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van Meenen, L.C.C.

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Laura van Meenen

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PRE- AND INTERHOSPITAL WORKFLOW IN LARGE VESSEL OCCLUSION STROKE

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CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

GENERAL INTRODUCTION

Large vessel occlusion stroke

Acute ischemic stroke occurs when an artery in the brain becomes occluded, usually by a blood clot, which causes part of the brain to be deprived of oxygen. This can cause symptoms such as weakness on one side of the body (face, arm and/or leg), difficulty speaking or understanding speech and impaired vision, and can lead to permanent disability or death. Worldwide, acute ischemic stroke affects approximately 9 million people per year.[1] In around a quarter to a third of cases,[2, 3] an acute ischemic stroke is caused by an occlusion of a large, proximal artery; this is called a large vessel occlusion (LVO) stroke. LVO strokes generally cause oxygen deprivation in a large area of the brain. As a result, in patients with an LVO stroke, neurological deficits are often severe, and the risks of permanent disability (sometimes requiring admission to a nursing home) and death are relatively high.[2]

Currently, there are two types of acute treatment for LVO stroke: intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). With IVT, medication that contains an enzyme that dissolves blood clots (recombinant tissue plasminogen activator) is intravenously administered (Figure 1A). In EVT, the blood clot is removed from the artery using a mechanical device, which is introduced through a catheter under image guidance, then passed through the thrombus, and finally expanded and pulled backwards, removing the thrombus (Figure 1B). While IVT can be used in all types of acute ischemic stroke, efficacy of EVT has only been proven in patients with an LVO stroke. However, not all patients with an LVO stroke are eligible for both IVT and EVT. A feared complication of IVT is the occurrence of an intracerebral hemorrhage, which occurs in 2-9% of cases.[4] Because IVT disrupts the coagulation of the blood (i.e. 'thins' the blood), pre-existing conditions, medication use and patient characteristics that cause an increased risk of bleeding are contraindications for this treatment. Although there are less contraindications for EVT, it is a relatively invasive procedure and also carries the risk of complications, such as an arterial dissection, thromboembolic complications and intracranial hemorrhage.[5] Therefore, the treating physician may refrain from EVT if – based on patient characteristics and/or CT scan findings – high risks or low benefit are expected from the treatment.

Time is brain

For both IVT and EVT, it is very important that treatment is started as soon as possible, because this improves the prognosis of patients.[6, 7] In patients with an LVO stroke, every hour that the affected brain tissue is deprived of oxygen, approximately 120 million brain cells perish.[8] An hour delay in time to initiation of treatment in these patients decreases the chance of functional independence (i.e. being able to function in regular daily life without assistance) after stroke by approximately 5%.[7] Over the past

years, multiple studies have examined the in-hospital workflow for the diagnosis and treatment of LVO stroke,[9-12] and several innovations to decrease in-hospital treatment delay have been studied and successfully implemented.[10-14] However, the workflow prior to arrival at the hospital where the treatment takes place – prehospital and interhospital workflow – has only recently started to gain more attention,[15-17] and is currently deemed one of the most important 'bottlenecks' (i.e. remaining challenges) in the acute management of LVO stroke patients.[18, 19]

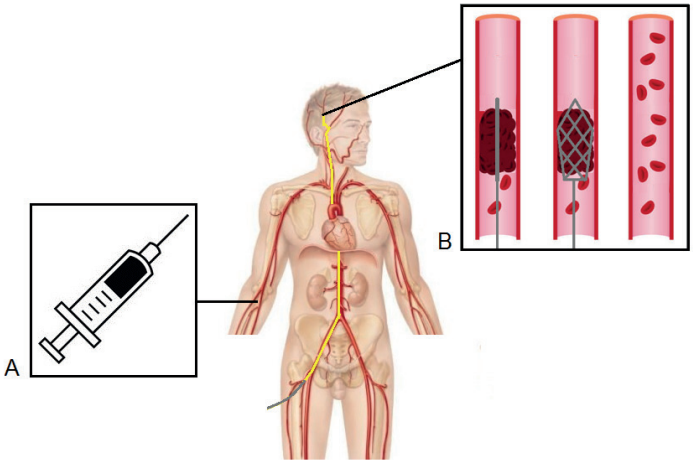

Figure 1. Schematic depiction of intravenous thrombolysis and endovascular thrombectomy. A. Intravenous thrombolysis: medication that contains an enzyme that dissolves blood clots (recombinant tissue plasminogen activator) is intravenously administered. B. Endovascular thrombectomy: a catheter is inserted into the femoral artery and moved all the way up to the occluded vessel in the brain under image guidance. Then, a stent retriever is inserted into the catheter. The stent retriever is passed through the thrombus that is causing the occlusion. Finally, the stent retriever is expanded and pulled backwards, removing the thrombus.

