Scutelnic Adrian (Orcid ID: 0000-0001-9053-584X)
Mbroh Joshua (Orcid ID: 0000-0002-0108-9161)
Sanchez van Kammen Mayte (Orcid ID: 0000-0001-5614-9689)
Lindgren Erik (Orcid ID: 0000-0002-7628-5044)
Putaala Jukka Markus (Orcid ID: 0000-0002-6630-6104)
RAPOSO Nicolas (Orcid ID: 0000-0002-9152-4445)
Timsit Serge (Orcid ID: 0000-0003-0346-8576)
Palma Vincenzo (Orcid ID: 0000-0002-5178-7793)
Schnenberger Silvia (Orcid ID: 0000-0002-3348-6719)
Giammello Fabrizio (Orcid ID: 0000-0002-2828-1305)
Garcia-Esperon Carlos (Orcid ID: 0000-0001-8843-5890)
Gattringer Thomas (Orcid ID: 0000-0002-6065-6576)
Kristoffersen Espen Saxhaug (Orcid ID: 0000-0002-8999-5424)
Cordonnier Charlotte (Orcid ID: 0000-0002-5697-6892)
Heldner Mirjam (Orcid ID: 0000-0002-3594-2159)

Management of cerebral venous thrombosis due to adenoviral COVID-19 vaccination

Running head: Management and mortality of VITT-CVT

Adrian Scutelnic, MD[1*], Katarzyna Krzywicka, MD, Mphil[2*], Joshua Mbroh, MD, MSc[3,4], Anita van de Munckhof, MD[2], Mayte Sánchez van Kammen, MD[2], Diana Aguiar de Sousa, MD, PhD[5], Erik Lindgren, MD[6], Katarina Jood, MD, PhD[6], Albrecht Günther, MD[7], Sini Hiltunen, MD[8], Jukka Putaala, MD, PhD[8], Andreas Tiede MD, PhD[9], Frank Maier, MD[10], Rolf Kern MD, PhD[11], Thorsten Bartsch, MD, PhD[12], Katharina Althaus, MD[13], Alfonso Ciccone, MD, PhD[14], Markus Wiedmann, MD, PhD[15], Mona Skjelland, MD, PhD[15], Antonio Medina, MD[16], Elisa Cuadrado-Godia, MD, PhD[17], Thomas Cox, MD[18], Avinash Aujayeb, MBBS MRCP[19], Nicolas Raposo, MD, PhD[20], Katia Garambois. MD, PhD[21], Jean-Francois Payen, MD, PhD[21], Fabrice Vuillier, MD, PhD[22], Guillaume Franchineau, MD[23], Serge Timsit, MD, PhD[24], David Bougon, MD[25], Marie-Cécile Dubois, MD[26], Audrey Tawa, MD[27], Clement Tracol, MD[28], Emmanuel De Maistre, MD, PhD[29], Fabrice Bonneville, MD, PhD[30], Caroline Vayne, PharmD, MD[31], Annerose Mengel, MD[32], Dominik Michalski, MD[33], Johann Pelz, MD[33], Matthias Wittstock, MD, PhD[34], Felix Bode, MD[35], Julian Zimmermann, MD[35], Judith Schouten, MD, PhD[36], Alina Buture, MD[37], Sean Murphy, MD[37], Vincenzo Palma, MD[38], Alberto Negro, MD, PhD[38], Alexander Gutschalk, MD[39], Simon Nagel, MD[39], Silvia Schoenenberger, MD[39], Giovanni Frisullo, MD, PhD[40], Carla Zanferrari, MD[41], Francesco Grillo, MD, PhD[42], Fabrizio Giammello, MD[43], Mar Morin Martin, MD[44], Alvaro Cervera, MD, PhD[45], Jim Burrow, MD[45], Carlos Garcia Esperon, MD, PhD[46], Beng Lim Alvin Chew, MD[46], Timothy J. Kleinig, MBBS(Hons), PhD[47], Cristina Soriano, MD[48], Domenico S. Zimatore, MD[49], Marco Petruzzellis, MD[50], Ahmed Elkady, MD, MSc[51], Miguel S. Miranda, MD, MSc[52], João Fernandes, MD[53], Åslög Hellström Vogel, MD[54], Elias Johansson, MD, PhD[55], Anemon Puthuppallil Philip, MD[56], Shelagh B. Coutts, MD[57], Simerpreet Bal, MD[57], Brian Buck, MD[58], Catherine Legault, MD[59], Dylan Blacquiere, MD[60], Hans D. Katzberg, MD[61], Thalia S. Field, MD, MHSc[62], Vanessa Dizonno, MD[62], Thomas Gattringer, MD, PhD[63], Christian Jacobi, MD[64], Annemie Devroye, MD[65], Robin Lemmens, MD[65], Espen Saxhaug Kristoffersen, MD[66], Monica Bandettini di Poggio, MD, PhD[67], Masoud Ghiasian, MD[68], Theodoros Karapanayiotides, MD[69], Sophie Chatterton, MD[70], Miriam Wronski, MD[71], Karl Ng, MD[72], Robert Kahnis, MD[73], Thomas Geeraerts, MD[74], Peggy Reiner, MD[75], Charlotte Cordonnier, MD, PhD[76], Saskia Middeldorp, MD, PhD[77], Marcel Levi, MD, PhD[78], Eric C. M. van Gorp, MD, PhD[79], Diederik van de Beek, MD, PhD[2], Justine Brodard, MSc[80], Johanna A. Kremer Hovinga, MD[80], Marieke J.H.A. Kruip, MD, PhD[81], Turgut Tatlisumak, MD, PhD[4], José M. Ferro, MD, PhD[82], Jonathan M. Coutinho, Md. PhD[2], Marcel Arnold, MD[1], Sven Poli, MD, MSc[3,4**], Mirjam R. Heldner, MD, MSc[1**]
Shared first* and last** co-authorship

