

## BRIEF REPORT

# Outcomes of Cerebral Venous Thrombosis due to Vaccine-Induced Immune Thrombotic Thrombocytopenia After the Acute Phase

Anita van de Munckhof<sup>1</sup>, MD; Erik Lindgren<sup>2</sup>, MD; Timothy J. Kleinig<sup>3</sup>, MBBS (Hons), PhD; Thalia S. Field, MD, MHSc; Charlotte Cordonnier<sup>4</sup>, MD, PhD; Katarzyna Krzywicka<sup>5</sup>, MD, MPhil; Sven Poli<sup>6</sup>, MD, MSc; Mayte Sánchez van Kammen<sup>7</sup>, MD, MSc; Afshin Borhani-Haghighi, MD; Robin Lemmens<sup>8</sup>, MD, PhD; Adrian Scutelnic<sup>9</sup>, MD; Alfonso Ciccone<sup>10</sup>, MD; Thomas Gattringer<sup>11</sup>, MD, PhD; Matthias Wittstock, MD, PhD; Vanessa Dizonno, MSc; Annemie Devroye; Ahmed Elkady, MD, MSc; Albrecht Günther<sup>12</sup>, MD; Alvaro Cervera<sup>13</sup>, MD, PhD; Annerose Mengel<sup>14</sup>, MD; Beng Lim Alvin Chew, MD; Brian Buck<sup>15</sup>, MD; Carla Zanferrari, MD; Carlos Garcia-Esperon, MD, PhD; Christian Jacobi<sup>16</sup>, MD; Cristina Soriano, MD; Dominik Michalski<sup>17</sup>, MD; Zohreh Zamani, MD; Dylan Blacquiere, MD; Elias Johansson<sup>18</sup>, MD, PhD; Elisa Cuadrado-Godia<sup>19</sup>, MD, PhD; Fabrice Vuillier, MD, PhD; Felix J. Bode<sup>20</sup>, MD; François Caparros<sup>21</sup>, MD; Frank Maier, MD; Georgios Tsivgoulis<sup>22</sup>, MD, PhD; Hans D. Katzberg, MD; Jiangang Duan<sup>23</sup>, MD, PhD; Jim Burrow, MD; Johann Pelz, MD; Joshua Mbroh<sup>24</sup>, MD, MSc; Joyce Oen, MD; Judith Schouten, MD, PhD; Julian Zimmermann<sup>25</sup>, MD; Karl Ng<sup>26</sup>, MBBS (Hons 1), PhD; Katia Garambois, MD, PhD; Marco Petruzzellis<sup>27</sup>, MD; Mariana Carvalho Dias<sup>28</sup>, MD; Masoud Ghiasian, MD; Michele Romoli<sup>29</sup>, MD; Miguel Miranda<sup>30</sup>, MD, MSc; Miriam Wronski<sup>31</sup>, MD; Mona Skjelland, MD, PhD; Mostafa Almasi-Dooghaee<sup>32</sup>, MD; Pauline Cuisenier, MD; Seán Murphy, MD; Serge Timsit<sup>33</sup>, MD, PhD; Shelagh B. Coutts<sup>34</sup>, MD, MSc; Silvia Schönenberger, MD; Simon Nagel<sup>35</sup>, MD; Sini Hiltunen, MD, PhD; Sophie Chatterton<sup>36</sup>, MD; Thomas Cox, MD; Thorsten Bartsch<sup>37</sup>, MD, PhD; Vahid Shaygannejad, MD; Zahra Mirzaasgari, MD; Saskia Middeldorp<sup>38</sup>, MD, PhD; Marcel M. Levi, MD, PhD; Johanna A. Kremer Hovinga<sup>39</sup>, MD; Katarina Jood, MD, PhD; Turgut Tatlisumak<sup>40</sup>, MD, PhD; Jukka Putaala<sup>41</sup>, MD, PhD; Mirjam R. Heldner<sup>42</sup>, MD, MSc; Marcel Arnold, MD; Diana Aguiar de Sousa, MD, PhD; José M. Ferro<sup>43</sup>, MD, PhD\*; Jonathan M. Coutinho<sup>44</sup>, MD, PhD\*; for the Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group

**BACKGROUND:** Cerebral venous thrombosis (CVT) due to vaccine-induced immune thrombotic thrombocytopenia (VITT) is a severe condition, with high in-hospital mortality rates. Here, we report clinical outcomes of patients with CVT-VITT after SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccination who survived initial hospitalization.