Current workflow

While treatment with IVT can be given in all hospitals that provide acute stroke care, EVT can be performed in specialized hospitals only. Hospitals that offer IVT, but not EVT, are called primary stroke centers (PSCs). A hospital in which both IVT and EVT are available, is called a comprehensive stroke center (CSC). In the Netherlands, for every CSC, there are approximately 4 PSCs (Chapter 4), and in the USA, the CSC to PSC ratio is about 1 to 11.[20] Currently, in most countries, paramedics transport patients with a suspected stroke to the nearest hospital for diagnostic procedures, which generally include a non-contrast CT scan and a CT angiography of the brain, and initiation of IVT. Because there are many more PSCs than there are CSCs, most suspected stroke patients are first presented to a PSC. If a patient is primarily presented to a PSC and turns out to have an LVO stroke, the patient must again be transported by paramedics: this time from the PSC to the nearest CSC. On arrival

at the CSC, the treating physician repeats the physical examination and sometimes also repeats the CT scans that were performed in the PSC, to ultimately decide whether the patient is eligible for EVT. This logistical system, the so-called 'drip-and-ship model' (Figure 2A), applies to approximately 45 to 83% of all patients with an LVO stroke.[21-24] Treatment with EVT is substantially delayed in these patients: EVT is initiated 40 to 106 minutes later than in patients who are presented directly to a CSC.[6, 7] This results in worse clinical outcome: in patients who are transported according to the drip-and-ship model, the chance of functional independence is decreased by approximately 8%.[21, 22]

Although the drip-and-ship model has important disadvantages, it is widely used for two reasons. First, since only approximately 12% of all patients with a *suspected* stroke ultimately have an LVO stroke,[25] transporting all suspected stroke patients directly to a CSC would overburden these hospitals. Second, direct presentation to a CSC of all suspected stroke patients would lead to longer initial ambulance travel times and thereby may delay treatment with IVT. This is particularly disadvantageous for patients with an acute ischemic stroke who are not eligible for EVT, which is the case for the majority of this population.

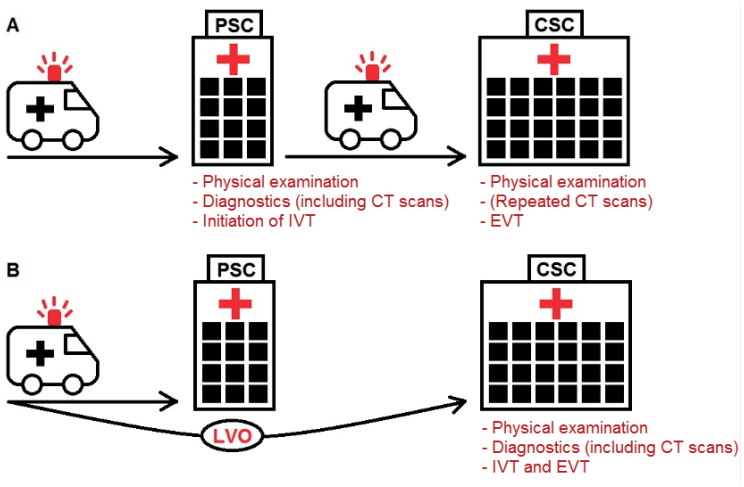

Figure 2. Illustration of the drip-and-ship model and the ideal logistical model. A. The drip-and-ship model: patients with a suspected stroke are first transported to the nearest PSC for a diagnostic work-up and initiation of IVT. Patients with an LVO stroke are subsequently transported from the PSC to a CSC, where the patient undergoes a second physical examination and CT scans may be repeated, to ultimately decide whether the patient is eligible for EVT. B. The ideal logistical model: patients with an LVO stroke are transported directly to a CSC, while all other patients with a suspected stroke are brought to the nearest PSC. CSC = comprehensive stroke center; EVT = endovascular thrombectomy; IVT = intravenous thrombolysis; LVO = large vessel occlusion; PSC = primary stroke center.

Improving the workflow

Ideally, paramedics would be able to transport patients with an LVO stroke directly to a CSC, while all other suspected stroke patients are brought to the nearest PSC (Figure 2B). To achieve this, a method for prehospital detection of LVO stroke is necessary. Several methods have been proposed for this purpose, such as clinical scales, which contain items for scoring the severity of neurological deficit and thereby predict the probability of an LVO stroke, Mobile Stroke Units, which are ambulances equipped to perform CT scans of the brain, and transcranial Doppler, which detects LVO stroke by using ultrasound.[26] However, none of these methods currently seem suitable for prehospital implementation. Electroencephalography (EEG) has recently been proposed as an alternative instrument for prehospital LVO stroke detection. EEG measures the electrical activity of the brain and is most commonly used for the diagnosis and classification of epilepsy and sleep disorders (Figure 3A). Because EEG is sensitive to cerebral hypoxia, it is also used for the monitoring of brain activity during carotid artery surgery. If the clamping of one of the carotid arteries causes oxygen deprivation in the brain, this is immediately visible on the EEG.[27, 28] Because LVO strokes cause oxygen deprivation in similar areas in the brain, one may hypothesize that this type of stroke results in similar EEG abnormalities. Indeed, a small previous study has provided preliminary data that suggest that EEG can be used to detect LVO stroke in the emergency department with relatively high accuracy.[29] However, an important disadvantage of EEG is that it normally requires experienced users and preparation times of approximately 20 to 30 minutes, in which the skin is scrubbed and all individual electrodes are applied in the designated electrode positions using conductive gel or paste. For application in the prehospital setting, this would take too much time and training, and is therefore not feasible. Fortunately, solutions for faster and easier application are available, that may enable performing EEG measurements in the prehospital setting. For example, use of dry electrodes, which can be applied without conductive gel or paste, can reduce EEG preparation time to less than 5 minutes (Figure 3B).[16]

As long as an effective method for prehospital for LVO stroke detection has not yet been found and the 'drip-and-ship model' is still in place, we must aim to improve the pre- and interhospital workflow within this model. To do so, we need to look at the time spent prior to arrival at the PSC, inside the PSC, transporting the patient from the PSC to the CSC, and inside the CSC. These different time intervals may be shortened by streamlining the logistics within emergency medical services, PSCs and CSCs, and by improving the way these partners work together.