[1]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[3]Hertie Institute for Clinical Brain Research, Eberhard-Karls University, Tuebingen, Germany

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ana.26431

[4]Department of Neurology & Stroke, Eberhard-Karls University, Tuebingen, Germany
[5]CEEM and Institute of Anatomy, Faculty of Medicine, University of Lisbon
[6]Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden and Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Sweden
[7]Department of Neurology, Jena University Hospital, Jena, Germany
[8]Department of Neurology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[9]Clinic for Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany
[10]Department of Neurology, Caritas Hospital Saarbrücken, Saarbrücken, Germany
[11]Department of Neurology, Kempten Hospital, Kempten, Germany
[12]Department of Neurology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany
[13]Department of Neurology, Ulm University Hospital, Ulm, Germany
[14]Department of Neurology, Carlo Poma Hospital, Azienda Socio Sanitaria Territoriale di Mantova, Mantua, Italy
[15]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway
[16]Department of Neurology, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain
[17]Department of Neurology, University Hospital del Mar, Barcelona, Spain
[18]Department of Neurology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
[19]Respiratory Department, Northumbria Healthcare NHS Foundation Trust, Cramlington, United Kingdom
[20]Department of Neurology, Toulouse University Hospital, Toulouse, France
[21]Stroke Unit, University Hospital of Grenoble, Grenoble, France
[22]Stroke Unit, University Hospital of Besancon, Besancon, France
[23]Department of Intensive Care, Centre Hospitalier Intercommunal de Poissy Saint Germain en Laye, Poissy, France
[24]Neurology and Stroke Unit, Centre Hospitalier Universitaire de Brest, CHU Brest, Brest, France
[25]Department of Critical Care, Annecy Genevois Hospital, Annecy, France
[26]Department of Anesthesia and Intensive Care, University Hospital of Poitiers, Poitiers, France
[27]Department of Anesthesia and Intensive Care, University Hospital of Rennes, Rennes
[28]Department of Neurology, CHU Rennes, Rennes, France
[29]Department of Biological Haematology, CHU Dijon, Dijon, France
[30]Department of Neuroradiology, Toulouse University Hospital, Toulouse, France
[31]Department of Hematology and Hemostasis, Tours University Hospital, Tours, France
[32]Department of Neurology and Stroke, Eberhard-Karls University, Tuebingen, Germany
[33]Department of Neurology, Leipzig University Hospital, Leipzig, Germany
[34]Department of Neurology, University Hospital Rostock, Rostock, Germany
[35]Department of Neurology, Universitätsklinikum Bonn, Bonn, Germany
[36]Department of Neurology, Rijnstate Hospital Arnhem, Arnhem, the Netherlands
[37]Acute Stroke Service, Mater Misericordiae University Hospital, Dublin, Ireland
[38]Department of Neuroradiology, Ospedale del Mare, Naples, Italy
[39]Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany
[40]Department of Neurology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[41]Department of Neurology, Azienda Ospedaliera di Melegnano e della Martesana, Melegnano, Italy
[42]Stroke Unit, Department of Clinical and Experimental Medicine, University Hospital G. Martino, Messina, Italy
[43]Translational Molecular Medicine and Surgery, XXXV Cycle, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[44]Department of Neurology, Hospital Complex of Toledo, Toledo, Spain
[45]Department of Neurology, Royal Darwin Hospital, Tiwi, Australia

