ND
CVST risk factors			
Any conventional CVST risk factor	19/78 (24)	16/38 (42)	110/172 (64.0)
Oral contraceptives ^a	11/63 (17)	9/30 (30)	61/144 (42.4)
Hormone therapy among women ^a	2/63 (3)	1/30 (3)	0
Pregnancy ^a	0	0	14/145 (9.7)
Recent delivery ^a	0	1/30 (3)	4/145 (2.8)
Any infection	5/78 (6)	0	19/206 (9.2)
Previous thromboembolism	1/78 (1) ^b	1/38 (3) ^c	17/202 (8.4)
Known thrombophilia	1/78 (1) ^d	1/38 (3) ^e	17/181 (9.4)
Cancer	3/78 (4)	3/38 (8)	20/207 (9.7)
Clinical presentation of CVST			
Time from symptom onset to CVST diagnosis, median (IQR), d	3 (2-4)	3 (0-8)	5 (2-11)
Headache	75/78 (96)	30/38 (79)	185/207 (89.4)
Focal neurologic deficits	41/78 (53)	14/38 (37)	128/206 (62.1)
Seizure	8/78 (10)	13/38 (34)	62/205 (30.2)
Coma	18/75 (24)	1/37 (3)	10/207 (4.8)
Baseline imaging characteristics of CVST			
Thrombosis location ^f			
Sinus			
Superior sagittal	43/77 (56)	15/38 (39)	102/207 (49.3)
Lateral ^g	67/77 (87)	27/38 (71)	129/207 (62.3)
Straight	17/77 (22)	3/38 (8)	24/207 (11.6)
Deep venous system ^h	10/77 (13)	1/38 (3)	23/207 (11.1)
Cortical vein	17/77 (22)	12/38 (32)	38/207 (18.4)
Intracerebral hemorrhage	53/78 (68)	10/38 (26)	72/207 (34.8)
Focal edema only	4/75 (5)	4/38 (11)	30/207 (14.5)

Abbreviation: ND, not determined.

^a Includes female patients only.

^b Deep vein thrombosis.

^c Cerebral venous thrombosis.

^d Prothrombin G20210A variant.

^e MTHFR heterozygous variant.

^f Multiple locations are possible for each individual.

^g Transverse or sigmoid sinus.

^h Vein of Galen, basal vein of Rosenthal, internal cerebral vein, inferior longitudinal sinus, thalamostriate, or caudate veins.

proximately half of all patients. This clinical profile was distinct from both patients with postvaccination CVST who did not fulfill the criteria for TTS as well as a control group of patients with CVST from prior to the COVID-19 pandemic. The age- and sex-adjusted risk of death was higher for patients with CVST-TTS than for control patients with CVST. In contrast, patients with postvaccination CVST who did not fulfill the TTS criteria were largely similar to those in the control group with regard to both clinical manifestations and outcome.

The current findings support the usefulness of the interim case definition for TTS from the Brighton Collaboration for case finding purposes.⁷ Nevertheless, it is important to note that 3 patients with TTS in our study had a normal platelet count at baseline and developed thrombocytopenia

only during hospital admission. Two of these patients also were positive for PF4 antibodies, while this was not tested with ELISA in the third patient. On the other hand, while the Brighton case definition uses a platelet count cutoff of $150 \times 10^3/\mu\text{L}$, 73 of 78 patients (94%) in this study had a baseline platelet count of less than $100 \times 10^3/\mu\text{L}$. Positivity for PF4 antibodies was also high in the TTS group (63 of 69 tested patients [91%]). As also noted in previous reports,¹ a small minority of patients (3 in our study) fulfilling criteria for TTS tested negative for PF4 antibodies despite the use of an ELISA test. However, the sensitivity of different PF4 ELISA tests has been found to vary.¹⁴

In accordance with prior reports,^{1,2} most patients fulfilling the criteria for TTS presented after vaccination with

Table 3. Clinical Course, Treatment, and Outcomes of Patients With Cerebral Venous Sinus Thrombosis (CVST) After SARS-CoV-2 Vaccination With and Without Thrombocytopenia Syndrome (TTS)

Treatment and outcome	Group, No./total No. (%)		
	TTS (n = 78)	No TTS (n = 38)	Control (n = 207)
CVST treatment			
Any anticoagulant treatment	67/78 (86) ^a	38/38 (100)	200/206 (97.1)
Intensive care unit admission	60/74 (81)	8/38 (21)	32/179 (17.9)
Endovascular treatment	16/77 (21)	1/38 (3)	1/207 (0.5)
Hemicraniectomy	23/77 (30)	1/38 (3)	10/207 (4.8)
Immunomodulation treatment			
Any immunomodulation treatment	52/78 (67)	NA	NA
Intravenous immunoglobulins	47/78 (60)	NA	NA
Plasma exchange	6/78 (8)	NA	NA
Corticosteroids	25/78 (32)	NA	NA
Ecilizumab	2/78 (3)	NA	NA
Rituximab	1/78 (1)	NA	NA
Platelet transfusion	20/78 (26)	NA	NA
Because of neurosurgical intervention	13/78 (17)	NA	NA
Outcomes			
Any concomitant thromboembolism	25/70 (36)	2/35 (6)	10/206 (4.9)
Splanchnic vein thrombosis	10/70 (14)	1/35 (3)	0
Deep vein thrombosis	6/70 (9)	0	3/206 (1.5)
Pulmonary embolism	16/70 (23)	0	3/206 (1.5)
Pelvic vein thrombosis	6/70 (9)	1/35 (3)	0
Other thrombosis	6/70 (9) ^b	1/35 (3) ^c	1/206 (0.5)
Any major bleeding complication ^d	9/76 (12)	3/37 (8)	9/206 (4.4)
New intracranial hemorrhage	8/76 (11)	3/37 (8)	ND
Other major bleeding	4/76 (5) ^e	0	ND
Mortality at discharge	36/76 (47)	2/37 (5)	8/207 (3.9)

