

INTERNATIONAL CVT RESEARCH CONSORTIUM

RESEARCH PROPOSAL

TITLE of project	Cerebral venous thrombosis (CVT) after COVID-19 vaccination
Core group of this project	Jonathan Coutinho (Amsterdam University Medical Centers, The Netherlands, lead investigator) Mirjam Heldner (University of Bern, Switzerland) José Ferro (University of Lisbon, Portugal) Turgut Tatlisumak (University of Gothenburg, Sweden) Saskia Middeldorp (Radboud University Medical Center, The Netherlands) Marcel Levi (University College London, United Kingdom) Mayte Sanchez van Kammen (Amsterdam University Medical Centers, The Netherlands) Marcel Arnold (University of Bern, Switzerland)
Contact details project leader	Dr. Jonathan Coutinho, MD, PhD, FESO Amsterdam University Medical Centers, location AMC Department of neurology Room H2-260 Meibergdreef 9 1105 AZ Amsterdam The Netherlands T (020) 732 22 89 (=cell phone) j.coutinho@amsterdamumc.nl

PROJECT SUMMARY

Background and aim	<p>In March 2020, WHO declared coronavirus disease 2019 (COVID-19) to be a pandemic.</p> <p>COVID-19 has been shown to be prothrombotic causing venous thrombosis, pulmonary embolism and arterial vessel occlusions in a large proportion of patients. Several case reports on cerebral venous thrombosis (CVT) and COVID-19 have been published to date. Although it is difficult to draw conclusions on causality based on data from uncontrolled studies, the sheer number of case reports seems to suggest that COVID-19 indeed increases the risk of CVT [1-6]. Several COVID-19 patients have been demonstrated to have elevated d-dimers and strong reactivity in</p>
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PF4/heparin antigen tests [7].

COVID-19 vaccines have been developed at an impressive speed. At this time, a number of COVID-19 vaccines have been approved and are being used for vaccination in many countries around the world. Recently, several patients who developed CVT 4-16 days after COVID-19 vaccination with the Astra Zeneca vaccine have been reported. This generally concerned patients aged 20-60 years and women appeared more frequently affected than men. Most patients also had thrombocytopenia, which indicates an immunological event as the cause of the tendency to thrombosis. Interestingly, numbers of deep vein thrombosis and pulmonary embolism in the absence of thrombocytopenia did not appear to be increased [8-10].

Based on work by the lab from Andreas Greinacher, Greifswald (Germany) a probable pathophysiological explanation for the complication has been uncovered. Based on laboratory assessment in a number of cases, they found that the vaccination leads to the formation of antibodies against platelet antigens. These antibodies subsequently induce massive platelet activation via the Fc receptor analogous to heparin- induced thrombocytopenia (HIT) [10].

Different institutions have issued reports and updated recommendations concerning the Astra Zeneca COVID-19 vaccination, including the European Medicines Agency (EMA), the Paul-Ehrlich Institute/Germany, the Society of Thrombosis and Haemostasis (GTH) and the Government of the United Kingdom (GOV UK). The current conclusion is that the benefit of the Astra Zeneca COVID-19 vaccination outweighs its potential risk of CVT [10-13].

In spite of the work that has been done, a detailed analysis of CVT cases that developed after COVID-19 vaccination has yet to be performed. As a result, important research questions remain, including:

- How often does CVT develop after COVID-19 vaccination?
- What are the clinical manifestations, laboratory and imaging findings, and outcome of these patients?
- What proportion of patients with CVT after COVID-19 vaccination have thrombocytopenia and a HIT-like disease?
- Is the CVT complication after vaccination specific for the Astra