[46]Department of Neurology, John Hunter Hospital, Newcastle, Australia
[47]Department of Neurology, Royal Adelaide Hospital, Adelaide, Australia
[48]Department of Neurology, Hospital General de Castellón, Castelló, Spain
[49]Department of Neuroradiology, Policlinico di Bari, Bari, Italy
[50]Department of Neurology, AOU Consorziale Policlinico di Bari, Bari, Italy
[51]Department of Neurology, Saudi German Hospital, Jeddah, Saudi Arabia
[52]Department of Neurology, Hospital de Cascais Dr José de Almeida, Cascais, Portugal (Miranda)
[53]Department of Neurology, Norra Älvsborgs Länssjukhus, Trollhattan, Sweden
[54]Department of Internal Medicine, Skåne University Hospital, Lund, Sweden
[55]Clinical Science, Neurosciences, Umeå University, 901 87, Umeå, Sweden; Wallenberg Centre for Molecular Medicine, Umeå University, 901 87 Umeå, Sweden
[56]Department of Neurology, Hamilton General Hospital, Hamilton, Ontario, Canada
[57]Department of Clinical Neurosciences, Radiology, and Community Health Sciences, Foothills Medical Centre, Calgary, Alberta, Canada
[58]Division of Neurology, University of Alberta Hospital, Edmonton, Alberta, Canada
[59]Department of Neurology and Neurosurgery, McGill University Health Centre, Montreal, Quebec, Canada
[60]Division of Neurology, The Ottawa Hospital, Ottawa, Ontario, Canada
[61]Department of Neuromuscular Medicine, Toronto General Hospital, Toronto, Ontario, Canada
[62]Division of Neurology, University of British Columbia, Vancouver Stroke Program, Vancouver, British Columbia, Canada
[63]Department of Neurology, Medical University of Graz, Graz, Austria
[64]Department of Neurology, Nordwest Hospital, Frankfurt am Main, Germany
[65]Department of Neurology, University Hospitals Leuven, 3000, Leuven, Belgium
[66]Department of Neurology, Akershus University Hospital, Lørenskog, Norway
[67]Department of Neuroscience, Policlinic San Martino Hospital, Genoa, Italy
[68]Department of Neurology, Sina Hospital, Hamadan University of Medical Science, Iran
[69]Department of Neurology, AHEPA University Hospital, Greece
[70]Department of Neurology, St Vincent's Hospital, 390 Victoria Road, Sydney, Australia
[71]Royal North Shore Hospital, Sydney, NSW, Australia
[72]Department of Neurology and Clinical Neurophysiology, Royal North Shore Hospital and The University of Sydney, Reserve Rd, St Leonards, Sydney, NSW, Australia
[73]Department of Neurology, Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany
[74]Department of Anaesthesiology and Critical Care, University Toulouse 3-Paul-Sabatier, University Hospital of Toulouse, Hôpital Pierre-Paul Riquet, CHU Toulouse-Purpan, 31059 Toulouse, France
[75]Service de neurologie, hôpital Lariboisière, université Paris-7, AP–HP, 75475 Paris cedex 10, France
[76] Univ. Lille, Inserm, CHU Lille, U1172 - LilNCog - Lille Neuroscience & Cognition, F-59000 Lille, France
[77]Department of Internal Medicine & Radboud Institute of Health Sciences (RIHS), Radboud University Medical Center, Nijmegen, the Netherlands
[78]National Institute for Health Research University College London Hospitals (UCLH) Biomedical Research Centre, London, UK and Department of Vascular Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[79]Department of Viroscience, Erasmus Medical Center Rotterdam, 3015GD Rotterdam, The Netherlands
[80]Department of Hematology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[81]Department of Hematology, Erasmus University Medical Center, Rotterdam, the Netherlands
[82]Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Portugal

