

Algemene gegevens / General Information

Programma / Programme : **COVID-19 Programma**
 Subsidieronde / Subsidy round : **Bottom-up ronde COVID-19 aandachtsgebied 1**
 Projecttitel / Project title : **COVID-19 and ischemic stroke - How to tame a dozing monster**
 Projecttaal / Project language : **Engels / English**
 Geplande startdatum / Planned start date : **15-07-2020**
 Geplande duur / Planned duration : **24 maanden / months**
 Datum indienen / Date of application : **14-05-2020**
 Projecttype / Project type : **Toegepast onderzoek**
 Vervolg eerder ZonMw-project / Continuation previously funded project : **Nee / No**
 ZonMw

Projectleden / Project members

5.1.2e
 Functie / Position: 5.1.2e | Opleiding / Education:
 Studierichting / Subject:
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Leids Universitair Medisch Centrum
 Department of Internal Medicine
 Thrombosis and Hemostasis
 Albinusdreef 2
 2333 ZA LEIDEN

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Radboudumc
 Neurologie
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 6500 HB NIJMEGEN

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Aanvraagformulier GGG_digitaal / Applicationform GGG digital

Dossier nummer / Dossier number: 5.1.1c

Erasmus MC
Intensive Care Volwassenen
Postbus 2040
3000 CA ROTTERDAM

5.1.2e 1.2e

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Postbus 9101
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Radboudumc
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Algemene Interne Geneeskunde 463
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6500 HB Nijmegen

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T: 5.1.2e | F: | E: 5.1.2e @umcutrecht.nl

Universitair Medisch Centrum Utrecht
Divisie Hersenen
Neurologie
Postbus 85500
3508 GA UTRECHT

Projectgegevens / Project information**Aandachtsgebieden / Focus**

- 1.1 Thema's aandachtsgebied 1
- Behandeling
 - Risicoanalyse en prognostiek
- 1.3 Setting
- Transmuraal
 - Ziekenhuiszorg

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number:

5.1.1c

Samenvatting / Summary

COVID-19 pneumonia is complicated by a high risk of thrombotic complications, occurring with a cumulative incidence of 49% in intensive care unit (ICU) patients. These thrombotic complications are strongly associated with poor clinical outcome and death. Pulmonary embolism is the most common complication, but an emerging problem is the increase in number of reported ischemic strokes of currently unknown magnitude and impact. Our hypothesis is that the ischemic stroke is either caused by intensive coagulation-induced local thrombosis and intracranial vessel wall inflammation, and/or the result of a paradoxical embolism through a patent foramen ovale. In three work packages we will: 1) get an accurate estimate of the incidence of symptomatic ischemic stroke in all COVID-19 ICU patients (admitted to 15 Dutch hospitals as well as the prevalence of silent brain lesions as detected by MRI in a random sample of COVID-19 ICU survivors (n=100); 2) unravel its causes and impact on the basis of imaging studies, biomaterial and measures of functional outcomes, anxiety and depression; and 3) establish the optimal prevention of this unwanted thrombotic complication in COVID-19 patients by comparing incidences of ischemic stroke under different thrombosis prophylaxis strategies. Our multidisciplinary team, with complementary key expertise in all relevant aspects of the field, who were the first to report on the very high risk of thrombotic COVID-19 complications, is very capable of rapidly addressing this urgent problem of ischemic stroke in COVID-19.

Trefwoorden / Keywords

COVID-19; ischemic stroke; Intensive Care Unit; etiology; prevention

Samenwerking / Collaboration**Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:**

Ja / Yes

Inhoud / Content**Disciplines / Disciplines**

- Cardiovasculaire aandoeningen / Cardiovascular diseases
- Neurologie / Neurology
- Bloed- en lymfeziekten / Haematology

Financiële gegevens / Financial data**ZonMw budget**

Kostenpost	Jaar / Year								Totaal / Total
	1	2	3	4	5	6	7	8	
Personeel	5.1.1c								395.042
Materieel									20.000
Implementatie									27.500
Apparatuur									50.000
Overig									7.000
Totaal / Total									499.542

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status
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Bijzondere gegevens / Additional information**Vergunningen / Permits**