**METHODS:** We used data from an international registry of patients who developed CVT within 28 days of SARS-CoV-2 vaccination, collected until February 10, 2022. VITT diagnosis was classified based on the Pavord criteria. Outcomes were mortality, functional independence (modified Rankin Scale score 0–2), VITT relapse, new thrombosis, and bleeding events (all after discharge from initial hospitalization).

**RESULTS:** Of 107 CVT-VITT cases, 43 (40%) died during initial hospitalization. Of the remaining 64 patients, follow-up data were available for 60 (94%) patients (37 definite VITT, 9 probable VITT, and 14 possible VITT). Median age was 40 years and 45/60 (75%) patients were women. Median follow-up time was 150 days (interquartile range, 94–194). Two patients died during follow-up (3% [95% CI, 1%–11%]). Functional independence was achieved by 53/60 (88% [95% CI, 78%–94%]) patients. No new venous or arterial thrombotic events were reported. One patient developed a major bleeding during follow-up (fatal intracerebral bleed).

Correspondence to: Jonathan M. Coutinho, MD, PhD, Department of Neurology, Amsterdam UMC, location AMC, Meibergdreef 9, Amsterdam, the Netherlands. Email [j.coutinho@amsterdamumc.nl](mailto:j.coutinho@amsterdamumc.nl)

J.M. Ferro and J.M. Coutinho are joint last authors.

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**CONCLUSIONS:** In contrast to the high mortality of CVT-VITT in the acute phase, mortality among patients who survived the initial hospitalization was low, new thrombotic events did not occur, and bleeding events were rare. Approximately 9 out of 10 CVT-VITT patients who survived the acute phase were functionally independent at follow-up.

**GRAPHIC ABSTRACT:** A [graphic abstract](#) is available for this article.

**Key Words:** hospitalization ■ intracranial thrombosis ■ mortality ■ thrombocytopenia ■ vaccination ■ venous thrombosis

## Nonstandard Abbreviations and Acronyms

<b>CVT</b>	cerebral venous thrombosis
<b>ISCVT</b>	International Study on Cerebral Vein and Dural Sinus Thrombosis
<b>PF4</b>	platelet factor 4
<b>VITT</b>	vaccine-induced immune thrombotic thrombocytopenia

Cerebral venous thrombosis (CVT) due to vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare adverse event of adenovirus-based SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccines.<sup>1–3</sup> CVT-VITT has substantially higher in-hospital mortality rates (20%–50%), compared with CVT unrelated to VITT (4%).<sup>2–4</sup> We aimed to report clinical and functional outcomes of patients with CVT-VITT who survived initial hospitalization.

## METHODS

We used data from an international registry on CVT after COVID-19 vaccination collected until February 10, 2022. Details have been described.<sup>3</sup> Inclusion criteria were radiologically or autopsy-confirmed CVT and symptom onset within 28 days of any SARS-CoV-2 vaccine. The ethical review committee of Amsterdam UMC waived formal approval for this observational study. This article follows the Strengthening of Reporting of Observational Studies in Epidemiology reporting guidelines. Original data are available upon reasonable request.

VITT classification was based on the Pavord criteria<sup>2</sup> (Table S1). We included cases with definite, probable, or possible CVT-VITT. We excluded CVT-VITT patients who died during initial hospitalization, patients with missing follow-up data, and cases with CVT after mRNA vaccines, which do not cause VITT.<sup>5</sup>

We used the information from the last available visit. Outcome measures were mortality, functional independence (modified Rankin Scale score 0–2), VITT relapse after initial clinical remission, new thrombosis, and new major bleeding events according to the criteria of the International Society on Thrombosis and Haemostasis.

Clinical remission was defined as fulfilling the following criteria at any time during follow-up: (1) platelet count  $>150 \times 10^9/L$ ; (2) no clinical evidence of new or progressive ischemic organ injury; and (3) no immunomodulatory treatment for 30 days. Relapse was defined as a decrease in platelet

count to  $<150 \times 10^9/L$  (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury, at any time after achieving clinical remission.