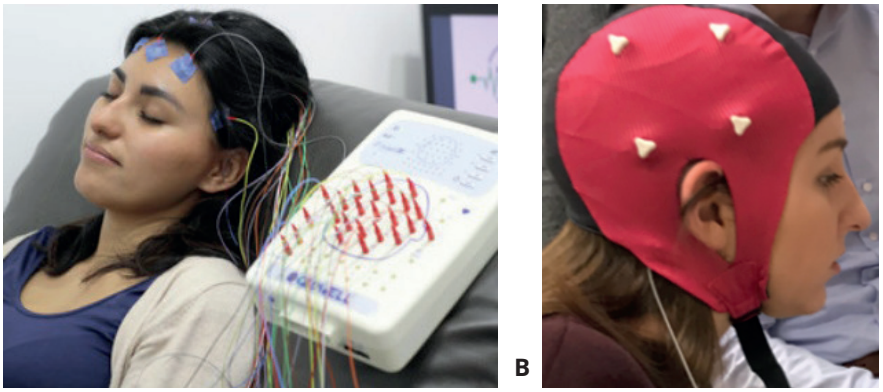

Figure 3. Regular EEG set-up and dry electrode EEG cap. A. Example of a regular EEG set-up. After scrubbing the skin, electrodes are applied to the scalp with a conductive gel or paste. B. Example of a dry electrode EEG cap (Waveguard touch, Eemagine, Berlin, Germany).

THESIS OUTLINE

The focus of this thesis is on the pre- and interhospital workflow leading up to EVT. Our ultimate goal is to find ways to improve this workflow, in order to shorten time to initiation of EVT and thereby improve the prognosis of patients with an LVO stroke.

In the first part of this thesis, we focus on the current workflow. In **chapter 2**, we assess the current prehospital time intervals in patients with an LVO stroke as observed in the Netherlands. **Chapter 3** describes the effects of interhospital transfer prior to EVT, compared to direct presentation to a CSC, in patients who are not eligible for IVT. In **chapter 4**, we examine the relationship between the volume of the referring PSC and EVT-related treatment times. In **chapter 5**, we assess the diagnostic yield and effect on treatment times of repeating CT scans of the brain at the CSC in patients transferred for EVT.

In the second part of this thesis, we shift our focus to the workflow that we envision for the future. **Chapter 6** outlines the necessity of and previously examined possibilities for a prehospital LVO detection method and proposes the EEG as an instrument that may be suitable for this purpose. In **chapter 7**, we present the first results of the ongoing ELECTRA-STROKE study. The main goal of this study is to investigate the diagnostic accuracy of dry electrode EEG for LVO stroke in the prehospital setting. To assess the feasibility of performing dry electrode EEGs in an acute setting and to examine which EEG features are most useful for detection of LVO stroke, suspected stroke patients in the emergency room were also included. In this chapter, the data of the first 100 patients who were enrolled in the emergency room are reported.

Chapter 8 contains a general discussion, including suggestions for future research.

REFERENCES

1. Collaborators GBDS. Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the global burden of disease study 2016. *Lancet Neurol*. 2019;18:439-458
2. Malhotra K, Gornbein J, Saver JL. Ischemic strokes due to large-vessel occlusions contribute disproportionately to stroke-related dependence and death: A review. *Front Neurol*. 2017;8:651
3. Dozois A, Hampton L, Kingston CW, Lambert G, Porcelli TJ, Sorenson D et al. Plumber study (prevalence of large vessel occlusion strokes in mecklenburg county emergency response). *Stroke*. 2017;48:3397-3399
4. Strbian D, Sairanen T, Meretoja A, Pitkaniemi J, Putaala J, Salonen O, et al. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. *Neurology*. 2011;77:341-348
5. Kaufmann TJ, Huston J, 3rd, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: Evaluation of 19,826 consecutive patients. *Radiology*. 2007;243:812-819
6. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309:2480-2488
7. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
8. Saver JL. Time is brain--quantified. *Stroke*. 2006;37:263-266
9. Goyal M, Almekhlafi MA, Fan L, Menon BK, Demchuk AM, Yeatts SD et al. Evaluation of interval times from onset to reperfusion in patients undergoing endovascular therapy in the interventional management of stroke iii trial. *Circulation*. 2014;130:265-272
10. Mehta BP, Leslie-Mazwi TM, Chandra RV, Bell DL, Sun CH, Hirsch JA et al. Reducing door-to-puncture times for intra-arterial stroke therapy: A pilot quality improvement project. *J Am Heart Assoc*. 2014;3:e000963
11. Aghaebrahim A, Streib C, Rangaraju S, Kenmuir CL, Giurgiutiu DV, Horev A et al. Streamlining door to recanalization processes in endovascular stroke therapy. *J Neurointerv Surg*. 2017;9:340-345
12. Kamal N, Smith EE, Menon BK, Eesa M, Ryckborst KJ, Poppe AY et al. Improving reperfusion time within the escape endovascular clinical trial. *Eur Stroke J*. 2017;2:64-69
13. Psychogios MN, Behme D, Schregel K, Tsogkas I, Maier IL, Leyhe JR et al. One-stop management of acute stroke patients: Minimizing door-to-reperfusion times. *Stroke*. 2017;48:3152-3155
14. Goldstein ED, Schnusenberg L, Mooney L, Raper CC, McDaniel S, Thorpe DA et al. Reducing door-to-reperfusion time for mechanical thrombectomy with a multitiered notification system for acute ischemic stroke. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:119-128
15. Helwig SA, Ragoschke-Schumm A, Schwindling L, Kettner M, Roumia S, Kulikovski J et al. Prehospital stroke management optimized by use of clinical scoring vs mobile stroke unit for triage of patients with stroke: A randomized clinical trial. *JAMA Neurol*. 2019;76:1484-1492.
16. Abilleira S, Perez de la Ossa N, Jimenez X, Cardona P, Cocho D, Purroy F et al. Transfer to the local stroke center versus direct transfer to endovascular center of acute stroke patients with suspected large vessel occlusion in the catalan territory (racecat): Study protocol of a cluster randomized within a cohort trial. *Int J Stroke*. 2019;14:734-744
17. Anadani M, Almallouhi E, Wahlquist AE, Debenham E, Holmstedt CA. The accuracy

of large vessel occlusion recognition scales in telestroke setting. *Telemed J E Health*. 2019;25:1071-1076