Correspondence:

Sven Poli, MD
Department of Neurology & Stroke,
University Hospital, Hoppe-Seyler-Str. 3,
72076 Tuebingen, Germany
E-mail: sven.poli@uni-tuebingen.de

Number of characters in the title, with spaces: 79

Abstract word count: 240

Introduction word count: 225

Discussion word count: 1186

Manuscript word count: 1442

Number of figures: 2

Number of tables: 6

Summary for Social Media if Published

@kat_krzywicka, @Diana_A_Sousa, @MiddeldorpS, @PrCCordonnier

1. What is the current knowledge on the topic?

Cerebral venous thrombosis caused by vaccine-induced immune thrombotic thrombocytopenia (VITT-CVT), is a rare adverse effect of adenovirus-based SARS-CoV-2 vaccines. After its autoimmune pathophysiology has been discovered, the recommendation was to treat these patients with immunomodulation, non-heparins and to avoid platelet transfusions.

2**. What question did this study address?**

This study evaluates whether physicians adhered to the VITT treatment recommendations when treating VITT-CVT patients and whether this was associated with lower mortality.

3. **What does this study add to our knowledge?**

In VITT-CVT patients, adherence to VITT treatment recommendations improved over time, and was associated with lower mortality. Particularly immunomodulation played an important role in reducing mortality in VITT-CVT patients.

4. **How might this potentially impact on the practice of neurology?**

Timely and adequate treatment can result in lower mortality among VITT-CVT patients.

Abstract

Objective

Cerebral venous thrombosis caused by vaccine-induced immune thrombotic thrombocytopenia (VITT-CVT) is a rare adverse effect of adenovirus-based 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 adenovirus-based SARS-CoV-2 vaccination. We analyzed possible, probable or definite VITT-CVT cases included until 18 January 2022. Immunomodulation entailed administration of intravenous immunoglobulins and/or plasmapheresis.

Results

99 VITT-CVT patients from 71 hospitals in 17 countries were analyzed. Five of 38 (13%), 11/24 (46%), and 28/37 (76%) of patients diagnosed in March, April, and from May onwards, 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 OR 0.43 (95%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 VITT-CVT patients, adherence to VITT treatment recommendations improved over time. Immunomodulation seems crucial for reducing mortality of VITT-CVT.

Introduction

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 28 March 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 VITT-CVT patients 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 three 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.[1,2] 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. 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 18 January 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 three conditions: (1) treatment with immunomodulation (i.e., 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 $50 \times 10^3/\mu L$); (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 two-sided probability value below 0.05 as significant. Confidence intervals 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 three time periods from before (i.e., March) to after introduction of VITT treatment recommendations (i.e., April and from May onwards).[1,7] The number of missing values for each variable is reported. Odds Ratios (OR) 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, N.Y., USA).

Results

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

Median age (IQR) was 47 (32-57) years and 75/99 (75%) were women. Ninety one of 99 (92%) received the ChAdOx1 nCov-19 vaccine and 8/99 (8%) 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 COVID-19 eight days after vaccination (three 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 (32-52) and 43 (30-62), patients diagnosed in March and in April, respectively, tended to be younger than those diagnosed in May and onwards (50 (39-63) years) (p=0.124). Cases diagnosed in March and April more frequently presented with ICH (87% vs. 71%, respectively) compared to cases diagnosed from May onwards (57%) (p=0.015). Early cases had a similar median (IQR) baseline platelet level of 39 (24-64) × 10^3 per µL vs. 50 (29-82) and 54 (29-85) × 10^3 per µL in those diagnosed in April and in May and onwards (p=0.152). Median (IQR) number of days between the vaccination and symptom onset were 8 (7-10) vs. 9 (7-11) vs. 9 (6-11) in cases diagnosed in March vs. April vs. from May onwards (p=0.776). Thirteen out of 99 (13%) patients died within 24 hours of admission.