	<p>Zeneca vaccine?</p> <p>To address these research questions, we aim to perform a study within the International Cerebral Venous Thrombosis Consortium (ICVTC). The ICVTC is an existing, global collaboration by academic researchers with the primary aim to perform investigator-initiated research on the epidemiology, manifestations, and outcome of CVT. The Consortium was formed in 2014 and its members annually meet at the European Stroke Organisation conferences. Participating hospitals are dedicated to collect detailed information on consecutive patients with CVT. Currently, 32 hospitals (Appendix A) are participating in the Consortium and we have already collected data of 1,308 patients with CVT. To date, the Consortium has published 18 papers on CVT in peer-reviewed medical journals (Appendix B). The Consortium has an informal leadership structure (Appendix C) and all participating researchers may propose and take the lead in new projects.</p>
Aim	To report clinical manifestations, laboratory findings, management, and outcome of patients with CVT after COVID-19 vaccination.
Inclusion criteria	<p>We will include data from all patients who are admitted to any of the centers participating in ICVTC or who are brought to the attention of members of ICVTC with:</p> <ul style="list-style-type: none"> - Radiologically confirmed CVT - Onset of CVT symptoms within 4 weeks of COVID-19 vaccination (any vaccine). - Informed consent for the use of coded data if required by local law.
Key variables of interest	<ul style="list-style-type: none"> - Demographics - COVID-19 details - CVT risk factors - Clinical manifestation and presentation - Baseline laboratory investigation, including thrombocytopenia details - Baseline imaging - Treatment - Clinical course - Outcome
Comparison group	Using case-control analysis, we will compare the findings with data from the existing ICVTC, which contains data of >1300 patients with CVT. Number permitting, we will also compare the post vaccination cases with

	CVT cases that developed after COVID-19 infection.
Statistical analysis	Statistical analysis will be performed using SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA).

RELEVANCE

Novelty	High external validity with data from multiple and experienced comprehensive centres with expertise in diagnosis and therapy of CVT.
Importance	COVID-19 vaccinations are novel vaccinations with a huge multidimensional global impact at present.

CONTRIBUTING CENTERS

Estimate about number of patients with data available already	Around 35 eligible cases reported to us so far.
Centers interested in actively contributing	Several worldwide among the CVT consortium.
Project design	Retrospective analysis including data of multiple centres worldwide.
Data analyses, presenting of the data and drafting a manuscript	The Amsterdam and Bernese stroke team. The study results will be published in an international peer-reviewed journal.
Ethical considerations	The approval for the study by the leading ethical review board (Amsterdam University) is pending, but is expected timely. Each centre will be responsible for obtaining adequate permission from local authorities for study participation and to acquire consent from the patient or patient's relatives for the use of their data in a coded form, if so required by local law.

REFERENCES

1. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol.* 2020 Sep;5(3):279–284.
2. Siegler JE, Cardona P, Arenillas JF, et al. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry. *Int J Stroke.* 2020 Sep 30:1747493020959216.
3. Klein DE, Libman R, Kirsch C, et al. Cerebral venous thrombosis: Atypical presentation of COVID-19 in the young. *J Stroke Cerebrovasc Dis.* 2020 Aug;29(8):104989.
4. Tu TM, Goh C, Tan YK, et al. Cerebral Venous Thrombosis in Patients with COVID-19 Infection: a Case Series and Systematic Review. *J Stroke Cerebrovasc Dis.* 2020 Dec;29(12):105379.

5. Sugiyama Y, Tsuchiya T, Tanaka R, et al. Cerebral venous thrombosis in COVID-19-associated coagulopathy: A case report. *J Clin Neurosci*. 2020 Sep;79:30-32.
6. Daviet F, Guervilly C, Baldesi O, et al. Heparin-Induced Thrombocytopenia in Severe COVID-19. *Circulation*. 2020;142:1875-7.
7. Baldini T, Asioli GM, Romoli M, et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: A systematic review and meta-analysis. *Eur J Neurol*. 2021 Jan 11.
8. https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/hp-news/faq-temporary-suspension-astrazeneca.pdf?__blob=publicationFile&v=7
9. <https://english.elpais.com/society/2021-03-16/spain-temporarily-suspends-use-of-astrazeneca-vaccine.html>
10. https://gth-online.org/wp-content/uploads/2021/03/GTH_Stellungnahme_AstraZeneca_3_24_2021.pdf
11. <https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>
12. <https://www.pei.de/EN/newsroom/hp-news/2021/210319-covid-19-vaccine-astrazeneca-safety-assessment-result-vaccine-safe-and-effective.html;jsessionid=E33D413329DCC4647D29B7FB8BF2C723.intranet241>
13. <https://www.gov.uk/government/news/uk-regulator-confirms-that-people-should-continue-to-receive-the-covid-19-vaccine-astrazeneca>