Abbreviations: NA, not applicable; ND, not determined.

^a Reasons for withholding anticoagulant treatment included early death (n = 7), intracranial hemorrhage (n = 3), and CVST diagnosed at autopsy (n = 1).

^b Kidney vein (n = 1), inferior vena cava (n = 3), aortic arch thrombus (n = 1), ventricular thrombus (n = 1), myocardial infarction (n = 2), and basilar artery (n = 1).

^c Inferior vena cava thrombosis and brainstem ischemic stroke (n = 1).

^d According to the criteria of the International Society on Thrombosis and Haemostasis.

^e Adrenal (n = 2), intraocular (n = 1), and thigh (n = 1).

ChAdOx1 nCov-19. One patient who fulfilled the criteria for TTS presented after vaccination with Ad26.COV2.S and 1 after vaccination with BNT162b2. The patient with TTS after BNT162b2 vaccination, however, had mild thrombocytopenia for which an alternative explanation was found and negative findings on PF4 antibody test. As a result, while this patient fulfilled the diagnostic criteria for TTS, a causal relation with the BNT162b2 vaccine is unlikely. As the criteria of the Brighton Collaboration for TTS are designed for case finding and surveillance purposes, it is expected that some TTS cases do not correspond to vaccine-induced immune thrombotic thrombocytopenia, as is exemplified by the fact that 1% of patients from the control group also fulfilled the criteria for TTS.

Half of patients with CVST-TTS died in this study. While the proportion of patients treated with decompressive hemicraniectomy and endovascular intervention was high, several patients with TTS did not receive medical treatment according to current recommendations for this condition, namely the use of nonheparin anticoagulants and intravenous immunoglobulins.¹⁵⁻¹⁷ Of note, this was especially common among patients diagnosed before March 19, 2021, when the syndrome was first brought to wide attention. The mortality rate appeared to be lower in CVST-TTS cases after March 19, 2021; however, given the small sample size and inability to properly adjust for confounding variables, we could not as-

sess whether the outcome has truly improved with the evolution of treatment specifically aimed at TTS. Of note, even if the mortality rate improved after implementation of treatment guidelines, it persisted to be very high in more recent cases, highlighting the need for further studies to improve recognition and determine optimal treatment of CVST-TTS.

Although CVST-TTS is clearly a severe condition, it is important to note that our study was not aimed at determining whether the risks of any SARS-CoV-2 vaccine outweigh the benefits. The denominator of persons receiving each of the SARS-CoV-2 vaccines is unknown, and therefore, we were not able to determine the absolute risk of CVST-TTS after vaccination. COVID-19 is associated with a substantial risk of hospitalization and death as well as an increased risk of thrombotic events, including ischemic stroke and CVST.¹⁸⁻²⁰ Of note, one study found that patients hospitalized for COVID-19 have a higher risk of developing CVST than people vaccinated against SARS-CoV-2.²¹

Strengths and Limitations

This study has a number of strengths. To our knowledge, this is the largest registry of post-SARS-CoV-2 vaccination CVST described to date and includes detailed information on risk factors, clinical manifestations, and imaging of CVST. The network of stroke centers that was recruited for this

Table 4. Treatment and Outcome of 78 Patients With Cerebral Venous Sinus Thrombosis (CVST) With Thrombocytopenia Syndrome Before and After March 19, 2021^a

Outcome	No./total No. (%) Before March 19, 2021 (n = 23)	After March 19, 2021 (n = 55)
Baseline characteristics		
Age, mean (SD), y	44 (11)	46 (15)
Sex		
Female	20/23 (87)	43/55 (78)
Male	3/23 (13)	12/55 (22)
Time from symptom onset to CVST diagnosis, median (IQR), d	3 (1-4)	4 (2-5)
Coma	6/23 (26)	12/52 (23)
Intracerebral hemorrhage	20/23 (87)	33/55 (60)
Treatment		
Intravenous immunoglobulins	8/23 (35)	39/55 (71)
Plasma exchange	3/23 (13)	3/55 (6)
Corticosteroids	9/23 (39)	16/55 (29)
Eculizumab	1/23 (4)	1/55 (2)
Rituximab	0	1/55 (2)
Platelet transfusion	10/23 (44)	10/55 (18)
First started anticoagulant treatment		
Heparin ^b	17/23 (74)	13/55 (24)
Nonheparin anticoagulant ^c	2/23 (9)	35/55 (64)
No anticoagulant treatment started	4/23 (17) ^d	7/55 (13) ^e
Decompressive hemicraniectomy	9/23 (39)	14/54 (26)
Intensive care unit admission	20/23 (87)	40/51 (78)
Outcome		
New VTE during admission	6/21 (29)	6/49 (12)
New major bleeding during admission ^f	4/22 (18)	5/54 (9)
In-hospital mortality	14/23 (61)	22/53 (42)

Abbreviation: VTE, venous thromboembolism.