In March 20/38 (53%) vs. April 13/24 (54%) vs. from May onwards 32/37 (87%) patients were treated with immunomodulation (p=0.003), 26/38 (68%) vs. 4/24 (16%) vs. 4/37 (10%) with heparins (p<0.001), and 7/38 (18%) vs. 4/24 (16%) vs. 1/37 (2%) 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: 5/38 (13%), 11/24 (46%), and 28/37 (76%) in March, April and from May onwards, respectively ($p<0.001$) (Table 3). Twenty of 38 (52%, 95%CI 37-67%) patients with VITT-CVT treated in March, 12/24 (50%, 95%CI 31-68%) treated in April and 11/37 (29%, 95% CI 17-45%) treated from May onwards, died (March and April vs. May, $p=0.034$).

Descriptive analysis of management

Forty-four of all 99 VITT-CVT patients (44%) were treated according to VITT recommendations. Among patients who were not treated according to recommendations, 32/55 (58%) were diagnosed before the pathophysiological mechanism was published. Interestingly, five patients received appropriate treatments even before VITT recommendations were published on 28 March 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 25/55 (45%) cases two criteria were not fulfilled, and in 6/55 (11%) cases all three.

Among patients who received immunomodulation, 61/65 (94%) received intravenous immunoglobulins, 1/65 (2%) plasma exchange, and 3/65 (5%) both. 25/65 (38%) patients received adjuvant steroids. Two patients received additional eculizumab 2/65 (2%). Among those who did not receive immunomodulation, 4/34 (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 27/99 (27%) patients who received platelet transfusion, 15/27 (56%) were transfused prior to planned surgery and 12/15 (80%) of these actually underwent surgery. Baseline platelet count was similar among patients who received platelet transfusion (median 48 (IQR 27-77) $\times 10^3$ per μL) and

patients who did not (49 (27-75) × 10^3 per μL) (p=0.712). Platelet nadir values, however, differed significantly between transfused (20 (11-32)) and non-transfused patients (37 (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 (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, 14/44 (32%, 95%CI 20-46%) died, compared to 29/55 (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), 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 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% 0.74-6.54)). In a sensitivity analysis including only patients with definite VITT-CVT, treatment modalities showed comparable results (Table 6).

Discussion

After the first VITT treatment recommendations were published, two 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 one 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 (Table 2). Because 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 three 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.

Lastly, 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 VITT patients.[20] More data are required to determine whether heparins can be safely used in patients with VITT. This question is of particular relevance since 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 (Table 4). Dedicated research is needed to establish the role of these therapies for CVT in general and in VITT-CVT patients.[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 pathomechamism.[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 VITT-CVT patients, 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] While 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 VITT-CVT patients lead to 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 four 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.

Lastly, it could be argued that physicians might have followed local or national but not ISTH recommendations that were used in this study (Table S1). Most recommendations, however, are very similar to each other with only few exceptions such as the recommendations proposed by the German Society of Thrombosis and Haemostasis Research that allow heparin administration to VITT patients.[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.

Acknowledgments

This research was funded by The Netherlands Organisation for Health Research and Development (ZonMw, grant number 10430072110005) and the Dr. C.J. Vaillant Foundation. No funding from commercial entities was received. The funding organization had no role in gathering, analyzing, or interpreting the data.

Author Contributions

AS, KK, AM, DAS, JMF, JMC, MA, SP, and MRH contributed to the conception and design of the study; all authors contributed to the acquisition and analysis of data; AS, KK, JMF, JMC, MA, SP and MRH contributed to drafting of the text and/or preparing the figures.