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X			X	
DEC		X			
WBO		X			

Aanvraagformulier GGG_digitaal / Applicationform GGG_digital

Dossier nummer / Dossier number: 5.1.1c

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity		X	
Code openheid dierproeven / Code Transparency of Animal Testing		X	

Andere vergunningen / Other permits

DAEB Format

Organisation	Type of organisation	Quoted costs	Quoted co-funding	Requested budget
Leiden University Medical Centre		5.1.1c	-	5.1.1c
			-	
			-	
			-	
			-	
			-	
			-	
			-	
Total			-	

Staff costs

Function (will be filled based on "staff" sheet)	Remarks	Organisation (dropdown menu)	Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
PostDoc		Leiden University Medical Centre	5.1.1c	€ -	5.1.1c
PostDoc		Leiden University Medical Centre		€ -	
Data Manager		Leiden University Medical Centre		€ -	
to be specified				€ -	
to be specified				€ -	
to be specified				€ -	
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to be specified				€ -	
to be specified				€ -	
			€ 395,042,40	€ -	€ 395,042,40

Material, equipment & consumer goods (itemised)

Discription	Remarks	Organisation (dropdown menu)	Costs	Own contribution / 3rd party co-funding	Requested budget ZonMw
Lab costs			5.1.1c	€ -	5.1.1c
				€ -	
				€ -	
				€ -	

List of 15 hospitals

Leids Universitair Medisch Centrum Leiden
Erasmus MC Rotterdam
Radboud UMC Nijmegen
Maastricht UMC Maastricht
Haga Ziekenhuis Den Haag
MC Haaglanden dn Haag
Alrijne Ziekenhuis Leiderdorp
Canisius Wilhelmina Ziekenhuis Nijmegen
Rijnstate Ziekenhuis Arnhem
Bernhoven Ziekenhuis Uden
Amphia Ziekenhuis Breda
Catharina Ziekenhuis Eindhoven
Jeroen Bosch Ziekenhuis Den Bosch
Antonius Ziekenhuis Nieuwegein
Zaans Medisch Centrum

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

**LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE "TOELICHTING
INDIENING PROJECTIDEE" VAN DE OPROEPTEKST ZORGVULDIG!**

Wanneer u het formulier heeft ingevuld:

1. Zet het formulier om naar een PDF file en controleer de details
 2. Upload het complete formulier als een bijlage bij uw indiening in Projectnet
(Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)
- ProjectNet: [Aandachtsgebied 1 \(voorspellende diagnostiek en behandeling\)](#)
ProjectNet: [Aandachtsgebied 2 \(zorg en preventie\)](#)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

Prof Dr MV Huisman and Prof Dr Frank-Erik de Leeuw

ORGANISATIE:

Leids Universitair Medisch Centrum and Radboud Universitair Medisch Centrum Nijmegen

PROJECTTITEL:

COVID-19 and ischemic stroke – how to tame a dozing monster

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de [ZonMw website](#) om de datastewards te informeren en ondersteunen.

☒ Ik betrek een datasteward bij mijn project:

Naam: Dr 5.1.2b

Instituut: LUMC, Afdeling Biomedical Data Sciences

E-mail: 5.1.2e @lumc.nl

Was aanwezig bij de webinar 5.1.2e

☐ Ik heb nog geen datasteward.

ONDERZOEKSVORSTEL max 3 pagina's A4 (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)
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1. PROBLEEMSTELLING EN DOELSTELLING(EN):