We calculated 95% CI using Wilson score method for main outcomes. Analyses were performed with IBM SPSS Statistics,

**Table 1. Patient Details of Initial Hospitalization**

	CVT-VITT patients who survived the acute phase (N=60)
Baseline characteristics	
Age, y	40 (27–56)
Female sex	45/60 (75)
Coma	4/60 (7)
Intracerebral hemorrhage	30/60 (50)
Concomitant VTE	14/60 (23)
Laboratory data	
Platelet count nadir, $\times 10^9/L$	47 (29–69)
Positive anti-PF4 antibodies	47/53 (89)
D-dimer level $>4$ mg/L FEU	51/56 (91)
Treatment data	
Anticoagulation	60/60 (100)
Heparin as first anticoagulant*	23/60 (38)
Immunomodulatory treatment	44/60 (73)
Intravenous immunoglobulin	44/60 (73)
Plasma exchange	4/60 (7)
Corticosteroids	17/60 (28)
Other	2/60 (3)
Platelet transfusion	10/60 (17)
Intensive care unit admission	37/58 (64)
Endovascular treatment	8/59 (14)
Decompressive surgery	10/59 (17)
Discharge data	
Duration hospital admission, median (IQR; range), d	14 (8–26; 1–53)†
Discharge disposition	
Home	38/59 (64)
Rehabilitation center	19/59 (32)
Other hospital	2/59 (3)

Discrete data are presented as n/N (%), continuous data as median (IQR). Denominators  $<60$  represent incomplete data points. CVT indicates cerebral venous thrombosis; FEU, fibrinogen equivalent units; IQR, interquartile range; PF4, platelet factor 4; VITT, vaccine-induced immune thrombotic thrombocytopenia; and VTE, venous thrombotic event.

\*Unfractionated heparin or low-molecular weight heparin.

†Three missing values.

version 28.0.1.0, RStudio version 1.3.1093 and R version 4.0.3 using the Hmisc package.

## RESULTS

Of 208 reported cases, 107 had CVT-VITT. In total, 43 (40%) died during initial hospitalization (Figure S1 and Table S2). Of the remaining 64 patients, follow-up data were available for 60 (94%) patients: 37 (62%) with definite VITT, 9 (15%) probable VITT, and 14 (23%) possible VITT.

Median age was 40 years (interquartile range, 27–56) and 45/60 (75%) patients were women (Table 1). Median follow-up time was 150 days (interquartile range, 94–194, Table 2). Two patients died during follow-up (3% [95% CI, 1%–11%]): one due to a new intracerebral hemorrhage and one of unknown causes (details in Table S3). The latter patient had a new thrombocytopenia during readmission for a COVID-19 infection, fulfilling the criteria for a VITT relapse. No other relapses or bleeding events were reported. No new venous or arterial thrombotic events were reported in any patient. Hospital readmission occurred in 9/54 (17%) cases, 4 of which were for a planned cranioplasty following decompressive hemicraniectomy (Table 2).

Functional independence was achieved by 53/60 (88% [95% CI, 78%–94%]) patients at follow-up, compared with 41/58 (71% [95% CI, 58%–81%]) at hospital

discharge (Figure and Figure S2). Overall, 21/40 (53%) patients had returned to work or school at follow-up.

Platelet count at follow-up was available for 39/60 (65%) patients, details of which are provided in Figure S3. At least one D-dimer value at follow-up was available for 27/60 (45%) CVT-VITT patients. D-dimer levels declined from >4 mg/L in the acute phase to ≤0.5 mg/L at follow-up in 19/27 (70%) patients (Figure S4).

## DISCUSSION

This study indicates that—in sharp contrast to the high mortality rate during the acute phase—mortality of patients with CVT-VITT who survive initial hospitalization is low and new thrombotic and bleeding events rarely occur after discharge. Almost 90% of patients who survived the acute phase were functionally independent at follow-up and half of the patients had returned to work and/or school. One VITT relapse was reported, although not all patients had achieved clinical remission of VITT at follow-up.