Conflicts of Interest

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

Data availability

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

References

1. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021;384(22):2092-2101.

2. 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.

3. Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384(23):2202-2211.

4. Krzywicka K, Heldner M, Sánchez van Kammen M, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency. Eur J Neurol. 2021 Nov;28(11):3656-3662.

5. 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.

6. Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med. 2021 Jun 10;384(23):2254-2256.

7. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost. 2017 Nov;15(11):2099-2114.

8. 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 Jul;52(7):2478-2482. doi: 10.1161/STROKEAHA.121.035564.

9. 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. 2021 Sep;6(3):CXVI-CXXI.

10. ISTH Interim Guidance for the Diagnosis and Treatment on Vaccine-Induced Immune Thrombotic Thrombocytopenia. ISTH_VITT_Guidance_2.pdf (ymaws.com). Accessed on 22.01.2022.

11. Huynh A, Kelton JG, Arnold DM, Daka M, Nazy I. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. Nature. 2021 Aug;596(7873):565-569.

12. Sánchez van Kammen M, Aguiar de Sousa D, Poli S, et al. Characteristics and Outcomes of Patients With Cerebral Venous Sinus Thrombosis in SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. JAMA Neurol. 2021 Nov 1;78(11):1314-1323.

13. Pavord S, Scully M, Hunt BJ, et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N Engl J Med. 2021 Oct 28;385(18):1680-1689.

14. 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 Apr;42(4):1158-92.

15. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005 Apr;3(4):692-4.

16. Ortega-Gutierrez S, Holcombe A, Aksan N, et al. Association of admission clinical predictors and functional outcome in patients with Cerebral Venous and Dural Sinus Thrombosis. Clin Neurol Neurosurg. 2020 Jan;188:105563.

17. van de Munckhof A, Krzywicka K, Aguiar de Sousa D, et al. Declining mortality of cerebral venous sinus thrombosis with thrombocytopenia after SARS-CoV-2 vaccination. Eur J Neurol. 2021 Sep 18. doi: 10.1111/ene.15113.

18. Uzun G, Althaus K, Singh A, et al. The use of IV immunoglobulin in the treatment of vaccine-induced immune thrombotic thrombocytopenia. Blood. 2021 Sep 16;138(11):992-996.

19. Douxfils J, Vayne C, Pouplard C, et al. Fatal exacerbation of ChadOx1-nCoV-19-induced thrombotic thrombocytopenia syndrome after initial successful therapy with intravenous immunoglobulins - a rational for monitoring immunoglobulin G levels. Haematologica. 2021 Dec 1;106(12):3249-3252.

20. Greinacher A, Langer F, Makris M, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Update on diagnosis and management considering different resources. J Thromb Haemost. 2022 Jan;20(1):149-156.

21. Wouters OJ, Shadlen KC, Salcher-Konrad M, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet. 2021 Mar 13;397(10278):1023-1034.

22. Chew HS, Al-Ali S, Butler B, et al. Mechanical Thrombectomy for Treatment of Cerebral Venous Sinus Thrombosis in Vaccine-Induced Immune Thrombotic Thrombocytopenia. AJNR Am J Neuroradiol. 2022 Jan;43(1):98-101.

23. Krzywicka K, van de Munckhof A, Zimmerman J, et al. Cerebral venous thrombosis due to vaccine-induced immune thrombotic thrombocytopenia after a second ChAdOx1 nCoV-19 dose. Blood. 2022 Mar 9:blood.2021015329.

24. Krzywicka K, van de Munckhof A, Sánchez van Kammen M, et al. Age-Stratified Risk of Cerebral Venous Sinus Thrombosis After SARS-CoV-2 Vaccination. Neurology. 2021 Dec 17:10.1212/WNL.0000000000013148.

25. Burke LG, Frakt AB, Khullar D, Orav EJ, Jha AK. Association Between Teaching Status and Mortality in US Hospitals. JAMA. 2017 May 23;317(20):2105-2113.

26. Oldenburg J, Klamroth R, Langer F, et al. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. Hamostaseologie. 2021 Jun;41(3):184-189.

