Management of Cerebral Venous Thrombosis Due to Adenoviral COVID-19 Vaccination

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Objective: Cerebral venous thrombosis (CVT) caused by vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare adverse effect of adenovirus-based severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) vaccines. In March 2021, after autoimmune pathogenesis of VITT was discovered, treatment recommendations were developed. These comprised immunomodulation, non-heparin anticoagulants, and avoidance of platelet transfusion. The aim of this study was to evaluate adherence to these recommendations and its association with mortality.
Methods: We used data from an international prospective registry of patients with CVT after the adenovirus-based SARS-CoV-2 vaccination. We analyzed possible, probable, or definite VITT-CVT cases included until January 18, 2022. Immunomodulation entailed administration of intravenous immunoglobulins and/or plasmapheresis.
Results: Ninety-nine patients with VITT-CVT from 71 hospitals in 17 countries were analyzed. Five of 38 (13%), 11 of 24 (46%), and 28 of 37 (76%) of the patients diagnosed in March, April, and from May onward, respectively, were treated in-line with VITT recommendations ($p < 0.001$). Overall, treatment according to recommendations had no statistically significant influence on mortality (14/44 [32%] vs 29/55 [52%], adjusted odds ratio [OR] = 0.43, 95% confidence interval [CI] = 0.16–1.19). However, patients who received immunomodulation had lower mortality (19/65 [29%] vs 24/34 [70%], adjusted OR = 0.19, 95% CI = 0.06–0.58). Treatment with non-heparin anticoagulants instead of heparins was not associated with lower mortality (17/51 [33%] vs 13/35 [37%], adjusted OR = 0.70, 95% CI = 0.24–2.04). Mortality was also not significantly influenced by platelet transfusion (17/27 [63%] vs 26/72 [36%], adjusted OR = 2.19, 95% CI = 0.74–6.54).
Conclusions: In patients with VITT-CVT, adherence to VITT treatment recommendations improved over time. Immunomodulation seems crucial for reducing mortality of VITT-CVT.

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Cases of cerebral venous thrombosis (CVT) have been reported after adenovirus-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination with ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca/Oxford) or Ad26.COV2.S (Janssen/Johnson & Johnson).[1–6] Due to an immune-mediated platelet-consuming mechanism, the condition has been named vaccine-induced immune thrombotic thrombocytopenia (VITT).[1–3] On March 28, 2021, after pathophysiological similarity between VITT and the autoimmune variant of heparin-induced thrombocytopenia (aHIT) became evident, treatment recommendations for VITT were proposed.[1,7] These differed radically from standard management of both CVT and thrombocytopenia.[1,8–10] Immunomodulation, which was known to limit the pathological immune response in aHIT, became a key component in the treatment of VITT.[9,11] Heparin, an established treatment for non-VITT CVT, was hypothesized to be harmful in patients with VITT-CVT due to cross-reactivity of platelet-activating antibodies against platelet factor 4 similar to those found in aHIT. Platelet transfusion, used as treatment for severe thrombocytopenia, was thought to carry a risk for worsening of thrombosis. Consequently, the new VITT treatment recommendations, comprised all 3 therapeutic approaches: (1) immunomodulation with intravenous immunoglobulins and/or plasma exchange (2) non-heparin-based anticoagulants (such as fondaparinux or argatroban), and, (3) when possible, avoidance of platelet transfusion.[1,8–10]

Using data from an international prospective registry, the aim of this study was (a) to analyze adherence of physicians to the published VITT treatment recommendations and (b) to determine whether adherence to treatment recommendations was associated with a reduction in mortality.

Methods

Study Design and Patient Selection

We analyzed data from an ongoing international CVT registry, details of which have been published.[12] In short, participating investigators were asked to report consecutive patients who developed CVT within 28 days of any SARS-CoV-2 vaccination from their hospital. Data were collected using a standardized electronic case report form (Castor EDC; Ciwit B.V., Amsterdam, The Netherlands). The ethical review committee of the Academic Medical Center Amsterdam gave a waiver of formal approval for this observational cohort study. Each center was responsible for obtaining permission from local authorities for study participation and for acquiring informed consent for the use of pseudonymized patient data if required by national law and hospital regulation. Authors A.S., K.K., S.P., and M.R.H. 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. The study was endorsed by the European Academy of Neurology and European Stroke Organisation.

For the current study, we included patients with possible, probable, or definite VITT-CVT according to the criteria proposed by an expert hematology panel by the British Society for Haematology,[13] who were reported to the consortium until January 18, 2022. In all included cases, CVT was confirmed radiologically or at autopsy,[14] and symptom onset was within 28 days of adenovirus-based SARS-CoV-2 vaccination.