The proportion of patients in our study who were functionally independent at follow-up is comparable to the proportion of patients with long-term functional independence after CVT not related to VITT, as reported in the ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis; 88% versus 89%, respectively).<sup>4</sup> The low number of adverse outcomes in surviving CVT-VITT patients may be explained by the fact that anti-PF4 (platelet factor 4) antibodies, which cause VITT,<sup>1</sup> are transient.<sup>6</sup> With the disappearance of the anti-PF4 antibodies, the triggering factor for VITT may have resolved.

In a study on the immune type of heparin-induced thrombocytopenia, a disorder that resembles VITT,<sup>1</sup> 5/28 (18%) patients developed new venous or arterial thrombosis.<sup>7</sup> A systematic review on CVT due to heparin-induced thrombocytopenia reported full recovery in only 4/18 (22%) cases, while all other cases had neurological sequelae.<sup>8</sup> The higher median age of the patients with CVT due to heparin-induced thrombocytopenia may be one of the explanatory factors for the worse outcome.

This study has limitations. First, because data were collected as part of routine clinical care, duration of follow-up varied and there was no central adjudication of study outcomes. In addition, laboratory tests were often not repeated during follow-up. Second, while follow-up rate was over 90%, we cannot exclude the possibility that clinical events occurred in the 4 patients for which follow-up was missing. Third, the median time from diagnosis to follow-up was ≈5 months. In CVT not related to VITT, recovery can occur up to 1 year after diagnosis, which may indicate that the CVT-VITT patients in this study may still recover further.<sup>4</sup>

In summary, in contrast to the severity of CVT-VITT during the acute phase, mortality of patients who survived initial hospital admission was low and new thrombotic and bleeding events were rare. Approximately 9

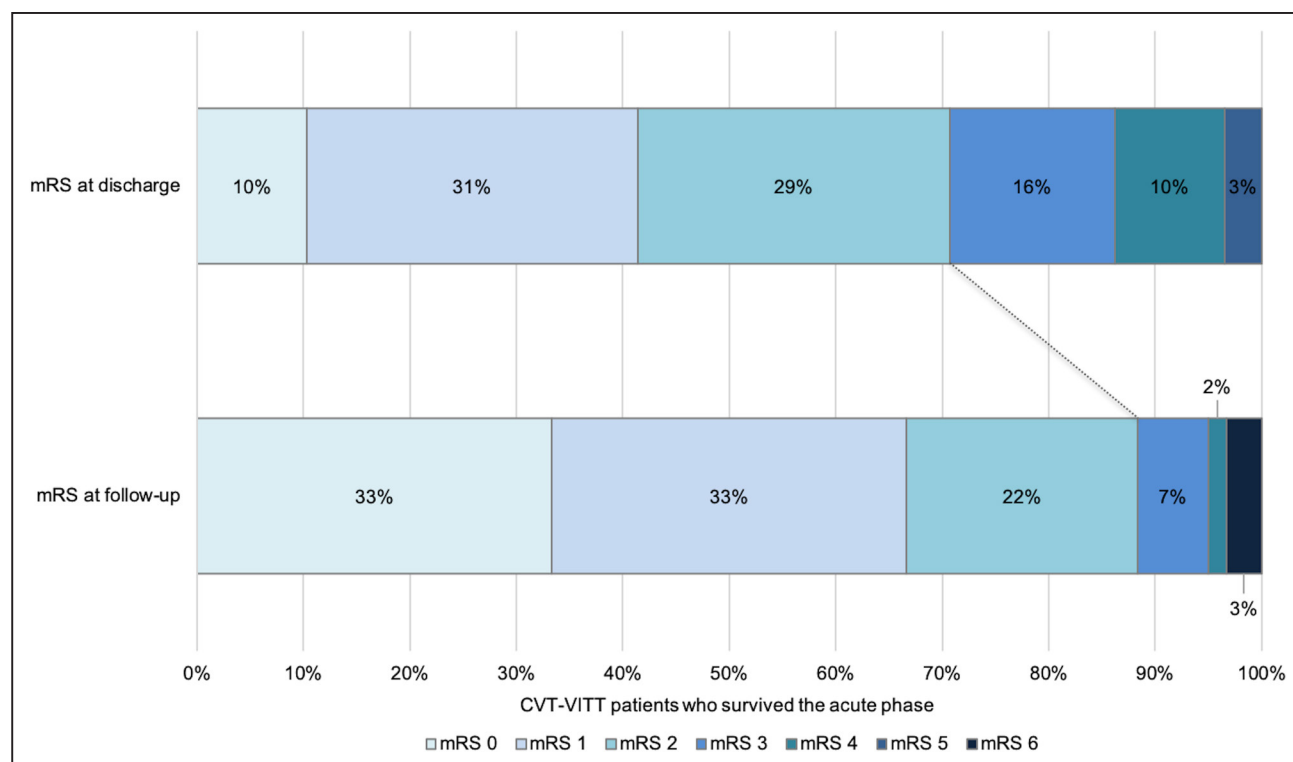
**Table 2. Outcomes of Patients Who Survived the Acute Phase of CVT-VITT**