Tables

Figures

Figure 1. Flowchart of patient selection.

Figure 2. Temporal changes in treatments given to VITT-CVT patients diagnosed in March, April, and from May onwards.

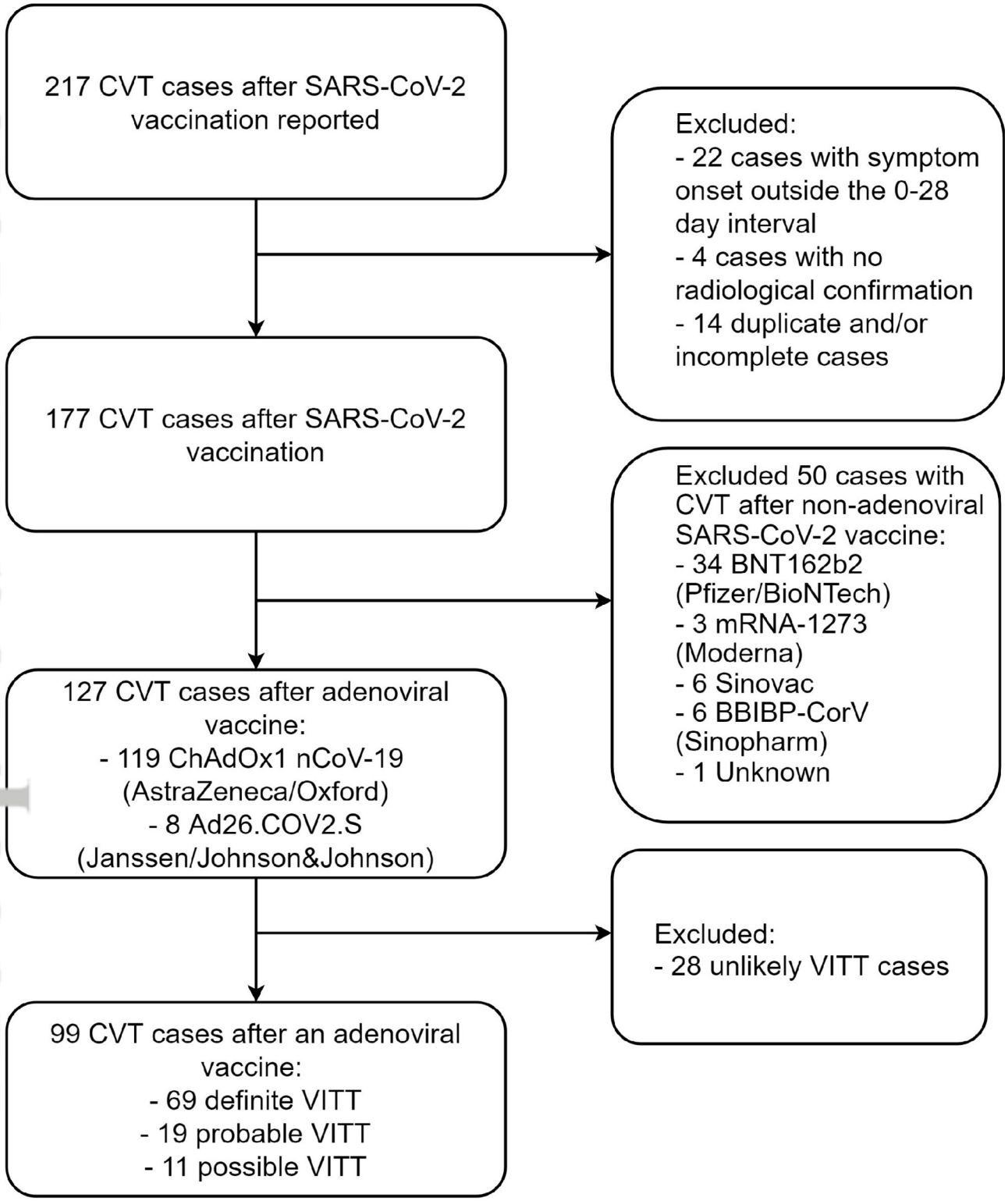

figure _1_flowchart_treat_170_324ppi.eps

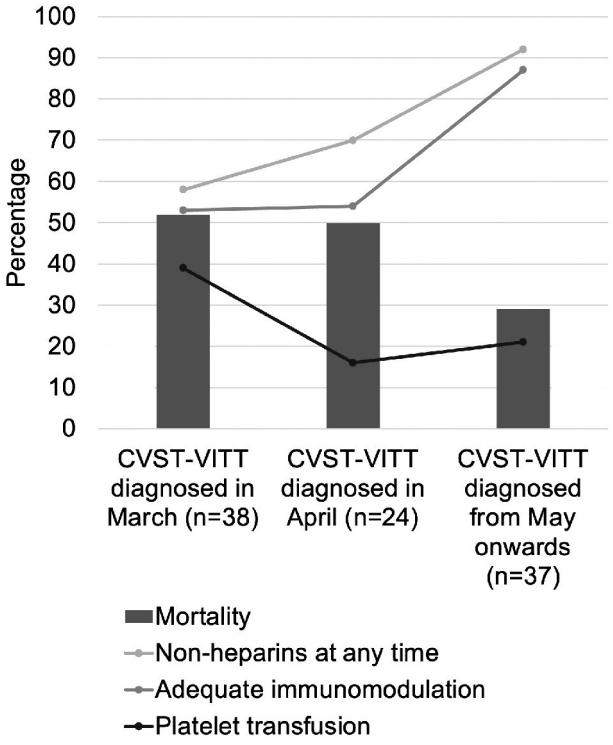

figure_2_80.eps

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 VITT-CVT patients diagnosed in March, April, and from May onwards.

	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, years*	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†	47/99 (47)	20/38 (53)	12/24 (50)	15/37 (41)	0.554
Additional VTE‡	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, $\times 10^3/\mu L$*	48 (27-75)	39 (24-64)	50 (29-82)	54 (29-85)	0.152
D-dimer, mg/L FEU*	20 (9-35)	31 (13-35)	17 (5-24)	18 (8-29)	0.049
Fibrinogen, g/L*	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*	9 (7-10)	8 (7-10)	9 (7-11)	9 (6-11)	0.776
Days from symptom onset to diagnosis*	3 (1-5)	3 (2-4)	2 (1-4)	4 (1-7)	0.253

CVT: cerebral venous thrombosis; FEU: fibrinogen equivalent units; PF4: platelet factor 4; VITT: vaccine-induced immune thrombotic thrombocytopenia; VTE: venous thromboembolism; *Median (IQR), all other data shown in n/N (%); †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; ‡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

Table 3. Treatment and outcomes in VITT-CVT patients diagnosed in March, April, and from May onwards.

	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 (%)

Table 4. Baseline characteristics, treatment and outcome in VITT-CVT patients in different treatment groups.