Definitions

VITT treatment recommendations were defined based on the recommendations of the International Society

of Thrombosis and Haemostasis (ISTH)[10] with national guidelines being very similar (Table S1). To be treated according to recommendations, patients needed to fulfill 3 conditions: (1) treatment with immunomodulation (ie, intravenous immunoglobulins and/or plasma exchange); (2) treatment with non-heparin anticoagulants only (regardless of the baseline platelet count), or no anticoagulants (if there was systemic bleeding or if the baseline platelet count was below 50×10^3/μl); and (3) no platelet transfusion, unless required for surgery. Heparins were defined as unfractionated heparin or low-molecular-weight heparins in any dosage. Non-heparin anticoagulants were defined as any anticoagulant apart from unfractionated heparin or low-molecular-weight heparins. Major bleeding was also defined according to ISTH criteria.[15] Coma was defined as Glasgow Coma Scale score lower than 9.

Data Analysis

We used descriptive statistics for temporal analysis, for analysis of adherence to the recommendations, and for treatments and outcomes of patients treated with different modalities. We used nonparametric statistics to determine significance and considered a 2-sided probability value below 0.05 as significant. Confidence intervals (CIs) were calculated using Wilson's method. Specifically tested were: frequencies of baseline variables (age, intracerebral hemorrhage [ICH] at baseline, and platelet count at admission), adherence to recommendations, treatment modalities given, and mortality between patients diagnosed in 3 time periods from before (ie, March) to after introduction of VITT treatment recommendations (ie, April and from May onward).[1,7] The number of missing values for each variable is reported. Odds ratios (ORs) for mortality per different treatment modality were calculated using binary logistic regression. Based on previous studies on predictors of mortality in CVT in general and in VITT-CVT, we adjusted for the following variables: age, coma, ICH at presentation, and baseline platelet count.[12,13,16] Primary outcome was in-hospital mortality. As a sensitivity analysis, we performed the same unadjusted and adjusted binary logistic regression including only definite VITT-CVT cases.

Analyses were performed with IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY).

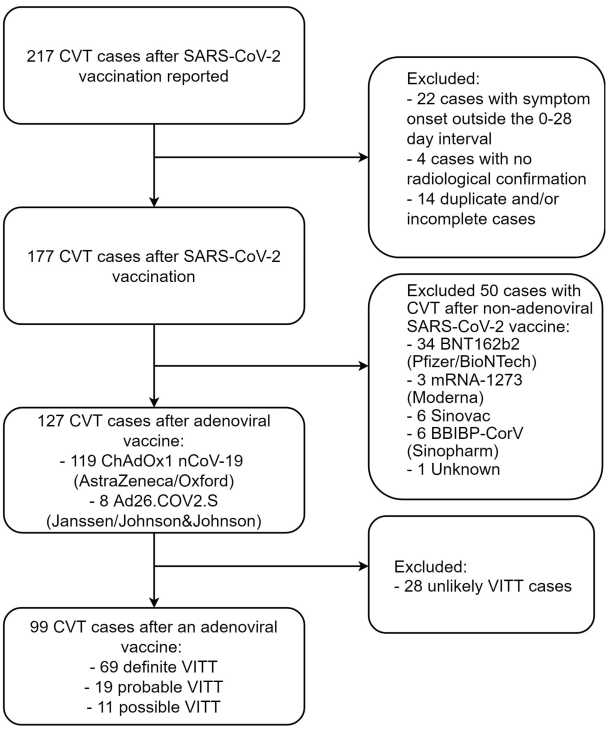

Figure 1: Flowchart of patient selection. CVT = cerebral venous thrombosis; nCOV = novel coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; VITT = vaccine-induced immune thrombotic thrombocytopenia.

Table 1. Participating Countries

Participating countries	No. of cases
Australia	10
Austria	2
Belgium	3
Canada	7
Finland	2
France	14
Germany	22
Iran	4
Ireland	1
Italy	13
Netherlands	4
Norway	5
Portugal	1
Saudi Arabia	3
Spain	3
Sweden	3
United Kingdom	2
Total	99

Table 2. Baseline Characteristics and Vaccination Details Among Patients with VITT-CVT Diagnosed in March, April, and from May Onward