Problem: The clinical course of COVID-19 pneumonia is complicated by a high risk of thrombotic complications, with a cumulative rate of 49% in patients on the intensive care unit (ICU) and 9.2% at the normal ward [1-3]. The occurrence of thrombotic complications is strongly associated with a poor clinical outcome and a higher risk of death [2]. While the majority of events occurs in the pulmonary circulation (pulmonary embolism), cases with ischemic stroke are being increasingly reported, although the magnitude of this emerging COVID-19 complication is completely unknown [2,4-6]. Whereas the venous thrombo-emboli could be expected to develop as a result of intensive inflammation and coagulation activation, combined with complete immobilization at the ICU, the alarming occurrence of ischemic stroke in COVID-19 patients was completely unexpected. Ischemic stroke is associated with an increased risk of death, and may result in life-long loss of independence in survivors. COVID-19 associated ischemic stroke may be the result of: generalized coagulopathy, originating from the lungs, but also of systemic embolism secondary to inflammation induced atrial fibrillation, arterial thrombosis in the arteries of the neck or brain combined with arterial wall inflammation, or the result of a paradoxical (venous) embolus due to a persistent open foramen ovale (PFO). Notably, the limited current literature shows that COVID-19 associated ischemic stroke can occur at any age, but also in young patients (<55 years), who do not have classical ischemic stroke risk factors, underlining the likely link with COVID-19 associated coagulopathy [6]. In view of this intense procoagulant and proinflammatory COVID-19 response, it seems plausible that, apart from symptomatic ischemic stroke, associated with a clear neurological deficit, also 'clinically silent' ischemic brain lesions may occur which also may reduce the chance of good recovery and return to functional independence. Knowledge of the cause of ischemic stroke, either clinically symptomatic or silent, in COVID-19 patients is crucial and urgently needed, as this will tailor diagnostic and treatment strategies early in the course of disease. Currently, its exact incidence, origin and optimal prophylactic strategy is unknown. The current grant application and proposed work packages (WPs) will fill these gaps of knowledge.

Goals: 1. to provide an accurate estimate of the incidence of symptomatic ischemic stroke and the prevalence of silent ischemic brain lesions; 2. to unravel its causes and prognosis, and 3. to establish the optimal prevention strategy of this highly relevant thrombotic complication in COVID-19 patients.

2. PLAN VAN AANPAK:

WP 1: Magnitude of the problem of ischemic stroke in COVID-19 patients at the ICU

Aim: to establish 1) the cumulative incidence of symptomatic ischemic stroke during ICU stay and 2) the prevalence of silent ischemic brain lesions in surviving COVID-19 patients.

Design and patients: 1) observational cohort study in all COVID-19 patients admitted to the ICUs of 15 Dutch hospitals (list provided) from the start of the COVID-19 outbreak until July 1st 2020. 2) In a random sample of 100 COVID-19 ICU survivors without clinically overt ischemic stroke, MRI/MRA of the brain will be performed, at first opportunity, to detect asymptomatic brain lesions (scan protocol identical as in symptomatic patients).

Outcome: 1) symptomatic ischemic stroke; 2) MRI identified silent ischemic brain lesions.

Statistical and power analysis: cumulative incidences of symptomatic ischemic stroke, from admission to and until 30 days after ICU discharge, will be estimated; the prevalence of silent ischemic brain lesions will be estimated at first opportunity after discharge; both for the complete population as well as for relevant subgroups (age, sex, prior cardiovascular disease).

Timeline and feasibility: We expect that the final analysis can be performed within 3 months following start of the study. All 15 ICUs have committed to the protocol (expected total number of patients=1000). In our study in 3 Dutch hospitals, the incidence of ischemic stroke was estimated to be as high as 8.2% (upper limit of the 95% CI) [7].

WP 2: Origin and impact of ischemic stroke in COVID-19 patients

Aim: to unravel the cause and establish the outcome of both symptomatic ischemic stroke and silent brain lesions in critically ill COVID-19 patients.

Design and patients: Case-control study: COVID-19 survivors with symptomatic ischemic stroke or silent brain lesions (cases; we expect 40-50 cases in total) and controls: COVID-19 patients without ischemic stroke and silent brain lesions on MRI (N=100 as identified in WP1).

Predictors: cases and controls will be subjected to identical investigations to identify stroke risk factors and to determine the cause of stroke: transthoracic bubble contrast echocardiography (PFO), brain MRI and MRA of the extracranial and intracranial arteries, 72-hour Holter rhythm monitoring, biomarker analysis, including a broad coagulation panel, ACE2 levels, Olink inflammation, cardiovascular and cardiometabolic panels. Whole blood will be stored for DNA and PAX gene tubes for transcriptomics. From both cases and controls,

biobank material collected during ICU admission will be available for additional biomarker analyses, which provides the opportunity to associate pathways with active disease leading to ischemic stroke.