Appendix A: Participating hospitals in the International Cerebral Venous Thrombosis Consortium

1. Amsterdam University Medical Center, location AMC, Amsterdam, The Netherlands
2. Helsinki University Central Hospital, Helsinki, Finland
3. Sahlgrenska University Hospital, Gothenburg, Sweden
4. University Health Network and the University of Toronto, Toronto, Canada
5. Vancouver Stroke Program, Vancouver, Canada
6. University Hospital Inselspital, Bern, Switzerland
7. Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Universidade de Lisboa, Lisbon, Portugal
8. National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico City, Mexico
9. Hospital La Catolica, San Jose, Costa Rica
10. XuanWu Hospital, Beijing, China
11. Hamadan University of Medical Science, Hamadan, Iran
12. Royal Adelaide Hospital, Adelaide, SA, Australia
13. Austin Health and Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, VIC, Australia
14. Hôpital Lariboisière, Paris, France
15. Centre Hospitalier Universitaire **de Lille, Lille**, France
16. Institute of Cardiovascular Research Royal Holloway, University of London, London, UK
17. Salford Royal NHS Foundation Trust, Salford, UK
18. Istanbul University, Istanbul, Turkey
19. University Hospital Policlinico Paolo Giaccone, Palermo, Italy
20. University of Insubria, Varese, Italy
21. Hadassah Medical Center, Jerusalem, Israel
22. Sverdlovsk Regional Clinical Hospital Yekaterinburg, Russia
23. King Faisal Specialist Hospital and Research Center, Riyadh, Saudi-Arabia
24. Kazimierz Pulaski University of Technology and Humanities, Radom, Poland
25. Haukeland University Hospital, Bergen, Norway
26. Christchurch Hospital, Christchurch, New Zealand
27. Rajendra Institute of Medical Sciences, New Delhi, India
28. Christian Medical College Hospital, Vellore, India
29. Heidelberg University Hospital, Heidelberg, Germany
30. Bispebjerg & Frederiksberg Hospitals, Copenhagen, Denmark
31. University Hospital Leuven, Leuven, Belgium
32. Sao Paulo University Hospital, Sao Paulo

Appendix B: list of publications by the International Cerebral Venous Thrombosis Consortium