	All VITT-CVT (N = 99)	VITT-CVT diagnosed in March (N = 38)	VITT-CVT diagnosed in April (N = 24)	VITT-CVT diagnosed from May onwards (N = 37)	*p* value
Baseline characteristics					
Age, yr[a]	47 (32–57)	44 (32–52)	43 (30–62)	50 (39–63)	0.124
Sex, female	75/99 (75)	33/38 (86)	17/24 (70)	25/37 (67)	0.122
Risk factor[b]	47/99 (47)	20/38 (53)	12/24 (50)	15/37 (41)	0.554
Additional VTE[c]	22/99 (22)	6/38 (15)	4/24 (16)	12/37 (32)	0.310
Coma	24/99 (24)	9/38 (23)	6/24 (25)	9/37 (24)	0.950
Intracerebral hemorrhagic lesion	71/99 (71)	33/38 (86)	17/24 (70)	21/37 (56)	0.015
Intracerebral non-hemorrhagic lesion	26/99 (26)	15/38 (39)	5/24 (20)	6/37 (16)	0.177
Platelet count, $\times 10^3$/μl[a]	48 (27–75)	39 (24–64)	50 (29–82)	54 (29–85)	0.152
D-dimer, mg/l FEU[a]	20 (9–35)	31 (13–35)	17 (5–24)	18 (8–29)	0.049
Fibrinogen, g/l[a]	2.0 (1.1–2.8)	1.8 (1.1–2.6)	2.3 (1.1–3.4)	2.2 (1.1–2.8)	0.448
Anti PF4 antibodies					**0.499**
Positive	79/99 (79)	28/38 (73)	20/24 (83)	31/37 (83)	
Negative	7/99 (7)	4/38 (10)	0/24 (0)	3/37 (8)	
Not tested	13/99 (13)	6/38 (15)	4/24 (16)	3/37 (8)	
VITT classification					**0.030**
Definite	69/99 (69)	26/38 (68)	14/24 (58)	29/37 (78)	
Probable	19/99 (19)	8/38 (21)	9/24 (37)	2/37 (5)	
Possible	11/99 (11)	4/38 (10)	1/24 (4)	6/37 (16)	
Vaccine type					**0.001**
ChAdOx1 nCoV-19	91/99 (91)	38/38 (100)	24/24 (100)	29/37 (78)	
Ad26.COV2.S	8/99 (8)	0/38 (0)	0/24 (0)	8/37 (12)	
Days from vaccination to symptom onset[a]	9 (7–10)	8 (7–10)	9 (7–11)	9 (6–11)	0.776
Days from symptom onset to diagnosis[a]	3 (1–5)	3 (2–4)	2 (1–4)	4 (1–7)	0.253

CVT = cerebral venous thrombosis; FEU = fibrinogen equivalent units; nCOV = novel coronarvisus; PF4 = platelet factor 4; VITT = vaccine-induced immune thrombotic thrombocytopenia; VTE = venous thromboembolism.

[a]Median (interquartile range [IQR]), all other data shown in n/N (%).

[b]Risk factors for CVT included = prothrombotic medication, recent delivery (12 weeks), pregnancy, recent head trauma (1 week), recent head or neck infection (1 week), recent central nervous system infection, other infection, history of autoimmune disease, previous VTE, known thrombophilia, dehydration (1 week), history of cancer (last 10 years), first degree relative with VTE.

[c]Additional VTE at presentation: pulmonary embolism n = 8, pulmonary embolism and portal vein thrombosis n = 2, pulmonary embolism, portal and hepatic vein thrombosis n = 1, pulmonary embolism, hepatic and iliac vein thrombosis n = 1, pulmonary embolism and uterine vein thrombosis n = 2, pulmonary embolism, cava and popliteal vein thrombosis n = 1, pulmonary embolism, vena cava thrombosis and right ventricular thrombus n = 1, hepatic vein thrombosis n = 2, hepatic and portal vein thrombosis n = 1, renal vein thrombosis n = 1, thrombosis of deep veins of the leg (not specified) n = 1, and deep vein thrombosis (not specified) n = 1.

Results

Of the 217 cases with CVT after SARS-CoV-2 vaccination reported in the registry until January 18, 2022, there were 99 patients from 71 hospitals in 17 countries who fulfilled the selection criteria and were included in the analysis. Patient selection is shown in Figure 1. Patients were diagnosed between March 3, 2021, and August 24, 2021. For distribution of patients between countries, see Table 1.

Median age (interquartile range [IQR]) was 47 (32–57) years and 75 of 99 (75%) of the patients were women. Ninety-one of 99 (92%) patients received the ChAdOx1 nCov-19 vaccine and 8 of 99 (8%) received the Ad26.COV2.S vaccine. Three patients (3%) developed VITT-CVT after a second dose of ChAdOx1 nCov-19 vaccine. One patient with definite VITT had confirmed coronavirus disease 2019 (COVID-19) 8 days after vaccination (3 days before CVT diagnosis). Further baseline characteristics are presented in Table 2.