18. Goyal M, Jadhav AP, Wilson AT, Nogueira RG, Menon BK. Shifting bottlenecks in acute stroke treatment. *J Neurointerv Surg*. 2016;8:1099-1100
19. Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier C, Guekht A et al. Action plan for stroke in europe 2018-2030. *Eur Stroke J*. 2018;3:309-336
20. Schieb LJ, Casper ML, George MG. Mapping primary and comprehensive stroke centers by certification organization. *Circ Cardiovasc Qual Outcomes*. 2015;8:S193-194
21. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, Haussen DC et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311-2321
22. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923-930
23. Pallesen LP, Winzer S, Barlinn K, Prakapenia A, Siepmann T, Gruener C et al. Safety of inter-hospital transfer of patients with acute ischemic stroke for evaluation of endovascular thrombectomy. *Scientific reports*. 2020;10:5655
24. Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ et al. Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making. *Eur Stroke J*. 2018;3:126-135
25. Duvekot MHC, Venema E, Rozeman AD, Moudrous W, Vermeij FH, Biekart M et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (presto): A prospective observational study. *Lancet Neurol*. 2021
26. Lumley HA, Flynn D, Shaw L, McClelland G, Ford GA, White PM et al. A scoping review of pre-hospital technology to assist ambulance personnel with patient diagnosis or stratification during the emergency assessment of suspected stroke. *BMC Emerg Med*. 2020;20:30
27. Lam AM, Manninen PH, Ferguson GG, Nantau W. Monitoring electrophysiologic function during carotid endarterectomy: A comparison of somatosensory evoked potentials and conventional electroencephalogram. *Anesthesiology*. 1991;75:15-21
28. Thirumala PD, Thiagarajan K, Gedela S, Crammond DJ, Balzer JR. Diagnostic accuracy of eeg changes during carotid endarterectomy in predicting perioperative strokes. *J Clin Neurosci*. 2016;25:1-9
29. Erani F, Zolotova N, Vanderschelden B, Khoshab N, Sarian H, Nazarzai L et al. Electroencephalography might improve diagnosis of acute stroke and large vessel occlusion. *Stroke*. 2020:Strokeaha120030150

PART I

CURRENT WORKFLOW

CHAPTER 2

PRE- AND INTERHOSPITAL WORKFLOW TIMES FOR PATIENTS WITH LARGE VESSEL OCCLUSION STROKE TRANSFERRED FOR ENDOVASCULAR THROMBECTOMY

Laura C.C. van Meenen[1], Frank Riedijk[2], Jeffrey Stolp[1], Bas van der Veen[3], Patricia H.A. Halkes[3], Taco C. van der Ree[4], Charles B.L.M. Majoie[5], Yvo B.W.E.M. Roos[1], Martin D. Smeekes[2], Jonathan M. Coutinho[1*]

[1] Department of Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands
[2] Emergency Medical Services North-Holland North, Alkmaar, the Netherlands
[3] Department of Neurology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands
[4] Department of Neurology, Dijklander Ziekenhuis, Hoorn, the Netherlands
[5] Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands

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ABSTRACT

Background

Patients with large vessel occlusion (LVO) stroke are often initially admitted to a primary stroke center (PSC) and subsequently transferred to a comprehensive stroke center (CSC) for endovascular thrombectomy (EVT). This interhospital transfer delays initiation of EVT. To identify potential workflow improvements, we analyzed pre- and interhospital time metrics for patients with LVO stroke who were transferred from a PSC for EVT.

Methods

We used data from the regional emergency medical services and our EVT registry. We included patients with LVO stroke who were transferred from three nearby PSCs for EVT (2014-2021). The time interval between first alarm and arrival at the CSC (call-to-CSC time) and other time metrics were calculated. We analyzed associations between various clinical and workflow-related factors and call-to-CSC time, using multivariable linear regression.

Results

We included 198 patients with LVO stroke. Mean age was 70 years (±14.9), median baseline NIHSS was 14 (IQR: 9-18), 136/198 (69%) were treated with intravenous thrombolysis, and 135/198 (68%) underwent EVT. Median call-to-CSC time was 162 minutes (IQR: 137-190). In 133/155 (86%) cases, the ambulance for transfer to the CSC was dispatched with the highest level of urgency. This was associated with shorter call-to-CSC time (adjusted β [95% CI]: -27.6 minutes [-51.2 to -3.9]). No clinical characteristics were associated with call-to-CSC time.

Conclusion

In patients transferred from a PSC for EVT, median call-to-CSC time was over 2.5 hours. The highest level of urgency for dispatch of ambulances for EVT transfers should be used, as this clearly decreases time to treatment.