	CVT-VITT patients who survived the acute phase (N=60)
Clinical events	
Time from diagnosis to follow-up, d	150 (94–194)*
New VTE	0/59
New ATE	0/57
Major bleeding event	1/55 (2)
Hospital readmission	9/54 (17)†
Treatment	
Anticoagulant treatment ongoing at last follow-up	44/53 (83)
Outcomes	
Clinical remission achieved	41/53 (77)
Relapse after remission	1/35 (3)
Mortality	2/60 (3)
Returned to work or school	21/40 (53)

Discrete data are presented as n/N (%), continuous data as median (IQR). Denominators <60 represent incomplete data points. ATE indicates arterial thrombotic event; CVT, cerebral venous thrombosis; IQR, interquartile range; VITT, vaccine-induced immune thrombotic thrombocytopenia; and VTE, venous thrombotic event.

\*Two missing values. In all cases, date of follow-up was after discharge.

†Reason readmission (multiple possible): COVID-19 infection (1), cranioplasty (4), encephalopathy (1), headache (1), hepatitis (1), increased intracranial pressure (1), infection (1), inflammatory bowel disease (1), progression of brain metastases (1), and urinary tract infection (1).



**Figure. Modified Rankin Scale (mRS) score of 60 patients with cerebral venous thrombosis due to vaccine-induced immune thrombotic thrombocytopenia (CVT-VITT) who survived the acute phase, at discharge and at follow-up.**

Note that CVT-VITT patients who died during initial hospitalization (43/107, 40%) are not included in the Figure. There are 2 missing mRS scores at discharge; both had mRS 0 at follow-up.

out of 10 CVT-VITT survivors were functionally independent at follow-up.

## ARTICLE INFORMATION

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### Affiliations

Department of Neurology (A.v.d.M., K.K., M.S.v.K., J.M.C.) and Department of Vascular Medicine (M.M.L.), Amsterdam University Medical Centers, University of Amsterdam, the Netherlands. Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden (E.L., K.J., T.T.). Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Sweden (E.L., K.J., T.T.). Department of Neurology, Royal Adelaide Hospital, Adelaide, Australia (T.J.K.). Division of Neurology, Vancouver Stroke Program, University of British Columbia, Vancouver, Canada (T.S.F., V.D.). University Lille, Inserm, CHU Lille, U1172 - LiNCog - Lille Neuroscience & Cognition, France (C.C., F.C.). Department of Neurology and Stroke, University Hospital Tuebingen (S.P., A.M., J.M.) and Hertie Institute for Clinical Brain Research (S.P., J.M.), Eberhard-Karls University, Germany. Clinical Neurology Research Center, Shiraz University of Medical Sciences, Iran (A.B.-H.). Department of Neurology, University Hospitals Leuven, Belgium (R.L., A.D.). Department of Neurology (A.S., M.R.H., M.A.) and Department of Hematology (J.A.K.H.), Inselspital, Bern University Hospital, University of Bern, Switzerland. Department of Neurology, Carlo Poma Hospital, Azienda Socio Sanitaria Territoriale di Mantova, Mantua, Italy (A. Ciccone). Department of Neurology, Medical University of Graz, Austria (T.G.). Department of Neurology, University Hospital Rostock, Germany (M. Wittstock). Department of Neurology, Saudi German Hospital, Jeddah, Saudi Arabia (A.E.). Department of Neurology, Jena University Hospital, Germany (A.G.). Royal Darwin Hospital, Darwin, Northern Territory, Australia (A. Cervera). Department of Neurology, John Hunter Hospital, Newcastle, Australia (B.L.A.C., C.G.-E.). Division of Neurology, University of Alberta Hospital, Edmonton, Canada (B.B.). Department of Neurology, Azienda Ospedaliera di Melegnano e della Martesana, Italy (C.Z.). Department of Neurology, Krankenhaus