Temporal Change in Management and Outcome

With a median age (IQR) of 44 (IQR = 32–52) and 43 (IQR = 30–62), patients diagnosed in March and in April, respectively, tended to be younger than those diagnosed in May and onward (50 [IQR = 39–63] years,

Table 3. Treatment and Outcomes in Patients With VITT-CVT Diagnosed in March, April, and from May Onward

	All VITT-CVT (N = 99)	VITT-CVT diagnosed in March (N = 38)	VITT-CVT diagnosed in April (N = 24)	VITT-CVT diagnosed from May onwards (N = 37)	*p* value
Immunomodulation	65/99 (66)	20/38 (53)	13/24 (54)	32/37 (87)	0.003
IVIG	64/99 (64)	19/38 (50)	13/24 (54)	32/37 (86)	0.002
Only IVIG	38/99 (38)	8/38 (21)	9/24 (37)	21/37 (56)	0.056
Plasma exchange	4/99 (4)	3/38 (8)	0/24 (0)	1/37 (2)	0.267
Anticoagulation					
Any anticoagulant	86/99 (86)	33/38 (86)	19/24 (79)	34/37 (92)	0.356
Heparins at any time	34/99 (34)	26/38 (68)	4/24 (16)	4/37 (10)	0.000
Non-heparins at any time	73/99 (34)	22/38 (58)	17/24 (70)	34/37 (92)	0.003
Non-heparins only	51/99 (51)	7/38 (18)	15/24 (62)	29/37 (78)	0.000
Platelet transfusion	27/99 (27)	15/38 (39)	4/24 (16)	8/37 (21)	0.090
Platelet transfusion for intended acute surgery	15/99 (15)	8/38 (21)	0/24 (0)	7/37 (18)	
Platelet transfusion not for intended acute surgery	12/99 (12)	7/38 (18)	4/24 (16)	1/37 (2)	
Treated according to all recommendations	44/99 (44)	5/38 (13)	11/24 (46)	28/37 (76)	0.000
Bleeding complication during admission	32/99 (32)	14/38 (36)	5/24 (20)	13/37 (35)	0.495
Worsening or new ICH	24/99 (24)	11/38 (29)	2/24 (8)	11/37 (29)	0.495
Outcome					
Death	43/99 (43)	20/38 (52)	12/24 (50)	11/37 (29)	0.102

CVT = cerebral venous thrombosis; heparins = unfractionated heparin and/or low-molecular-weight heparins; ICH = intracerebral hemorrhage; Immunomodulation = IVIG and/or plasmapheresis; IVIG = intravenous immunoglobulins; VITT = vaccine-induced immune thrombotic thrombocytopenia.
All data shown in n/N (%).

$p = 0.124$). Cases diagnosed in March and April more frequently presented with ICH (87% vs 71%, respectively) compared to cases diagnosed from May onward (57%, $p = 0.015$). Early cases had a similar median (IQR) baseline platelet level of 39 (IQR = 24–64) × 10^3 per μl versus 50 (IQR = 29–82) and 54 (IQR = 29–85) × 10^3 per μl in those diagnosed in April and in May and onward ($p = 0.152$). Median (IQR) number of days between the vaccination and symptom onset were 8 (IQR = 7–10) versus 9 (IQR = 7–11) versus 9 (IQR = 6–11) in cases diagnosed in March versus April versus from May onward ($p = 0.776$). Thirteen out of 99 (13%) patients died within 24 hours of admission.

In March, 20 of 38 (53%) patients versus April, 13 of 24 (54%) patients versus from May onward, 32 of 37 (87%) patients were treated with immunomodulation ($p = 0.003$), 26 of 38 (68%) versus 4 of 24 (16%) versus 4 of 37 (10%) with heparins ($p < 0.001$), and 7 of 38 (18%) versus 4 of 24 (16%) versus 1 of 37 (2%) patients were given platelet transfusion unrelated to surgery ($p = 0.084$; Table 3).

Overall, the proportion of patients treated according to VITT recommendations increased over time: 5 of 38 (13%), 11 of 24 (46%), and 28 of 37 (76%) in March, April, and from May onward, respectively ($p < 0.001$; see Table 3). Twenty of 38 (52%, 95% CI = 37–67%) patients with VITT-CVT treated in March, 12 of 24 (50%, 95% CI = 31–68%) treated in April, and 11 of 37 (29%, 95% CI = 17–45%) treated from May onward, died (Fig 2) (March and April vs May, $p = 0.034$).