INTRODUCTION

Endovascular treatment (EVT) is routine care for patients with large vessel occlusion (LVO) stroke of the anterior circulation.[1, 2] EVT can be performed in specialized hospitals only, so-called comprehensive stroke centers (CSC). In approximately 45 to 83% of cases,[3-6] patients with LVO stroke are first admitted to a primary stroke center (PSC), where they undergo diagnostic evaluation and, if indicated, treatment with intravenous thrombolysis (IVT). Patients who are potentially eligible for EVT are subsequently transferred to a CSC. This 'drip-and-ship' model delays initiation of EVT by 40 to 106 minutes.[3,4] Timely initiation of EVT is of vital importance, because it increases the chance of good clinical outcome.[7] Multiple studies have reported in detail on EVT-related time intervals after arrival at the CSC, such as door-to-CT and door-to-groin time,[8-11] and innovations to shorten these time intervals have been studied and successfully implemented.[9-13] In recent years, several measures to improve the prehospital and interhospital workflow prior to EVT have also been proposed.[14-16] However, little is known about the distribution of time intervals before arrival at the CSC. Toward future implementation of measures to decrease treatment delay, we aimed to study the pre- and interhospital time metrics in patients with LVO stroke who were transferred from a PSC to a CSC for EVT.

MATERIALS AND METHODS

Study design and population

For this study, we used prehospital and interhospital workflow data that were prospectively collected by emergency medical services (EMS) North-Holland North, the Netherlands. EMS North-Holland North has a catchment area of 1400 square kilometers with approximately 650.000 inhabitants. For clinical and in-hospital workflow data, we used the prospective stroke registry of the Amsterdam UMC, the Netherlands. Amsterdam UMC has a catchment area for EVT with approximately 3.3 million inhabitants and receives EVT referrals from 11 nearby PSCs. We included adult patients who had an LVO stroke between January 1 2014 and April 1 2021, who were first transported to one of three PSCs in North-Holland (Northwest Clinics locations Alkmaar and Den Helder, and Dijklander Hospital location Hoorn), and who were subsequently transferred to Amsterdam UMC to potentially undergo EVT. We excluded patients with an in-hospital stroke and patients of whom no EMS data were available.

All patients eligible for inclusion were sent a letter with detailed information about the study. The patient or legal representative had the opportunity to deny permission for use of data via an opt-out form, in accordance with the European Union General Data Protection Regulation and institutional guidelines.

Definitions, procedures and outcomes

Time of symptom onset was defined as the time of witnessed symptom onset or, if this was unknown, the time that the patient was last known to be well. In the Netherlands, for urgent ambulance dispatch, there are two levels of urgency: A1 and A2. The A1-dispatch is used for potentially life threatening situations and the target response time (time between ambulance dispatch and arrival at the patient's location) is 15 minutes. The A2-dispatch is used for urgent, but non-life threatening situations; the dispatched ambulance aims to arrive at the patient's location within 30 minutes. The National Institutes of Health Stroke Scale (NIHSS) was used to quantify the severity of neurological deficit on arrival at the PSC. EVT was defined as arterial puncture in the angiography suite, with the objective to perform mechanical thrombectomy with a stent retriever and/or thrombus aspiration.

We defined the following time points within the EVT-related workflow: time of symptom onset, time of first call to the dispatch center, time of first ambulance dispatch, time of first ambulance arrival at the patient's location, time of first ambulance departure from the patient's location, time of first ambulance arrival at the PSC, time of initiation of IVT, time of second call to the dispatch center, time of second ambulance dispatch, time of second ambulance arrival at the PSC, time of second ambulance departure from the PSC, time of second ambulance arrival at the CSC, and time of initiation of EVT (groin puncture).

All consecutive intervals between the different time points were calculated. Our primary workflow measure was the time between the first call to the dispatch center and patient arrival at the CSC (call-to-CSC time). Other outcomes were time between first ambulance arrival at the patient's location and first ambulance departure to the PSC (on-scene time), time between first call to the dispatch center and arrival at the PSC (call-to-PSC time), time between patient arrival at the PSC and time of second ambulance departure from the PSC (door-in-door-out time), and time between second ambulance departure from the PSC and arrival at the CSC (transfer time).

Statistical analysis

Baseline characteristics of patients who were excluded because of missing EMS data were compared to those of included patients, using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and χ^2 test for categorical variables. For included patients, baseline characteristics were reported for the population as a whole. For all consecutive intervals between the different time points, the median time in minutes was calculated. We used multivariable linear regression to perform an exploratory analysis of the associations between clinical and workflow-related factors and call-to-CSC time, call-to-PSC time, and door-in-door-out time. For our analysis of call-