	According to all recommendations		Immunomodulation		Non-heparins only†		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, years*	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, $\times 10^3/\mu L$*	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; *Median (IQR), all other data shown in n/N (%); †Patients with no anticoagulation were excluded (n=13)

Table 5. Odds Ratios for mortality in VITT-CVT patients in different treatment groups.

	Mortality per group, n/N (%)			
Treatment group	**Received treatment**	**Did not receive treatment**	**Unadjusted OR (95%CI)**	**Adjusted[*] 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[†]	19/65 (29)	24/34 (70)	0.17 (0.07-0.43)	0.19 (0.06-0.58)
Non-heparins only[‡]	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; OR: odds ratios

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

[†]Immunomodulation comprised intravenous immunoglobulins and/or plasma exchange

[‡]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 definite VITT-CVT patients in different treatment groups.

	Mortality per group, n/N (%)			
Treatment group	Received treatment	Did not receive treatment	Unadjusted OR (95%CI)	Adjusted* 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†	17/50 (34)	13/19 (68)	0.24 (0.08-0.74)	0.18 (0.06-0.85)
Non-heparins only‡	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; OR: odds ratios

*Adjusted for age, coma, intracranial hemorrhage and platelet count at presentation

†Immunomodulation comprised intravenous immunoglobulins and/or plasma exchange

‡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).