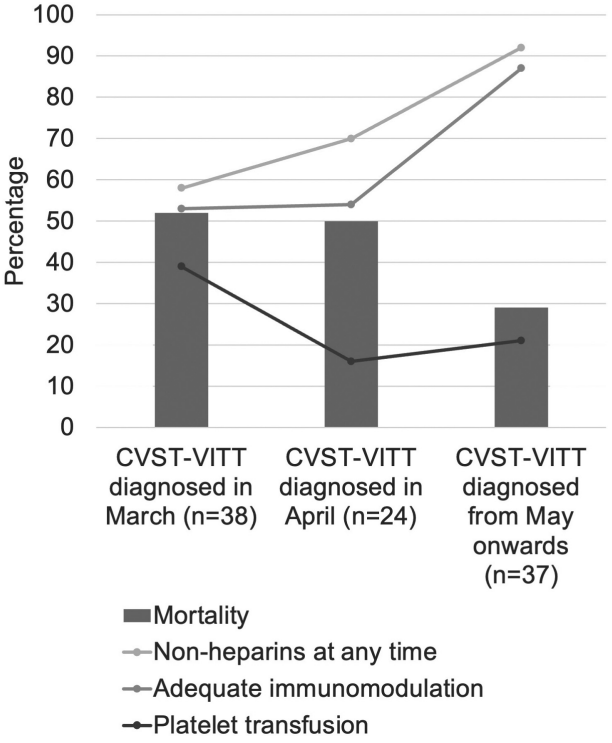

Figure 2: Temporal changes in treatments given to patients with VITT-CVT diagnosed in March, April, and from May onward. CVT = cerebral venous thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia.

Descriptive Analysis of Management

Forty-four of all 99 patients with VITT-CVT (44%) were treated according to VITT recommendations. Among patients who were not treated according to recommendations, 32 of 55 (58%) were diagnosed before the pathophysiological mechanism was published. Interestingly, 5 patients received appropriate treatments even before VITT recommendations were published on March 28, 2021. Among patients who did not fulfill one recommendation criterium (24/55, 44%), this was due to administration of heparins or withholding anticoagulation (16/24, 67%), lack of immunomodulation (6/24, 25%), and platelet transfusion without surgery indication (2/24, 8%). In 25 of 55 (45%) cases, 2 criteria were not fulfilled, and in 6 of 55 (11%) cases all 3 criteria were not fulfilled.

Among patients who received immunomodulation, 61 of 65 (94%) received intravenous immunoglobulins, 1 of 65 (2%) received plasma exchange, and 3 of 65 (5%) received both. Twenty-five of 65 (38%) patients received adjuvant steroids. Two patients received additional eculizumab, 2 of 65 (2%). Among those who did not receive immunomodulation, 4 of 34 (11%) received steroids only.

Eighty-six of 99 patients (86%) received any anticoagulation of whom 13 (15%) were treated only with heparins, 51 (59%) only with non-heparins, and 22 (26%) with both. Reasons for not administering anticoagulation were brain death on admission or soon thereafter (5/13, 38%), limitation of care due to poor prognosis (2/13, 15%), extensive intracranial hemorrhage (4/13, 31%), unawareness of VITT diagnosis (1/13, 8%) and unknown (1/13, 8%).

Out of 27 of 99 (27%) patients who received platelet transfusion, 15 of 27 (56%) were transfused prior to planned surgery and 12 of 15 (80%) of these actually underwent surgery. Baseline platelet count was similar among patients who received platelet transfusion (median 48 [IQR = 27–77] × 10^3 per μl) and patients who did not (49 [IQR = 27–75] × 10^3 per μl, $p = 0.712$). Platelet nadir values, however, differed significantly between transfused (20 [IQR = 11–32]) and non-transfused patients (37 [IQR = 25–61], $p < 0.001$). Furthermore, more patients treated with platelet transfusion had ICH at baseline (22/27 [81%] vs 49/72 [68%]), coma at baseline

Table 4. Baseline Characteristics, Treatment, and Outcome in Patients With VITT-CVT in Different Treatment Groups