to-CSC time, we used the following variables (unless reported otherwise, baseline characteristics were measured on arrival at the PSC): age, previous ischemic stroke or transient ischemic attack (TIA), baseline systolic blood pressure, baseline diastolic blood pressure, baseline NIHSS, location of occlusion, treatment with IVT, time between symptom onset and first call to dispatch center (onset-to-call time), time of first call to dispatch center (within or outside office hours), person making the first call to the dispatch center (non-medical person or general practitioner), urgency of first ambulance dispatch, and urgency of second ambulance dispatch. When analyzing call-to-PSC time, the following variables were used: age, previous ischemic stroke/TIA, baseline NIHSS, onset-to-call time, time of first call to dispatch center, person making first call to dispatch center, and urgency of first ambulance dispatch. For our analysis of door-in-door-out-time, we used age, previous ischemic stroke/TIA, baseline systolic blood pressure, baseline diastolic blood pressure, baseline NIHSS, location of occlusion, treatment with IVT, time between symptom onset and arrival at the PSC (onset-to-PSC time), time of arrival at the PSC (within or outside office hours), and urgency of second ambulance dispatch. For all regression analyses, we imputed missing values using multiple imputation, using the following variables: age, previous ischemic stroke/TIA, history of hypertension, history of diabetes mellitus, history of atrial fibrillation, pre-stroke modified Rankin Scale score, baseline systolic blood pressure, baseline diastolic blood pressure, baseline NIHSS, location of occlusion on CTA, treatment with IVT, treatment with EVT, 90-day mRS, time of first call to the dispatch center, person making the first call to the dispatch center, urgency of first ambulance dispatch, number of diagnostic procedures or interventions performed by ambulance paramedics on-scene, distance from patient's location to PSC, time of arrival at PSC, urgency of second ambulance dispatch, distance between PSC and CSC, call-to-CSC time, on-scene time, call-to-PSC time, door-in-door-out time, transfer time, onset-to-call time, onset-to-scene time and onset-to-PSC time. All analyses were be performed using SPSS (version 25; SPSS Inc., Chicago, IL, USA).

Data availability

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

RESULTS

During the study period, 288 patients were transferred from one of the three PSCs to our hospital to assess eligibility for EVT. Of these, 90 patients were excluded because no EMS data were available (n=68), they had an in-hospital stroke (n=16), they objected to use of data (n=5) or they were <18 years old (n=1). Therefore, 198/288 (69%) patients were included in the study (Supplemental Figure I). Baseline

characteristics of patients who were excluded because of missing EMS data did not differ from those of included patients, except for pre-stroke mRS scores, which were slightly lower among the excluded patients (median [IQR]: 0 [0-0] vs. 0 [0-1], p=0.01). Baseline characteristics are reported in Table 1. Included patients had a mean age of 70 (± 14.9), a median baseline NIHSS of 14 (IQR: 9-18), were treated with IVT in 136/198 (69%) and with EVT in 135/198 (68%) cases. The most common reasons for refraining from EVT were dissolution of the LVO upon arrival at the CSC (27/63 [43%]), unfavorable radiological characteristics (9/63 [14%]), and a combination of clinical and radiological characteristics (8/63 [13%]).

The first call to the dispatch center was made by a non-medical person in 103/108 (95%) and by a general practitioner in 5/108 (5%) cases, and was made outside office hours in 110/167 (66%). The urgency of the first ambulance dispatch was A1 in 163/167 (98%), while the urgency of the second ambulance dispatch was A1 in 133/155 (86%) cases. All patients were transported over ground.

All pre-defined consecutive median time intervals are shown in Figure 1. Median call-to-CSC time was 162 minutes (IQR 137-190). Median on-scene time was 15 minutes (IQR 11-20), call-to-PSC time 37 minutes (IQR 29-45), door-in-door-out time 85 minutes (IQR 70-113) and transfer time 28 minutes (IQR 26-30).

The following factors were associated with call-to-CSC time in univariable analyses: baseline systolic blood pressure (unadjusted β [95% CI]: 0.5 minutes [0.2 to 0.8]), baseline diastolic blood pressure (unadjusted β [95% CI]: 0.8 minutes [0.1 to 1.5]), baseline NIHSS (unadjusted β [95% CI]: -1.4 minutes [-2.8 to -0.8] and the person making the first call to the dispatch center (unadjusted β for general practitioner [95% CI]: 25.8 minutes [4.7 to 46.8]). In the multivariable model, only two factors were associated with call-to-CSC time: the person making the first call to dispatch center (adjusted β for general practitioner [95% CI]: 34.2 minutes [7.2 to 61.1]) and urgency level of dispatch of the transferring ambulance (adjusted β for A1 [95% CI]: -27.6 minutes [-51.2 to -3.9]; Table 2). Call-to-PSC time was only associated with onset-to-call time (adjusted β for every 10-minute increase [95% CI]: 0.1 minutes [0.04 to 0.2]; Supplemental Table I) and door-in-door-out time was associated with urgency level of dispatch of the transferring ambulance (adjusted β for A1 [95% CI]: -30.0 minutes [-56.4 to -3.7]; Supplemental Table II).

Table 1. Baseline characteristics

	All patients (n=198)
Clinical characteristics	
Age, years – mean ± SD	70 ± 14.9
Sex, male – no./total (%)	94/198 (48%)
Hypertension – no./total (%)	74/196 (38%)
Diabetes mellitus – no./total (%)	31/196 (16%)
Atrial fibrillation – no./total (%)	44/196 (22%)
Previous ischemic stroke/TIA – no./total (%)	36/196 (18%)
Pre-stroke mRS score[1] – median (IQR)	0 (0-1)
Systolic blood pressure on arrival at PSC[2] – mean ± SD	157 ± 27.6
Diastolic blood pressure on arrival at PSC[3] – mean ± SD	89 ± 15.7
NIHSS score on arrival at PSC[4] – median (IQR)	14 (9-18)
Intracranial occlusion site on CTA – no./total (%)	
Intracranial ICA	35/198 (18%)
M1	118/198 (60%)
M2	28/198 (14%)
Basilar artery	11/198 (6%)
Other	6/198 (3%)
Treatment with IVT – no./total (%)	136/198 (69%)
Workflow-related factors	
First call to dispatch center outside office hours – no./total (%)	110/167 (66%)
Person making first call to dispatch center – no./total (%)	
Non-medical person	103/108 (95%)
General practitioner	5/108 (5%)
Urgency of first ambulance dispatch, A1 – no./total (%)	163/167 (98%)
Distance between patient's location and PSC, kilometers[5] – median (IQR)	11 (5-17)
Arrival at PSC outside office hours – no./total (%)	109/167 (65%)
Urgency of second ambulance dispatch, A1 – no./total (%)	133/155 (86%)
Distance between PSC and CSC, kilometers – median (IQR)	54 (54-57)