^a The proportion of included patients who were classified as having thrombosis with thrombocytopenia syndrome was 66% (23 of 35) prior to March 19 and 68% (55 of 81) thereafter.^b Low-molecular-weight heparin or unfractionated heparin.^c Fondaparinux, argatroban, danaparoid, or direct oral anticoagulant.^d Reasons for withholding anticoagulant treatment included early death (n = 2), intracranial hemorrhage (n = 1), and CVST diagnosed at autopsy (n = 1).^e Reasons for withholding anticoagulant treatment included early death (n = 5) and intracranial hemorrhage (n = 2).^f According to the criteria of the International Society on Thrombosis and Haemostasis.

project has a wide geographical coverage, and we collected consecutive cases, irrespective of vaccine type or platelet count. This is crucial to guarantee a broad overview of the full spectrum of cases possibly related to SARS-CoV-2 vaccination. This is important to avoid early assumptions on the expected clinical profile of CVST in the setting of SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia, which could lead to circular reasoning. Also, we have included a large control group of historical nonexposed cases. Data collection was standardized, and information on SARS-CoV-2 testing and PF4 antibodies was available in a high proportion of patients.

The study has several limitations. First, the lack of central adjudication of CVST diagnosis and study outcome measures is a possible source of imprecision and bias, although we have focused our analysis mainly on hard end points, such as mortality. Second, information was available up to hospital discharge only, precluding evaluation of the long-term consequences of CVST-TTS, which should be the focus of future studies. Third, differences in patients with postvaccination CVST and the historical control group should be taken into account. For example, many countries used different SARS-CoV-2 vaccines for different age groups, and pregnant women were partly excluded from SARS-CoV-2 vaccination at the time of study recruitment. Furthermore, the postvaccination CVST cohort included patients from countries not included in the historical control group, each with their own unique health care context. Unfortunately, the limited sample size precluded us from performing a secondary analysis comparing only cases from similar countries. Fourth, although we collected detailed information on treatment approach, the sample size and observational design of the study limits conclusions on the contribution of each specific approach to prognosis.

Conclusions

In this cohort study of patients with CVST, those with CVST-TTS after SARS-CoV-2 vaccination had a clinical profile distinct from patients with CVST before the COVID-19 pandemic, with high rates of coma and intracerebral hemorrhage and a high mortality rate. By contrast, patients with post-SARS-CoV-2 vaccination CVST who did not fulfill the criteria for TTS appeared to have a similar clinical presentation and prognosis as patients with CVST before the COVID-19 pandemic.

ARTICLE INFORMATION

Accepted for Publication: August 13, 2021.**Published Online:** September 28, 2021.

doi:10.1001/jamaneurol.2021.3619

Author Affiliations: Department of Neurology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Sánchez van Kammen, van de Munckhof, Krzywicka, Coutinho); Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitario Lisboa Norte, University of Lisbon, Lisbon, Portugal (Aguar de Sousa, Ferro);

Department of Neurology and Stroke, Eberhard-Karls University, Tuebingen, Germany (Poli); Hertie Institute for Clinical Brain Research, Eberhard-Karls University, Tuebingen, Germany (Poli); Department of Neurosciences and Cognition, Lille University Hospital, Lille, France (Cordonnier); Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (Heldner, Arnold); Department of Internal Medicine, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands (van Haaps); Department of Neurology, Carlo Poma Hospital, Azienda Socio

Sanitaria Territoriale di Mantova, Mantua, Italy (Ciccone); Department of Internal Medicine, Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands (Middeldorp); National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, United Kingdom (Levi); Department of Hematology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (Kremer Hovinga); Department of Neurology, Albert Schweitzer Hospital, Dordrecht, the Netherlands (Silvis); Department of Neurology, Helsinki

University Hospital, University of Helsinki, Helsinki, Finland (Hiltunen, Putaala); Sina Hospital, Hamadan University of Medical Science, Hamadan, Iran (Mansour); National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico City, Mexico (Arauz); Neurosciences Department, Hospital Dr R.A. Calderón Guardia, San José, Costa Rica (Barboza); Division of Neurology, University of British Columbia, Vancouver Stroke Program, Vancouver, British Columbia, Canada (Field); Second Department of Neurology in National, Kapodistrian University of Athens School of Medicine, Athens, Greece (Tsigvoulis); Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany (Nagel); Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden (Lindgren, Tatlisumak, Jood); Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden (Lindgren, Tatlisumak, Jood).

The Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group: Aarti R. Sharma; Ahmed Elkady, MD, MSc; Alberto Negro, MD, PhD; Albrecht Günther, MD; Alexander Gutschalk, MD; Silvia Schönenberger, MD; Alina Buture, MD; Sean Murphy, MD; Ana Paiva Nunes, MD; Andreas Tiede, MD, PhD; Anemon Puthuppallil Philip, MD; Annerose Mengel, MD; Antonio Medina, MD; Åslög Hellström Vogel, MD; Audrey Tawa, MD; Avinash Aujayeb, MBBS, MRCP; Barbara Casolla, MD, PhD; Brian Buck, MD; Carla Zanferrari, MD; Carlos Garcia-Esperon, MD, PhD; Caroline Vayne, PharmD, PhD; Catherine Legault, MD; Christian Pfrepper, MD; Clement Tracol, MD; Cristina Soriano, MD; Daniel Guisado-Alonso, MD; David Bougon, MD; Domenico S. Zimatore, MD; Dominik Michalski, MD; Dylan Blacquiere, MD; Elias Johansson, MD, PhD; Elisa Cuadrado-Godia, MD, PhD; Emmanuel De Maistre, MD, PhD; Emmanuel Carrera, MD; Fabrice Vuillier, MD, PhD; Fabrice Bonneville, MD, PhD; Fabrizio Giammello, MD; Felix J. Bode, MD; Julian Zimmerman, MD; Florindo d'Onofrio, MD; Francesco Grillo, MD, PhD; Francois Cotton, MD, PhD; François Caparros, MD; Laurent Puy, MD; Frank Maier, MD; Giosue Gulli, MD; Giovanni Frisullo, MD, PhD; Gregory Polkinghorne, MBBS; Guillaume Franchineau, MD; Hakan Cangür, MD, PhD; Hans Katzberg, MD; Igor Sibon, MD, PhD; Irem Baharoglu, MD, MSc; Jaskiran Brar, MD; Jean-François Payen, MD, PhD; Jim Burrow, MD; João Fernandes, MD; Judith Schouten, MD, PhD; Katharina Althaus, MD; Katia Garambois, MD, PhD; Laurent Derex, MD, PhD; Lisa Humbertjean, MD, PhD; Lucia Lebrato Hernandez, MD; Lukas Kellermair, MD; Mar Morin Martin, MD; Marco Petruzzellis, MD; Maria Cotelli, MD; Marie-Cécile Dubois, MD; Marta Carvalho, MD; Matthias Wittstock, MD, PhD; Miguel Miranda, MD, MSc; Mona Skjelland, MD, PhD; Monica Bandettini di Poggio, MD, PhD; Moritz J. Scholz, MD; Nicolas Raposo, MD, PhD; Robert Kahnis, MD; Nyika Kruyt, MD, PhD; Olivier Huet, MD, PhD; Pankaj Sharma, MD, PhD; Paolo Candelaresi, MD; Peggy Reiner, MD; Ricardo Vieira, MD; Roberto Acampora, MD; Rolf Kern, MD, PhD; Ronen Leker, MD; Shelagh Coutts, MD; Simerpreet Bal, MD; Shyam S. Sharma; Sophie Susen, MD, PhD; Thomas Cox, MD; Thomas Geeraerts, MD, PhD; Thomas Gattringer, MD, PhD; Thorsten Bartsch, MD, PhD; Timothy J. Kleinig, MBBS(Hons), PhD; Vanessa Dizonno, MSc; Yildiz Arslan, MD, MSc.

Affiliations of The Cerebral Venous Sinus

Thrombosis With Thrombocytopenia Syndrome

Study Group: Imperial College London School of Medicine, Imperial College London, London, United Kingdom (A. R. Sharma); Department of Neurology, Saudi German Hospital, Jeddah, Saudi Arabia (Elkady); Department of Neuroradiology, Ospedale del Mare, Naples, Italy (Negro); Department of Neurology, Jena University Hospital, Jena, Germany (Günther); Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany (Gutschalk, Schönenberger); Acute Stroke Service, Mater Misericordiae University Hospital, Dublin, Ireland (Buture, Murphy); UCD School of Medicine, University College Dublin, Dublin, Ireland (Murphy); School of Medicine, University of Medicine and Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland (Murphy); Department of Neurology, Centro Hospitalar de Lisboa Central, Lisbon, Portugal (Paiva Nunes); Clinic for Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany (Tiede); Department of Neurology, Hamilton General Hospital, Hamilton, Ontario, Canada (Puthuppallil Philip); Department of Neurology and Stroke, University Hospital Tuebingen, Tuebingen, Germany (Mengel); Department of Neurology, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain (Medina); Department of Internal Medicine, Skåne University Hospital, Lund, Sweden (Hellström Vogel); Department of Anesthesia and Intensive Care, University Hospital of Rennes, Rennes, France (Tawa); Respiratory Department, Northumbria Healthcare NHS Foundation Trust, Cramlington, United Kingdom (Aujayeb, Casolla); Stroke Unit, Hôpital Pasteur 2, URRIS - UR2CA, Unité de Recherche Clinique Cote d'Azur, Cote d'Azur University, Nice, France (Casolla); Division of Neurology, University of Alberta Hospital, Edmonton, Alberta, Canada (Buck); Department of Neurology, Azienda Ospedaliera di Melegnano e della Martesana, Melegnano, Italy (Zanferrari); Department of Neurology, John Hunter Hospital, Newcastle, Australia (Garcia-Esperon); Department of Hematology and Hemostasis, Tours University Hospital, Tours, France (Vayne); Department of Neurology and Neurosurgery, McGill University Health Centre, Montreal, Quebec, Canada (Legault); Division of Hemostaseology, Leipzig University Hospital, Leipzig, Germany (Pfrepper); Department of Neurology, CHU Rennes, Rennes, France (Tracol); Department of Neurology, Hospital General de Castellón, Castelló, Spain (Soriano); Department of Neurology, Hospital de La Santa Creu i Sant Pau, Barcelona, Spain (Guisado-Alonso); Department of Critical Care, Annecy Genevois Hospital, Annecy, France (Bougon); Department of Neuroradiology, Policlinico di Bari, Bari, Italy (Zimatore); Department of Neurology, Leipzig University Hospital, Leipzig, Germany (Michalski); Division of Neurology, The Ottawa Hospital, Ottawa, Ontario, Canada (Blacquiere); Department Clinical Science, Wallenberg Center for Molecular Medicine, Umeå University, Umeå, Sweden (Johansson); Department of Neurology, University Hospital del Mar, Barcelona, Spain (Cuadrado-Godia); Department of Biological Haematology, CHU Dijon, Dijon, France (De Maistre); Department of Neurology, Hôpitaux Universitaires de Genève, Geneva, Switzerland (Carrera); Stroke Unit, University Hospital of Besancon, Besancon, France (Vuillier); Department