	According to all recommendations		Immunomodulation		Non-heparins only[b]		Platelet transfusion	
	Yes (N = 44)	No (N = 55)	Yes (N = 65)	No (N = 34)	Yes (N = 51)	No (N = 35)	Yes (N = 27)	No (N = 72)
Baseline characteristics								
Age, yr[a]	48 (37–62)	44 (31–54)	46 (32–58)	47 (32–57)	47 (33–60)	42 (27–50)	46 (33–60)	47 (31–57)
Sex, female	30/44 (68)	45/55 (81)	49/65 (75)	26/34 (76)	37/51 (72)	28/35 (80)	20/27 (74)	55/72 (76)
Coma	8/44 (18)	16/55 (29)	11/65 (17)	13/34 (38)	10/51 (19)	5/35 (14)	11/27 (40)	13/72 (18)
ICH	30/44 (68)	41/55 (74)	44/65 (67)	27/34 (79)	32/51 (62)	26/35 (74)	22/27 (81)	49/72 (68)
Intracerebral non-hemorrhagic lesion	9/44 (20)	17/55 (30)	13/65 (20)	13/34 (38)	13/51 (25)	10/35 (28)	8/27 (29)	18/72 (25)
Platelet count, $\times 10^3/\mu l$[a]	52 (29–79)	47 (24–68)	53 (29–77)	39 (22–61)	50 (29–76)	49 (27–75)	48 (27–77)	49 (25–75)
Immuno-modulation	44/44 (100)	21/55 (38)	–	–	44/51 (86)	18/35 (51)	17/27 (63)	48/72 (67)
IVIG	44/44 (100)	20/55 (36)	64/65 (98)	0/34 (0)	44/51 (86)	17/35 (48)	16/27 (59)	48/72 (66)
Only IVIG	30/44 (68)	8/55 (14)	38/65 (58)	0/34 (0)	30/51 (58)	7/35 (20)	9/27 (33)	29/72 (40)
Plasma exchange	1/44 (2)	3/55 (5)	4/65 (6)	0/34 (0)	1/51 (2)	3/35 (8)	2/27 (7)	2/72 (2)
Anticoagulation								
Any anticoagulant	42/44 (95)	44/55 (80)	62/65 (95)	24/34 (70)	–	–	22/27 (81)	64/72 (89)
No anticoagulant	2/44 (4)	11/55 (20)	3/65 (4)	10/34 (29)	–	–	5/27 (18)	8/72 (11)
Heparins at any time	0/44 (0)	35/55 (63)	18/65 (27)	17/34 (50)	–	35/35 (100)	11/27 (40)	23/72 (32)
Non-heparins only	42/44 (95)	9/55 (16)	44/65 (67)	7/34 (20)	51/51 (100)	–	11/27 (40)	40/72 (56)
Platelet transfusion								
Platelet transfusion for any reason	8/44 (18)	19/55 (34)	17/65 (26)	10/34 (29)	11/51 (21)	11/35 (31)	–	–
Platelet transfusion for acute surgery	8/44 (18)	7/55 (12)	12/65 (18)	3/34 (8)	8/51 (15)	6/35 (17)	15/27 (56)	–
Mechanical thrombectomy	7/44 (16)	10/55 (18)	12/65 (18)	5/34 (14)	10/51 (20)	7/35 (20)	4/27 (15)	13/72 (18)
Decompressive craniectomy	13/44 (29)	17/55 (31)	23/65 (35)	7/34 (20)	14/51 (27)	14/35 (40)	14/27 (52)	16/72 (22)
Complications								
New bleeding complication	17/44 (38)	15/55 (27)	23/65 (35)	9/34 (26)	19/51 (37)	9/35 (25)	16/27 (59)	16/72 (22)
Worsening of or new ICH	14/44 (31)	10/55 (18)	19/65 (29)	5/34 (14)	15/51 (29)	7/35 (20)	13/27 (48)	11/72 (15)
New VTE	6/44 (13)	9/55 (16)	10/65 (15)	5/34 (14)	7/51 (13)	6/35 (17)	9/27 (33)	6/72 (8)
Outcome								
Death	14/44 (32)	29/55 (52)	19/65 (29)	24/34 (70)	17/51 (33)	13/35 (37)	17/27 (63)	26/72 (36)

CVT = cerebral venous thrombosis; heparins = unfractionated heparin and/or low-molecular-weight heparins; ICH = intracerebral hemorrhage; immunomodulation = IVIG and/or plasmapheresis; IVIG = intravenous immunoglobulins; VITT = vaccine-induced immune thrombotic thrombocytopenia; VTE = venous thromboembolism.
[a]Median (interquartile range [IQR]), all other data shown in n/N (%);
[b]Patients with no anticoagulation were excluded (n = 13).

(11/27 [40%] vs 13/72 [18%]), and were treated with decompressive craniectomy (14/27 [52%] vs 16/72 [22%]).

Detailed descriptive analysis of patients who were treated using different modalities is shown in Table 4.

Association Between Management and in-Hospital Mortality

Among patients who were treated according to VITT recommendations, 14 of 44 (32%, 95% CI = 20–46%) died, compared to 29 of 55 (52%, 95% CI = 39–65%) patients who were not treated according to recommendations (adjusted OR = 0.43, 95% CI = 0.16–1.19; Table 5).

Patients who were treated with immunomodulation had a lower risk of death than patients who were not treated with immunomodulation (19/65 [29%] vs 24/34 [70%], adjusted OR = 0.19, 95% CI = 0.06–0.58; see Table 5). Treatment with non-heparins as the sole type of anticoagulation was not associated with the risk of death compared to use of heparins (17/51 [33%] vs 13/35 [37%], adjusted OR = 0.70, 95% CI = 0.24–2.04). All patients who were not treated with any anticoagulation died (13/13, 100%). Patients who received platelet transfusion (regardless of whether they received surgery or not) did not have a higher risk of death (17/27 [63%] vs 26/72 [36%], adjusted OR = 2.19, 95% CI = 0.74–6.54). In a sensitivity analysis including only patients with

Table 5. Odds Ratios for Mortality in Patients With VITT-CVT in Different Treatment Groups