A1 = the A1 ambulance dispatch (most urgent) is used for potentially life threatening situations; target response time is 15 minutes; CSC = comprehensive stroke center; CTA = computed tomography angiography; EVT = endovascular thrombectomy; ICA = internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; M1 = first segment of the middle cerebral artery; M2 = second segment of the middle cerebral artery; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; no. = number; PSC = primary stroke center; SD = standard deviation; TIA = transient ischemic attack. Number of missing values: [1]78; [2]38; [3]39; [4]7; [5]31.

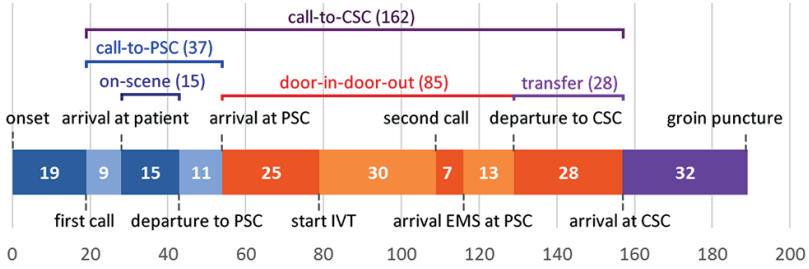

Figure 1. Median time intervals from symptom onset to arrival at the CSC. CSC = comprehensive stroke center; EMS = emergency medical services; IVT = intravenous thrombolysis; PSC = primary stroke center. Not included in figure: median time between first call to dispatch center and first ambulance dispatch: 1 minute; median time between second call to dispatch center and second ambulance dispatch: 1 minute.

Table 2. Clinical and workflow-related factors associated with call-to-CSC time

	Univariable model – unadjusted β in minutes (95% CI)	Multivariable model – adjusted β in minutes (95% CI)
Clinical factors		
Age	-0.1 (-0.7 to 0.5)	-0.2 (-0.9 to 0.5)
Previous acute ischemic stroke/TIA[1]	-23.1 (-46.5 to 0.4)	-17.0 (-40.8 to 6.8)
Systolic blood pressure on arrival at PSC[2]	0.5 (0.2 to 0.8)	0.3 (-0.1 to 0.8)
Diastolic blood pressure on arrival at PSC[3]	0.8 (0.1 to 1.5)	0.5 (-0.2 to 1.2)
NIHSS on arrival at PSC[4]	-1.4 (-2.8 to -0.8)	-1.0 (-2.4 to 0.4)
Location of occlusion, anterior circulation[5]	-9.5 (-42.0 to 23.1)	-1.1 (-35.0 to 32.9)
Treatment with IVT	-9.2 (-29.0 to 10.7)	6.2 (-17.3 to 29.8)
Workflow-related factors		
Onset-to-call time[6]	0.3 (-0.2 to 0.8)	0.4 (-0.2 to 1.0)
First call to dispatch center outside office hours[7]	10.8 (-8.9 to 30.4)	11.1 (-10.0 to 32.3)
Person making first call to dispatch center, general practitioner[8]	25.8 (4.7 to 46.8)	34.2 (7.2 to 61.1)
Urgency of first ambulance dispatch, A1[9]	-0.7 (-0.3 to 31.0)	-2.5 (-45.2 to 40.2)
Urgency of second ambulance dispatch, A1[10]	-24.7 (-50.6 to 1.3)	-27.6 (-51.2 to -3.9)

A1 = the A1 ambulance dispatch (most urgent) is used for potentially life threatening situations; target response time is 15 minutes; call-to-CSC time = time between first call to the dispatch center and arrival at the CSC; CI = confidence interval; CSC = comprehensive stroke center; IVT = intravenous thrombolysis; NIHSS = National Institutes of Health Stroke Scale; onset-to-call time = time between symptom onset and first call to the dispatch center; PSC = primary stroke center; TIA = transient ischemic attack.

Number of missing values: [1]2; [2]38; [3]39; [4]7; [6]35; [7]31; [8]90; [9]31; [10]43; call-to-CSC time: 75.

[5]Intracranial part of internal carotid artery, first of middle cerebral artery (M1), or second segment of middle cerebral artery.

[6]β is reported per 10-minute increase in onset-to-call time.

DISCUSSION

In this cohort study of patients transferred from a PSC for EVT in the Netherlands, median call-to-CSC time was more than 2.5 hours. We found that dispatching the transferring ambulance with the highest level of urgency was associated with a 28-minute decrease in time to arrival at the CSC. If the first call to the dispatch center was made by a general practitioner, this was associated with a delay of 34 minutes, although this was the case for only 5% of patients. Clinical characteristics were not independently associated with any of the prehospital or interhospital time intervals.