Nordwest, Frankfurt am Main, Germany (C.J.). Department of Neurology, Hospital General de Castellón, Castellón, Spain (C.S.). Department of Neurology, Leipzig University Hospital, Germany (D.M., J. Pelz). Department of Neurology, Firoozabadi Hospital (Z.Z.) and Department of Neurology (M.A.-D., Z.M.), Firoozgar Hospital, School of Medicine, Iran University of Medical Sciences, Tehran. Division of Neurology, The Ottawa Hospital, Canada (D.B.). Department Clinical Science, Wallenberg Center for Molecular Medicine (WCMM), Umeå University, Sweden (E.J.). Department of Neurology, University Hospital del Mar, Barcelona, Spain (E.C.-G.). Stroke Unit, University Hospital of Besancon, France (F.V.). Department of Neurology, Universitätsklinikum Bonn, Germany (F.J.B., J.Z.). Department of Neurology, Caritas Hospital Saarbrücken, Germany (F.M.). Second Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, Greece (G.T.). Department of Neuromuscular Medicine, Toronto General Hospital, Canada (H.D.K.). Department of Neurology and Emergency, Xuanwu Hospital, Capital Medical University, Beijing, China (J.D.). Department of Neurology, Royal Darwin Hospital, Tiwi, Australia (J.B.). Department of Neurology, Antonius Ziekenhuis, Sneek, the Netherlands (J.O.). Department of Neurology, Rijnstate Hospital Arnhem, the Netherlands (J.S.). Department of Neurology, Royal North Shore Hospital, Sydney, Australia (K.N., M. Wronski, S.C.). Department of Neurology, CHU Grenoble Alpes, France (K.G., P.C.). Department of Neurology, AOU Consorziale Policlinico di Bari, Italy (M.P.). Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, University of Lisbon, Portugal (M.C.D.). Department of Neurology, Sina Hospital, Hamadan University of Medical Science, Iran (M.G.). Neurology and Stroke Unit, Department of Neuroscience, Bufalini Hospital, Cesena, Italy (M.R.). Department of Neurology, Hospital de Cascais Dr. José de Almeida, Cascais, Portugal (M.M.). Department of Neurology, Oslo University Hospital, Norway (M.S.). Acute Stroke Service, Mater Misericordiae University Hospital, UCD School of Medicine and RCSI Medical School, Dublin, Ireland (S. Murphy). Department of Neurology, Stroke Unit, Hôpital de la Cavale Blanche, CHRU de Brest (University Hospital), Université de Bretagne Occidentale, Inserm 1078, Brest, France (S.T.). Department of Clinical Neurosciences, Radiology, and Community Health Sciences, Foothills Medical Centre, Calgary, Canada (S.B.C.). Department of Neurology, Heidelberg University Hospital, Germany (S.S., S.N.). Department of Neurology, Helsinki University Hospital, University of Helsinki, Finland (S.H., T.T., J. Putaala). Department of Neurology, University Hospital Southampton NHS Foundation Trust, United Kingdom (T.C.). Department of Neurology, University Medical Center Schleswig-Holstein, Campus Kiel, Germany (T.B.). Isfahan



University of Medical Sciences (IUMS), Isfahan Neurosciences Research Center (INRC), Iran (V.S.). Department of Internal (INRC), Iran (V.S.). Department of Internal Medicine and Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands (S. Middeldorp). National Institute for Health Research, University College London Hospitals (UCLH), Biomedical Research Centre, London, United Kingdom (M.M.L.). Stroke Centre, Lisbon Central University Hospital Centre, Portugal (D.A.d.S.). Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Portugal (D.A.d.S., J.M.F.).

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## Supplemental Material

Figures S1–S4

Tables S1–S3

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