	Mortality per group, n/N (%)			
Treatment group	**Received treatment**	**Did not receive treatment**	**Unadjusted OR (95% CI)**	**Adjusted[a] OR (95% CI)**
According to all recommendations	14/44 (32)	29/55 (52)	0.42 (0.18–0.96)	0.43 (0.16–1.19)
Immunomodulation[b]	19/65 (29)	24/34 (70)	0.17 (0.07–0.43)	0.19 (0.06–0.58)
Non-heparins only[c]	17/51 (33)	13/35 (37)	0.85 (0.34–2.1)	0.70 (0.24–2.04)
Platelet transfusion	17/27 (63)	26/72 (36)	3.01 (1.20–7.50)	2.19 (0.74–6.54)

95% CI = 95% confidence interval; CVT = cerebral venous thrombosis; OR = odds ratios; VITT = vaccine-induced immune thrombotic thrombocytopenia.

[a]Adjusted for age, coma, intracranial hemorrhage, and platelet count at presentation.

[b]Immunomodulation comprised intravenous immunoglobulins and/or plasma exchange.

[c]Patients who received only non-heparins compared with patients who received unfractionated heparin and/or low-molecular weight heparins at any time. Patients with no anticoagulation were excluded (n = 13).

Table 6. Odds Ratios for Mortality in Patients With Definite VITT-CVT in Different Treatment Groups

	Mortality per group, n/N (%)			
Treatment group	**Received treatment**	**Did not receive treatment**	**Unadjusted OR (95% CI)**	**Adjusted[a] OR (95% CI)**
According to all recommendations	13/35 (37)	17/34 (50)	0.52 (0.23–1.54)	0.58 (0.18–1.85)
Immunomodulation[b]	17/50 (34)	13/19 (68)	0.24 (0.08–0.74)	0.18 (0.06–0.85)
Non-heparins only[c]	13/37 (35)	10/25 (40)	0.81 (0.29–2.31)	0.59 (0.17–2.00)
Platelet transfusion	11/17 (65)	19/52 (31)	3.18 (1.01–10.00)	1.36 (0.36–5.08)

95%CI = 95% confidence interval; CVT = cerebral venous thrombosis; OR = odds ratios; VITT = vaccine-induced immune thrombotic thrombocytopenia.

[a]Adjusted for age, coma, intracranial hemorrhage, and platelet count at presentation.

[b]Immunomodulation comprised intravenous immunoglobulins and/or plasma exchange.

[c]Patients who received only non-heparins compared with patients who received unfractionated heparin and/or low-molecular weight heparins at any time. Patients with no anticoagulation were excluded (n = 7).

definite VITT-CVT, treatment modalities showed comparable results (Table 6).

Discussion

After the first VITT treatment recommendations were published, 2 crucial questions arose: (1) whether treating physicians adhered to these recommendations, and (2) whether these recommendations were associated with lower mortality. We attempted to address these questions in the present study.

We found that: (1) over time, a higher proportion of patients was treated according to the VITT treatment recommendations, and (2) mortality was lower in patients treated with immunomodulation.

This is, to our knowledge, the first large multicenter study analyzing adherence to VITT treatment recommendations. Within only approximately 1 month of the publication date of the recommendations, three quarters of patients with VITT-CVT received the adapted treatment. At the same time mortality started declining, which is in line with recently published findings.[17] Causal inference with implementation of VITT treatment recommendations, however, cannot be determined from this observational study.

Alternative contributors to a decrease in mortality should be considered. Our data suggest that over time, reported VITT-CVT cases were less severe, as potentially reflected by a significantly lower proportion of hemorrhagic lesions at baseline imaging (see Table 2). Because the median numbers of days between symptom onset and diagnosis did not differ, this shift cannot be explained by a shorter delay in diagnosis overall, but rather by increased diagnosis and reporting of less severely affected patients in the later study periods, likely due to increased awareness of VITT-CVT among physicians. In agreement with this hypothesis, after adjusting for severity markers, such as age, coma, ICH, and platelet counts at presentation, mortality was not lower in patients treated according to all 3 treatment recommendations (OR = 0.43, 95% CI = 0.16–1.19).

When looking at the effects of separate modalities, however, immunomodulation was associated with a reduction in mortality. This is in accordance with the findings from previous case reports and small case series, and supports the hypothesis that modulation of the immune system limits the pathological immune response causing VITT.[1,18,19]

Astonishingly, platelet transfusion was not associated with higher mortality. On the one hand, patients who received platelet transfusion more often presented with coma and ICH and were treated with hemicraniectomy, reflecting more severe disease. On the other hand, platelet transfusion might have aggravated VITT reflected by an increased rate of worsening or new ICH and new VTE during admission (see Table 4). The lack of significance after adjustment could be a result of a low number of patients who were treated with platelet transfusion.