1. [Late seizures in cerebral venous thrombosis.](#)
Sánchez van Kammen M, Lindgren E, Silvis SM, Hiltunen S, Heldner MR, Serrano F, Zelano J, Zuurbier SM, Mansour M, Aguiar de Sousa D, Canhão P, Al-Asady S, Ekizoglu E, Redfors P, Yesilot N, Ghiasian M, Barboza MA, Arnao V, Aridon P, Punter MNM, Ferro JM, Arauz A, Tatlisumak T, Arnold M, Putaala J, Jood K, Coutinho JM.
Neurology. 2020 Sep 22;95(12):e1716-e1723. doi: 10.1212/WNL.0000000000010576. Epub 2020 Aug 5.
PMID: 32759195
2. [Acute symptomatic seizures in cerebral venous thrombosis.](#)
Lindgren E, Silvis SM, Hiltunen S, Heldner MR, Serrano F, de Scisco M, Zelano J, Zuurbier SM, Sánchez van Kammen M, Mansour M, Aguiar de Sousa D, Penas S, Al-Asady S, Ekizoglu E, Redfors P, Ahmed A, Yesilot N, Ghiasian M, Barboza MA, Arnao V, Aridon P, Punter MNM, Ferro JM, Kleinig T, Arauz A, Tatlisumak T, Arnold M, Putaala J, Coutinho JM, Jood K.
Neurology. 2020 Sep 22;95(12):e1706-e1715. doi: 10.1212/WNL.0000000000010577. Epub 2020 Aug 5.
PMID: 32759191
3. [Prediction of cerebral venous thrombosis with a new clinical score and D-dimer levels.](#)
Heldner MR, Zuurbier SM, Li B, Von Martial R, Meijers JCM, Zimmermann R, Volbers B, Jung S, El-Koussy M, Fischer U, Kohler HP, Schroeder V, Coutinho JM, Arnold M.
Neurology. 2020 Aug 18;95(7):e898-e909. doi: 10.1212/WNL.0000000000009998. Epub 2020 Jun 23.
PMID: 32576633
4. [Features of intracranial hemorrhage in cerebral venous thrombosis.](#)
Afifi K, Bellanger G, Buyck PJ, Zuurbier SM, Esperon CG, Barboza MA, Costa P, Escudero I, Renard D, Lemmens R, Hinteregger N, Fazekas F, Conde JJ, Giralt-Steinhauer E, Hiltunen S, Arauz A, Pezzini A, Montaner J, Putaala J, Weimar C, Schlamann M, Gattringer T, Tatlisumak T, Coutinho JM, Demaerel P, Thijs V.
J Neurol. 2020 Nov;267(11):3292-3298. doi: 10.1007/s00415-020-10008-0. Epub 2020 Jun 22.
PMID: 32572620
5. [Anaemia at admission is associated with poor clinical outcome in cerebral venous thrombosis.](#)
Silvis SM, Reinstra E, Hiltunen S, Lindgren E, Heldner MR, Mansour M, Ghiasian M, Jood K, Zuurbier SM, Groot AE, Arnold M, Barboza MA, Arauz A, Putaala J, Tatlisumak T, Coutinho JM; International CVT Consortium.
Eur J Neurol. 2020 Apr;27(4):716-722. doi: 10.1111/ene.14148. Epub 2020 Jan 24.
PMID: 31883169 **Free PMC article.**
6. [Coagulation Factor XIII in Cerebral Venous Thrombosis.](#)
Li B, Heldner MR, Arnold M, Coutinho JM, Zuurbier SM, Meijers JCM, Kohler HP, Schroeder V.
TH Open. 2019 Jul 22;3(3):e227-e229. doi: 10.1055/s-0039-1693487. eCollection 2019 Jul.
PMID: 31338488 **Free PMC article.** No abstract available.
7. [Diagnostic accuracy of noncontrast CT imaging markers in cerebral venous thrombosis.](#)
Buyck PJ, Zuurbier SM, Garcia-Esperon C, Barboza MA, Costa P, Escudero I, Renard D, Lemmens R, Hinteregger N, Fazekas F, Conde JJ, Giralt-Steinhauer E, Hiltunen S, Arauz A, Pezzini A, Montaner J, Putaala J, Weimar C, Churilov L, Gattringer T, Asadi H, Tatlisumak T, Coutinho JM, Demaerel P, Thijs V.
Neurology. 2019 Feb 19;92(8):e841-e851. doi: 10.1212/WNL.0000000000006959. Epub 2019 Jan 18.
PMID: 30659138
8. [Postpartum Period Is a Risk Factor for Cerebral Venous Thrombosis.](#)
Silvis SM, Lindgren E, Hiltunen S, Devasagayam S, Scheres LJ, Jood K, Zuurbier SM, Kleinig TJ, Silver FL, Mandell DM, Middeldorp S, Putaala J, Cannegieter SC, Tatlisumak T, Coutinho JM.