of Neuroradiology, Toulouse University Hospital, Toulouse, France (Bonneville); Translational Molecular Medicine and Surgery, XXXV Cycle, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy (Giammello); Department of Neurology, Universitätsklinikum Bonn, Bonn, Germany (Bode, Zimmermann); Department of Neurology, San Giuseppe Moscati Hospital, Avellino, Italy (d'Onofrio); Stroke Unit, Department of Clinical and Experimental Medicine, University Hospital G. Martino, Messina, Italy (Grillo); Department of Radiology, Lyon University Hospital, Lyon, France (Cotton); Department of Neurosciences and Cognition, Lille University Hospital, Lille, France (Caparros, Puy); Department of Neurology, Caritas Hospital Saarbrücken, Saarbrücken, Germany (Maier); Department of Medicine, Ashford and St Peters Hospital NHS Foundation Trust, Surrey, United Kingdom (Gulli); Department of Neurology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy (Frisullo); Princess Alexandra Hospital, Brisbane, Australia (Polkinghorne); Department of Intensive Care, Centre Hospitalier Intercommunal de Poissy Saint Germain en Laye, Poissy, France (Franchineau); Department of Neurology, Hospital of the City of Wolfsburg, Wolfsburg, Germany (Cangür); Department of Neuromuscular Medicine, Toronto General Hospital, Toronto, Ontario, Canada (Katzberg); Department of Neurology, Bordeaux University Hospital, Bordeaux, France (Sibon); Department of Neurology, Haga Hospital, The Hague, the Netherlands (Baharoglu); Department of Neurology, Surrey Memorial Hospital, Surrey, British Columbia, Canada (Brar); Department of Anesthesia and Critical Care, CHU Grenoble, Grenoble, France (Payen); Department of Neurology, Royal Darwin Hospital, Tiwi, Australia (Burrow); Department of Neurology, Norra Älvsborgs Länssjukhus, Trollhattan, Sweden (Fernandes); Department of Neurology, Rijnstate Hospital Arnhem, Arnhem, the Netherlands (Schouten); Department of Neurology, Ulm University Hospital, Ulm, Germany (Althaus); Stroke Unit, University Hospital of Grenoble, Grenoble, France (Garambois); Department of Neurology, Hospices Civils de Lyon, Lyon, France (Derex); Stroke Unit, University Hospital of Nancy, Nancy, France (Humbertjean); Department of Neurology, Virgen del Rocío University Hospital, Seville, Spain (Lebrato Hernandez); Department of Neurology, Johannes Kepler University Linz, Linz, Austria (Kellermair); Department of Neurology, Hospital Complex of Toledo, Toledo, Spain (Morin Martin); Department of Neurology, AOJ Consorziale Policlinico di Bari, Bari, Italy (Petruzzellis); Department of Neurology, ASL Vallecampaonica-Sebino, Breno, Italy (Cotelli); Department of Anesthesia and Intensive Care, University Hospital of Poitiers, Poitiers, France (Dubois); Department of Neurology, Centro Hospitalar Universitário de São João, Faculdade de Medicina da Universidade do Porto, Porto, Portugal (Carvalho); Department of Neurology, University Hospital Rostock, Rostock, Germany (Wittstock); Department of Neurology, Hospital de Cascais Dr José de Almeida, Cascais, Portugal (Miranda); Department of Neurology, Oslo University Hospital, Oslo, Norway (Skjelland); Department of Neuroscience, Policlinic San Martino Hospital, Genoa, Italy (Bandettini di Poggio); Department of Neurology, Vivantes Auguste-Viktoria-Klinikum,