Outcome: Results of above described diagnostic evaluation and biomarker analyses, PROMS of depression and anxiety as well as the modified Rankin scale to assess functional outcomes.

Statistical and power analysis: cases and controls will be compared with respect to the prevalence of all outcomes using logistic regression models. Also, PROMS and functional status will be compared between cases and controls.

Timeline: all clinical examinations will be performed in hospital or following hospital discharge.

Feasibility: Most routine clinical data are currently available, and biomarkers and biomaterial have already been collected. This WP can therefore be completed in 2 years. If we conservatively expect 35 cases and 95 controls we have a power of 80% to demonstrate a relative risk of 3 (alpha 0.05), such as for example for PFO, which has a prevalence of 45% in stroke cases and 20% in the population. Considering the anticipated 40-50 patients, we will have more than enough power to come to valid conclusions.

WP3: optimal strategies for prevention of ischemic stroke in COVID-19 ICU patients

Aim: to investigate the efficacy and safety of different thromboprophylaxis strategies for prevention of stroke in COVID-19 patients admitted to the ICU.

Design and patients: observational cohort study in all COVID-19 patients admitted to the ICU of 15 Dutch hospitals from the start of the COVID-19 outbreak until July 1st 2020.

Intervention: 3 clusters of hospitals, each giving different doses of LMWH prophylaxis: standard, intermediate and full-dose.

Outcome: ischemic stroke, major bleeding [8] and death at day 30 after discharge from the ICU.

Statistical analysis: Variation between high and low dose prophylaxis in time and between hospitals is used to compare thromboprophylaxis regimens, using an instrumental variable analysis, with 'hospital' as instrumental variable. Cumulative incidence and risk difference between high and lower doses of LMWH will be analysed, by taking competing risk of death into account and adjusted for potential confounders. A low risk of confounding by indication is expected, since the choice of a type of prophylactic treatment per hospital is predominantly determined by the preference of the treating physicians.

Time line and feasibility: We expect that the final analysis can be performed within 3 months following start of the study. All 15 ICUs have committed to the protocol, and a survey among the participating ICUs suggested sufficient variation in the local prophylaxis protocols for a valid analysis.

3. HAALBAARHEID VAN HET PROJECT:

As described in chapter 2, we expect to be able to report the results of WP1 and WP 3 within 2-3 months, and the results of WP2 in the course of 2 years. Our competent research group, with key leaders in the field, is very apt to tackle the urgent problems (magnitude and optimal prophylaxis) of ischemic stroke in COVID-19 within 2 months after start of the project. Our collaborative research group involves thrombosis experts (Huisman, Klok, Cannegieter), intensivists (Gommers), neurologists (de Leeuw, Tuladhar, Wermer, van der Worp), and clinical epidemiologists (Cannegieter), as well as local experts representing the ICU's of 15 large academic and non-academic hospitals across the Netherlands, who have agreed to participate in this project. All hospitals have built databases of COVID-19 patients, by which it is easy to retrieve relevant data. Besides, we are in close contact with the CAPACITY registry (<https://capacity-covid.eu/>; F.E. Asselbergs), founded by DutchCardioVascularAlliance, which is active in more than 50 sites and included more than 3,000 COVID-19 patients. For WP 1 and WP 3, based on pivotal earlier studies, in which thrombotic complications in three large ICUs were analysed [2,7] with use of CASTOR database we have formed a very practical and solid framework, from which we can retrieve all patients with COVID-19 who are on the ICU, or are discharged to the wards or rehabilitation centers. For WP 2 we already have blood samples taken and stored in most of the ICUs.

4. RELEVANTIE VOOR DE PRAKTIJK:

1. Dit programma beoogt impact te hebben op het verloop van deze pandemie en de gevolgen hiervan voor de Nederlandse bevolking en samenleving: Ischemic stroke is a devastating complication of COVID-19 with life-long consequences for both the patient, who faces loss of functional independence, as well as for society with stroke belonging to the top 3 of most expensive diseases. Our studies will provide important knowledge on cause of stroke and its optimal prevention within two to three months.