- Stroke. 2019 Feb;50(2):501-503. doi: 10.1161/STROKEAHA.118.023017.
PMID: 30621526 Clinical Trial.
9. [The benefit of EXtending oral antiCOAgulation treatment \(EXCOA\) after acute cerebral vein thrombosis \(CVT\): EXCOA-CVT cluster randomized trial protocol.](#)
Miranda B, Aaron S, Arauz A, Barinagarrementeria F, Borhani-Haghighi A, Carvalho M, Conforto AB, Coutinho JM, Stam J, Canhão P, Ferro JM.
Int J Stroke. 2018 Oct;13(7):771-774. doi: 10.1177/1747493018778137. Epub 2018 May 17.
PMID: 29771211
 10. [Elevated factor VIII increases the risk of cerebral venous thrombosis: a case-control study.](#)
Vecht L, Zuurbier SM, Meijers JCM, Coutinho JM.
J Neurol. 2018 Jul;265(7):1612-1617. doi: 10.1007/s00415-018-8887-7. Epub 2018 May 8.
PMID: 29737426
 11. [Cerebral Venous Thrombosis in Older Patients.](#)
Zuurbier SM, Hiltunen S, Lindgren E, Silvis SM, Jood K, Devasagayam S, Kleinig TJ, Silver FL, Mandell DM, Putaala J, Tatlisumak T, Coutinho JM.
Stroke. 2018 Jan;49(1):197-200. doi: 10.1161/STROKEAHA.117.019483. Epub 2017 Dec 4.
PMID: 29203685
 12. [Cancer and risk of cerebral venous thrombosis: a case-control study.](#)
Silvis SM, Hiltunen S, Lindgren E, Jood K, Zuurbier SM, Middeldorp S, Putaala J, Cannegieter SC, Tatlisumak T, Coutinho JM. J Thromb Haemost. 2018 Jan;16(1):90-95. doi: 10.1111/jth.13903.
Epub 2017 Dec 1. PMID: 29125690
 13. [Cerebral venous thrombosis.](#)
Silvis SM, de Sousa DA, Ferro JM, Coutinho JM.
Nat Rev Neurol. 2017 Sep;13(9):555-565. doi: 10.1038/nrneurol.2017.104. Epub 2017 Aug 18.
PMID: 28820187 Review.
 14. [Towards the genetic basis of cerebral venous thrombosis-the BEAST Consortium: a study protocol.](#)
Cotlarciuc I, Marjot T, Khan MS, Hiltunen S, Haapaniemi E, Metso TM, Putaala J, Zuurbier SM, Brouwer MC, Passamonti SM, Bucciarelli P, Pappalardo E, Patel T, Costa P, Colombi M, Canhão P, Tkach A, Santacroce R, Margaglione M, Favuzzi G, Grandone E, Colaizzo D, Spengos K, Arauz A, Hodge A, Ditta R, Debette S, Zedde M, Pare G, Ferro JM, Thijs V, Pezzini A, Majersik JJ, Martinelli I, Coutinho JM, Tatlisumak T, Sharma P; ISGC (International Stroke Genetics Consortium) and BEAST investigators. BMJ Open. 2016 Nov 22;6(11):e012351. doi: 10.1136/bmjopen-2016-012351.
PMID: 27881526 **Free PMC article.**
 15. [Risk Factors for Cerebral Venous Thrombosis.](#)
Silvis SM, Middeldorp S, Zuurbier SM, Cannegieter SC, Coutinho JM.
Semin Thromb Hemost. 2016 Sep;42(6):622-31. doi: 10.1055/s-0036-1584132. Epub 2016 Jun 6.
PMID: 27272966 Review.
 16. [Risk of Cerebral Venous Thrombosis in Obese Women.](#)
Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, Meisterernst J, Nemeth B, Meulendijks ER, Stam J, Cannegieter SC, Coutinho JM.
JAMA Neurol. 2016 May 1;73(5):579-84. doi: 10.1001/jamaneurol.2016.0001.
PMID: 26974867
 17. [Admission Hyperglycemia and Clinical Outcome in Cerebral Venous Thrombosis.](#)
Zuurbier SM, Hiltunen S, Tatlisumak T, Peters GM, Silvis SM, Haapaniemi E, Kruyt ND, Putaala J, Coutinho JM.
Stroke. 2016 Feb;47(2):390-6. doi: 10.1161/STROKEAHA.115.011177. Epub 2015 Dec 15.
PMID: 26670083
 18. [Association Between Anemia and Cerebral Venous Thrombosis: Case-Control Study.](#)
Coutinho JM, Zuurbier SM, Gaartman AE, Dikstaal AA, Stam J, Middeldorp S, Cannegieter SC.
Stroke. 2015 Oct;46(10):2735-40. doi: 10.1161/STROKEAHA.115.009843. Epub 2015 Aug 13.
PMID: 26272383

Appendix C: Leadership International Cerebral Venous Thrombosis Consortium

- Prof. Dr. M. Arnold (Inselspital, Bern, Switzerland)
- Dr. J.M. Coutinho (Amsterdam UMC, Amsterdam, the Netherlands)
- Prof. Dr. J.M. Ferro (Hospital de Santa Maria, Lisbon, Portugal)
- Dr. J. Putaala (Helsinki University Hospital, Helsinki, Finland)
- Prof. Dr. T. Tatlisumak (Sahlgrenska University Hospital, Gothenburg, Sweden)