Berlin, Germany (Scholz); Department of Neurology, Toulouse University Hospital, Toulouse, France (Raposo, Kahnis); Department of Neurology, Leiden University Medical Centre, Leiden, the Netherlands (Kruij); UFR de Bio-médecine, Hospital de la Cavale Blanche, CHRU de Brest, Brest, France (Huet); Institute of Cardiovascular Research, Royal Holloway University of London, London, United Kingdom (P. Sharma); Department of Neurology and Stroke, Cardarelli Hospital, Naples, Italy (Candelaresi); Department of Neurology, Lariboisière Hospital, Paris, France (Reiner); Department of Hematology, Universidade Federal do Cariri, Juazeiro do Norte, Brazil (Vieira); Department of Neurology, Ospedale del Mare, Naples, Italy (Acampora); Department of Neurology, Kempten Hospital, Kempten, Germany (Kern); Department of Neurology, Hadassah University Medical Center, Jerusalem, Israel (Leker); Department of Clinical Neurosciences, Radiology, and Community Health Sciences, Foothills Medical Centre, Calgary, Alberta, Canada (Coutts, Bal); Edinburgh Medical School, University of Edinburgh, Edinburgh, United Kingdom (S. S. Sharma); Department of Hematology and Transfusion, Lille University Hospital, Lille, France (Susen); Department of Neurology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom (Cox); Department of Anesthesiology and Critical Care, Toulouse University Hospital, Toulouse, France (Geeraerts); Department of Neurology, Medical University of Graz, Graz, Austria (Gattringer); Department of Neurology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany (Bartsch); Department of Neurology, Royal Adelaide Hospital, Adelaide, Australia (Kleinig); Division of Neurology, University of British Columbia, Vancouver Stroke Program, Vancouver, British Columbia, Canada (Dizonno); Neurology Clinic, Medicana İzmir International Hospital, İzmir, Turkey (Arslan).

Author Contributions: Drs Sánchez van Kammen and van de Munkhof had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Sánchez van Kammen and Aguiar de Sousa contributed equally as co-first authors, and Drs Arnold and Coutinho contributed equally as co-last authors.

Study concept and design: Sánchez van Kammen, Aguiar de Sousa, Middeldorp, Levi, Field, Tatlisumak, Ferro, Arnold, Coutinho, Vuillier, d'Onofrio, Cotelli, Arslan.

Acquisition, analysis, or interpretation of data: Sánchez van Kammen, Aguiar de Sousa, Poli, Cordonnier, Heldner, van de Munkhof, Krzywicka, van Haaps, Ciccone, Levi, Kremer Hovinga, Silvis, Hiltunen, Mansour, Barboza, Field, Tsivgoulis, Nagel, Lindgren, Tatlisumak, Jood, Putaala, Ferro, Arnold, Coutinho, A. Sharma, Elkady, Negro, Günther, Gutschalk, Buture, Paiva Nunes, Tiede, Puthuppallil Philip, Mengel, Medina, Hellström Vogel, Tawa, Aujayeb, Casolla, Buck, Zanferrari, Garcia-Esperon, Vayne, Legault, Pfrepper, Tracol, Soriano, Guisado-Alonso, Bougon, Zimatore, Michalski, Blacquièrre, Johansson, Cuadrado-Godia, De Maistre, Carrera, Bonneville, Giamello, Bode, d'Onofrio, Grillo, Cotton, Caparros, Puy, Maier, Gulli, Frisullo, Polkinghorne, Franchineau, Cangür, Katzberg, Sibon, Baharoglu, Brar, Payen, Burrow, Fernandes, Schouten, Zimmermann, Althaus, Garambois, Derex, Humbertjean, Lebrato

Hernandez, Kellermair, Morin Martin, Petruzzellis, Dubois, Carvalho, Wittstock, Miranda, Skjelland, Bandettini di Poggio, Scholz, Raposo, Kruij, Huet, P. Sharma, Candelaresi, Reiner, Vieira, Kahnis, Acampora, Kern, Leker, Murphy, Coutts, S. Sharma, Schönenberger, Bal, Susen, Cox, Geeraerts, Gattringer, Bartsch, Kleinig, Dizonno.

Drafting of the manuscript: Sánchez van Kammen, Aguiar de Sousa, Heldner, Barboza, Coutinho, A. Sharma, Hellström Vogel, Tawa, Zimatore, Bonneville, d'Onofrio, Cotton, Brar, Humbertjean, Cotelli, Scholz, Arslan.