Last, the observed little-to-no effect on mortality with use of non-heparins instead of heparins for anticoagulation in both unadjusted and adjusted analysis, is in line with recent reports, suggesting that VITT antibodies cross-react with heparin/platelet factor 4 complexes in only a minority of patients with VITT.[20] More data are required to determine whether heparins can be safely used in patients with VITT. This question is of particular relevance because availability of non-heparin anticoagulants is limited in developing countries, which are currently the main users of adenovirus-based SARS-CoV-2 vaccines.[21]

Importantly, despite decreasing mortality rates potentially associated with the implementation of the recommendations into VITT-CVT therapy, particularly with immunomodulation, the percentage of deceased patients (29%, 95% CI = 17–45%) remains much higher than in CVT unrelated to vaccination (3.9%).[12]

Besides treatments recommended by the ISTH, mechanical thrombectomy and decompressive craniectomy have also been used in our study population (see Table 4). Dedicated research is needed to establish the role of these therapies for CVT in general and in patients with VITT-CVT.[22]

Clinical and laboratory characteristics of patients developing VITT-CVT after their second dose of ChAdOx1 nCoV-19 vaccine appear to resemble those of patients who develop the condition after the first dose, suggesting a similar pathomechanism.[23] Therefore, we did not exclude cases of VITT-CVT after a second vaccine dose from our study.

Strengths and Limitations

The main strength of this multicenter study is that it provides a detailed account of clinical, laboratory, and imaging characteristics, as well as treatments and outcomes. This allows for a robust descriptive analysis reflecting complexity of approaches taken for management of patients with VITT-CVT, and their evolution over time. Furthermore, the data originated from one of the largest, international post-SARS-CoV-2 vaccination CVT registries, which due to its wide international participation, results in higher generalizability compared to national studies. Its prospective design and standardized data collection consisting of consecutive cases limits the reporting bias and guarantees inclusion of cases with a different severity. The detailed nature of the data allows for

studying only CVT cases that fulfilled VITT criteria, which are highly specific and this limits risk of inclusion of patients who experience CVT due to different pathophysiology. In-hospital mortality as a primary outcome, is a reliable and relevant measure, which reflects effectiveness of the VITT-CVT treatment.

Main limitations of the study are its small sample size, which does not allow for robust statistical analysis of all subgroups, and its observational design. Nevertheless, it is still one of the largest studies on this extremely rare disease, for which power calculations and an interventional randomized study is not feasible.[24] Although true consecutiveness of cases in all countries participating in the registry remains a challenge, we attempted to minimize this bias ensuring inclusion of consecutive patients from the participating centers. Furthermore, complex patterns of management of patients with VITT-CVT led to the presence of confounders which were difficult to account for and make the results vulnerable to confounding by indication. Treatment approaches shifted not only over time, but also may have reflected changing disease severity. Prior to widespread awareness of VITT and proposed mechanisms, severity on presentation may have in turn been influenced by the initial management and interactions between administered treatments. Although we adjusted for 4 indicators of severity at presentation (age, coma, ICH at presentation, and baseline platelet count), we could not eliminate all potential confounders.

Despite increased awareness about VITT-CVT, patients presenting with either only mild or very severe symptoms may have remained undiagnosed or unreported, and hence not treated, which could have induced a reporting bias. Conversely, given that most participants in this registry were treated in academic hospitals, it is possible that participating investigators were more likely to be aware of VITT and associated published guidelines, whereas knowledge dissemination may have been slower to reach community hospitals.[25]

Given the international nature of the study, it is important to mention that limited availability and the high costs of non-heparins and intravenous immunoglobulins in some centers or countries could have presented another potential source of bias.

Last, it could be argued that physicians might have followed local or national but not ISTH recommendations that were used in this study (see Table S1). Most recommendations, however, are very similar to each other with only a few exceptions, such as the recommendations proposed by the German Society of Thrombosis and Haemostasis Research that allow heparin administration to patients with VITT.[26] Nevertheless, not a single patient reported from Germany had received heparins after March 2021.

In conclusion, among patients with VITT-CVT, adherence to international treatment recommendations improved over time and this adherence was associated with decreased mortality. In particular, patients who were treated with immunomodulation had lower death rates. Nevertheless, mortality of VITT-CVT remained high, emphasizing the need for further research on diagnosis and treatment of this serious condition.

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Author Contributions

A.S., K.K., A.M., D.A.S., J.M.F., J.M.C., M.A., S.P., and M.R.H. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. A.S., K.K., J.M.F., J.M.C., M.A., S.P., and M.R.H. contributed to drafting of the text and/or preparing the figures.

Potential Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

Data Availability Statement

For original data, please contact j.coutinho@amsterdamumc.nl.

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