2. Het voorstel maakt duidelijk dat Nederland een unieke positie heeft om dit onderzoek te doen: We have the unique infrastructure and complimentary expertise for this project by bringing together all relevant researchers including FAK,DG, SCC and MVH, who performed the two first, seminal analyses of thrombotic complications and key expert vascular neurologists (FEdL, AT, MW, BvdW).

3. Het onderzoek vindt niet al elders plaats: Our study proposal is not being performed elsewhere; we checked with Dutch academic neurologists and the Dutch Society of Neurology. In addition we performed a search (May 14, 2020) in Clin.Trial.Gov and COVID-19 Health database.

4. Het voorstel maakt duidelijk dat publieke financiering aangewezen/noodzakelijk is: The proposed studies cannot be performed at the intended speed without financial support of ZonMw.

5. Borging: de ontwikkelde structuur/interventie/kennis kan in de toekomst opnieuw gebruikt worden: This research proposal had brought together a unique academic infrastructure and expertise, complemented with a nationwide network of dedicated ICUs in top clinical hospitals (STZ), in an organizational structure that is sustainable, and is easily upscaled, in case of future health threats, e.g. a second wave pandemic.

6. Opschaalbaarheid: de structuur/interventie/kennis moet op regionaal/ landelijk niveau toegepast kunnen worden: We will contribute to a new prophylaxis protocol in the prevention of COVID-19 related thrombotic complications, including ischemic stroke. The team has experience and authority to advise, when guidelines are adapted and implemented on a regional and national level [9]. The close collaboration with intensivists and neurologists warrants easy knowledge transfer and dissemination to other medical disciplines.

7. Samenwerking: een ketenbenadering en samenwerking tussen disciplines en met relevante stakeholders is het uitgangspunt voor de aanvraag: We envision an integrated, multidisciplinary collaboration between all relevant specialists in the acute stage of care (intensivists, neurologists) to the subacute phase of COVID-19 associated ischemic stroke (neurologists, internists). There is close interaction with patients and the program is endorsed by relevant charity organizations representing patients (Harteraad). There is a constructive intention for a sustainable public-private partnership (see also 5).

8. Toegevoegde waarde: de bijdrage van het project voor betrokken discipline(s), stakeholders en doelgroepen moet in relevante termen duidelijk beschreven en aantoonbaar zijn: Our proposal will deliver a prophylactic treatment strategy to prevent and reduce the burden COVID-19 related ischemic stroke. This will result in lower number of lives lost, but also in less functional dependence as stroke is a major cause of disability.

9. Maatschappij en economie: het effect van het project op de maatschappelijke en economische vraagstukken die de COVID-19 pandemie oproept, moet inzichtelijk zijn: Patients who will suffer a COVID-19 related stroke may not be able to return to work and take care for their families. Our studies will lead to a better understanding and prevention of ischemic stroke in COVID-19 patients, which will ultimately lead to considerable economic and societal benefit.

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

We are in constructive discussion with the Dutch Heart Foundation to support our project. The Harteraad formally supports our proposal (5.1.2b). We will form a patient panel to advise the steering committee on all important aspects of the planned studies. All vascular internists and vascular neurologists, intensivists and thrombosis specialists of the participating hospitals have agreed to participate and are fully involved. The European Stroke Organisation (ESO) is the voice of stroke in Europe, which will be heard by including its current President (5.1.2b) as applicant. PFOs have a key role as a potential cause of stroke in COVID-19 patients. PFO's can routinely be closed with specific devices. There is potential for public-private partnership as a major pharmaceutical industry (Abbott), manufacturing these devices, has expressed constructive interest to further collaborate with us in this application.

6. LITERATUURREFERENTIES (optioneel):

1) Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020. pii: blood.202006000; 2) Klok FA, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020 pii: S0049-3848(20)30157; 3) Middeldorp S, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 doi: 10.1111/jth.14888; 4) Beyrouti RI, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020 pii: jnnp-2020-323586; 5) Lodigiani C, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020 Apr 23;191:9-14. 6) Oxley TJ, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med. 2020 doi: 10.1056/NEJMc2009787; 7) Klok FA, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020:S0049-3848(20)30120-1; 8) Schulman S, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4; 9) www.demedischspecialist.nl/nieuws/leidraad-covid-19-coagulopathie.