Critical revision of the manuscript for important intellectual content: Aguiar de Sousa, Poli, Cordonnier, Heldner, van de Munkhof, Krzywicka, van Haaps, Ciccone, Middeldorp, Levi, Kremer Hovinga, Silvis, Hiltunen, Mansour, Barboza, Field, Tsivgoulis, Nagel, Lindgren, Tatlisumak, Jood, Putaala, Ferro, Arnold, Coutinho, Elkady, Negro, Günther, Gutschalk, Buture, Paiva Nunes, Tiede, Puthuppallil Philip, Mengel, Medina, Aujayeb, Casolla, Buck, Zanferrari, Garcia-Esperon, Vayne, Legault, Pfrepper, Tracol, Soriano, Guisado-Alonso, Bougon, Michalski, Blacquièrre, Johansson, Cuadrado-Godia, De Maistre, Carrera, Vuillier, Giamello, Bode, d'Onofrio, Grillo, Caparros, Puy, Maier, Gulli, Frisullo, Polkinghorne, Franchineau, Cangür, Katzberg, Sibon, Baharoglu, Payen, Burrow, Fernandes, Schouten, Zimmermann, Althaus, Garambois, Derex, Lebrato Hernandez, Kellermair, Morin Martin, Petruzzellis, Cotelli, Dubois, Carvalho, Wittstock, Miranda, Skjelland, Bandettini di Poggio, Raposo, Kruij, Huet, P. Sharma, Candelaresi, Reiner, Vieira, Kahnis, Acampora, Kern, Leker, Murphy, Coutts, S. Sharma, Schönenberger, Bal, Susen, Cox, Geeraerts, Gattringer, Bartsch, Kleinig, Dizonno.

Statistical analysis: Sánchez van Kammen, Aguiar de Sousa, van Haaps, Aujayeb.

Obtained funding: Cordonnier, Tiede, Buck, Vuillier, Humbertjean.

Administrative, technical, or material support: Sánchez van Kammen, Cordonnier, Heldner, van de Munkhof, Krzywicka, Levi, Silvis, Barboza, Field, Tatlisumak, Putaala, Ferro, Buture, Tiede, Aujayeb, Buck, Zanferrari, Garcia-Esperon, Pfrepper, Michalski, Carrera, Bode, d'Onofrio, Cotton, Baharoglu, Burrow, Schouten, Zimmermann, Althaus, Cotelli, Carvalho, Miranda, Skjelland, P. Sharma, Candelaresi, Kern, Murphy, S. Sharma, Schönenberger, Bal, Susen, Cox, Geeraerts, Dizonno, Arslan.

Study supervision: Ciccone, Levi, Kremer Hovinga, Silvis, Hiltunen, Putaala, Arnold, Coutinho, Tiede, Medina, Zimatore, De Maistre, d'Onofrio, Frisullo, Morin Martin, Bandettini di Poggio, Acampora, Geeraerts, Bartsch.

Conflict of Interest Disclosures: Dr Aguiar de Sousa has received travel support from Boehringer Ingelheim and personal fees for advisory board participation from AstraZeneca. Dr Poli has received personal fees from AstraZeneca, Werfen, Portola, Bristol Myers Squibb/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Bayer; grants from the German Federal Ministry of Education and Research (REVISION randomized trial), German Federal Joint Committee Innovation Fund (APICES project), Daiichi Sankyo (SPOCT-DOAC 1 study), Bristol Myers Squibb/Pfizer (ATTICUS randomized trial), and European Union (PROOF randomized trial); and nonfinancial support from Werfen and Boehringer Ingelheim (REVISION randomized trial).

Dr Cordonnier has received speaker honoraria from

Boehringer Ingelheim, personal fees for advisory board participation from AstraZeneca and Biogen, and personal fees for steering committee participation from Biogen and Bristol Myers Squibb. Dr Heldner has received grants from the Swiss Heart Foundation and Bangerter Foundation; travel support from Bayer; personal fees for data safety monitoring board or advisory board participation from Amgen; and is a member of the European Stroke Organisation Board of Directors and European Stroke Organisation Education Committee. Dr Krzywicka has received travel support from Amgen. Dr Middeldorp has received grants from Bayer, Pfizer, Boehringer Ingelheim, and Daiichi Sankyo paid to her institution and personal fees from Bayer, Bristol Myers Squibb/Pfizer, Boehringer Ingelheim, AbbVie, Portola/Alexion, and Daiichi Sankyo paid to her institution. Dr Kremer Hovinga has received grants from Baxalta as well as personal fees paid to her institution from Shire, Ablynx, Roche, Sobi, and the Swiss Federal Office of Public Health. Dr Barboza has received payment or honoraria from Abbott, Pfizer, Roche, and Bayer. Dr Field has received grants and nonfinancial support from Bayer Canada as well as personal fees from Servier. Dr Nagel has received personal fees from Brainomix, Boehringer Ingelheim, and Pfizer. Dr Lindgren has received grants from the Swedish Neurological Society Academic, Elsa and Gustav Lindh's Foundation, Per Olof Ahl's Foundation, and Ulla Amlöv Foundation. Dr Tatlisumak has received personal fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Portola Pharmaceuticals. Dr Putaala has received personal fees from Boehringer Ingelheim, Bayer, Herantis Pharma, and Abbott and owns stock in Vital Signum. Dr Ferro has received personal fees from Boehringer Ingelheim, Bayer, and Daiichi Sankyo as well as grants from Bayer. Dr Arnold has received personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Covidien, Daiichi Sankyo, Medtronic, Novartis, Sanofi, Pfizer, and Amgen and grants from the Swiss National Science Foundation and Swiss Heart Foundation. Dr Coutinho has received grants paid to his institution from Boehringer Ingelheim and Bayer and payments paid to his institution for data safety monitoring board participation by Bayer. Dr Günther has received personal fees from Bayer Vital, Bristol Myers Squibb, and Daiichi Sankyo. Dr Blacquièrre has received personal fees from Servier Canada. Dr Johansson has received grants from WCMM Umeå, Region Västerbotten, Svenska Läkaresällskapet, Strokerisförbundet, and Hjärt-lungfonden. Dr d'Onofrio has received personal fees from Lilly, Teva, and Novartis. Dr Kern has received personal fees from Bristol Myers Squibb/Pfizer and Sanofi Genzyme. Dr Leker has received personal fees from Boehringer Ingelheim, Abbott, and Janssen. Dr Bartsch has received personal fees from Roche and Biogen and grants from Novartis. Dr Kleinig has received personal fees from Boehringer Ingelheim. No other disclosures were reported.

Additional Contributions: We thank Laura van Meenen, MD (Department of Neurology, Amsterdam UMC, Amsterdam, the Netherlands), for her help with the construction of the online case record form. She did not receive any compensation for her assistance.

REFERENCES

- Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. 2021;384(22):2092-2101. doi:10.1056/NEJMoa2104840
- Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384(22):2124-2130. doi:10.1056/NEJMoa2104882
- See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. *JAMA*. 2021;325(24):2448-2456. doi:10.1001/jama.2021.7517
- European Medicines Agency. Use of Vaxzevira to prevent COVID-19—article 5(3) procedure: assessment report. Accessed July 13, 2021. https://www.ema.europa.eu/en/documents/referral/use-vaxzevira-prevent-covid-19-article-53-procedure-assessment-report_en.pdf
- MacNeil JR, Su JR, Broder KR, et al. Updated recommendations from the Advisory Committee on Immunization Practices for use of the Janssen (Johnson & Johnson) COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome among vaccine recipients—United States, April 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(17):651-656. doi:10.15585/mmwr.mm7017e4
- Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost*. 2017;15(11):2099-2114. doi:10.1111/jth.13813
- Brighton Collaboration. Interim case definition of thrombosis with thrombocytopenia syndrome (TTS). Accessed July 13, 2021. <https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition>
- Zuurbier SM, Arnold M, Middeldorp S, et al. Risk of cerebral venous thrombosis in obese women. *JAMA Neurol*. 2016;73(5):579-584. doi:10.1001/jamaneurol.2016.0001
- Lindgren E, Silvis SM, Hiltunen S, et al. Acute symptomatic seizures in cerebral venous thrombosis. *Neurology*. 2020;95(12):e1706-e1715. doi:10.1212/WNL.00000000000010577
- Ferro JM, Boussier MG, Canhão P, et al; European Stroke Organization. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis—endorsed by the European Academy of Neurology. *Eur J Neurol*. 2017;24(10):1203-1213. doi:10.1111/ene.13381
- Saposnik G, Barinagarrementeria F, Brown RD Jr, et al; American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158-1192. doi:10.1161/STR.0b013e31820a8364
- Williamson DR, Albert M, Heels-Ansdell D, et al; PROTECT Collaborators, the Canadian Critical Care Trials Group, and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. *Chest*. 2013;144(4):1207-1215. doi:10.1378/chest.13-0121
- van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607. doi:10.1161/01.STR.19.5.604
- Vayne C, Rollin J, Gruel Y, et al. PF4 immunoassays in vaccine-induced thrombotic thrombocytopenia. *N Engl J Med*. 2021;385(4):376-378. doi:10.1056/NEJMc2106383
- Nazy I, Sachs UJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC Subcommittee on Platelet Immunology. *J Thromb Haemost*. 2021;19(6):1585-1588. doi:10.1111/jth.15341
- Furie KL, Cushman M, Elkind MSV, Lyden PD, Saposnik G; American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced immune thrombotic thrombocytopenia. *Stroke*. 2021;52(7):2478-2482. doi:10.1161/STROKEAHA.121.035564
- Ferro JM, de Sousa DA, Coutinho JM, Martinelli I. European Stroke Organization interim expert opinion on cerebral venous thrombosis occurring after SARS-CoV-2 vaccination. *Eur Stroke J*. Published online July 20, 2021. doi:10.1177/23969873211030842
- Baldini T, Asioli GM, Romoli M, et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: a systematic review and meta-analysis. *Eur J Neurol*. Published online January 11, 2021. doi:10.1111/ene.14727
- Mowla A, Shakibajahromi B, Shahjouei S, et al. Cerebral venous sinus thrombosis associated with SARS-CoV-2: a multinational case series. *J Neurol Sci*. 2020;419:117183. doi:10.1016/j.jns.2020.117183
- Al-Mufti F, Amuluru K, Sahni R, et al. Cerebral venous thrombosis in COVID-19: a New York Metropolitan cohort study. *AJNR Am J Neuroradiol*. 2021;42(7):1196-1200. doi:10.3174/ajnr.A7134
- Bikdeli B, Chatterjee S, Arora S, et al. Cerebral venous sinus thrombosis in the U.S. population, after adenovirus-based SARS-CoV-2 vaccination, and after COVID-19. *J Am Coll Cardiol*. 2021;78(4):408-411. doi:10.1016/j.jacc.2021.06.001