Ever since EVT has become standard care for patients with LVO stroke and its effect has been shown to be highly time-dependent,[7] many studies have examined measures to improve EVT-related logistics inside the CSC, leading to a fairly streamlined in-hospital workflow.[8-13] However, the workflow prior to arrival at the CSC – pre- and interhospital workflow – has only recently started to gain attention,[14-16] and is currently considered one of the main 'bottlenecks' in acute stroke management.[17, 18] Few previous studies have reported in detail on time metrics prior to arrival at the CSC. However, in the field of acute myocardial infarction, which deals with logistical challenges similar to stroke regarding transportation of patients to hospitals capable of percutaneous coronary intervention (PCI), pre- and interhospital time intervals are regularly reported. It is noteworthy that in this field, compared to that of acute ischemic stroke, time metrics are generally substantially shorter. The average time between first alarm and initiation of PCI (call-to-balloon time) for patients who are transferred from a non-PCI-capable hospital is 143-160 minutes.[19-21] Taking into account that this includes time between arrival at the intervention center and initiation of PCI, which is around 36-43 minutes on average,[20-22] time from first alarm to arrival at the intervention center in these studies is significantly shorter than our call-to-CSC time of 162 minutes. Our door-in-door-out times, which were very similar to those reported in previous literature,[23, 24] were also substantially longer than those found in interventional cardiology studies: 85 minutes versus 52 minutes.[21] Although these differences may be partly explained by substantive differences between myocardial infarction and acute ischemic stroke, e.g. regarding diagnostic procedures and treatment, it seems as though pre- and interhospital logistics are more optimally streamlined in the field of interventional cardiology than in that of acute ischemic stroke. Further research may focus on identifying potential measures for improvement of the EVT workflow that have been shown to decrease pre- and interhospital delay in patients being transferred to undergo PCI.

Our finding that in 14% of patients the transferring ambulance was not dispatched with the highest level of urgency is somewhat surprising. Although the nationwide protocol for ambulance care in the Netherlands does not mention a recommended level of urgency for dispatch of ambulances transferring patients for EVT,[25] both regional and national stroke care protocols state that ambulances for EVT transfers should be requested with

the highest level of urgency.[26, 27] In other countries, stroke care protocols differ in their recommendations. The National Stroke Service Model of the NHS (United Kingdom) recommends that interhospital transfers for EVT should be treated at least as a category 2 call; this is the second highest level of urgency for ambulance dispatch, for which the response target time is 18 minutes.[28] The American Stroke Association has stated that stroke warrants a priority ambulance dispatch and that rapid transfer of stroke patients for EVT should be ensured, but has not made recommendations regarding the urgency with which transferring ambulances should be dispatched.[29, 30] The necessity of dispatching ambulances for EVT transfer with the highest level of urgency needs to be conveyed to EMS and dispatch organizations, as well as referring PSCs. Incorporating a recommended highest level of urgency for dispatch of ambulances for EVT transfers into stroke care protocols should be considered, as this clearly decreases door-in-door-out time and overall call-to-CSC time.

The association between the general practitioner making the first call to the dispatch center and longer call-to-CSC time may be explained by patients with mild or fluctuating neurological deficits potentially being inclined to visit a general practitioner first, while (bystanders of) patients with evident, severe neurological deficits may be more likely to directly contact the dispatch center. Because patients with mild or fluctuating neurological deficits may be more difficult to diagnose or may be observed for a longer time before transfer to a CSC is initiated, call-to-CSC time may be longer in these patients. Nonetheless, since contacting a general practitioner first is associated with substantially longer call-to-CSC times, and may even cause further delay prior to the first call to the dispatch center, efforts should be taken to promote directly contacting the local emergency phone number in case of symptoms of a potential stroke. Considering that only 5% of calls to the dispatch center were made by a general practitioner in our cohort, this does not seem to be a major contributing factor to prehospital treatment delay in the Netherlands.

Finally, it should be noted that our median time between initiation of IVT and the second call to the dispatch center was 30 minutes, which seems fairly long considering that acquisition of acute neuroimaging is often completed prior to initiation of IVT. Factors that may contribute to delay within this time interval are acquisition and/or assessment of CT angiography after initiation of IVT, evaluation of the clinical response to IVT before initiating transfer, and assessment of neuroimaging by a CSC radiologist prior to initiating transfer. According to several guidelines, CT angiography should be acquired – in patients who are potentially eligible for EVT – either prior to or immediately after initiation of IVT. Furthermore, patients should not be observed for assessment of clinical response to IVT prior to initiating the process of transfer to a CSC.[26, 27, 29] However, it is unknown how often these guidelines are adhered to in clinical practice. When it comes to forwarding neuroimaging to the CSC, technical issues may be a cause of delay.[24] Therefore, a fast and reliable system for forwarding imaging should be implemented,

and – in straight-forward cases – requesting the transferring ambulance prior to receiving definitive approval by the CSC may be considered.

There are two important limitations to this study. First, data collection for this study took place in the Netherlands, where ambulance care is provided by the government in partnership with private organizations and is coordinated by overarching dispatch centers. Furthermore, it is a densely populated country where hospitals are located relatively close to one another. The Netherlands also has an overall good road and highway infrastructure, which makes even remote hospitals relatively easy to reach. In a recent cohort study of patients transferred for EVT in the USA,[31] average time between first call to the dispatch center and arrival of EMS at the patient's location when travelling over ground was 16 minutes, compared to 7 minutes in our study. Average travel distance between PSC and CSC was 47 miles, resulting in a transfer time of 50 minutes, while in our study the median travel distance was 54 kilometers (33 miles), with a median transfer time of 28 minutes. Because ambulance travel times in the Netherlands are relatively short, our findings should be extrapolated to other countries with caution. The second limitation to this study is that we had relatively high numbers of missing data for some variables. Because EMS data could not be retrieved in 90/288 (31%) patients who were transferred for EVT during the study period, these patients were excluded from the study. Among the included patients, we had high numbers of missing values for the person making the first call to the dispatch center (45%), call-to-CSC time (38%) and door-in-door-out time (38%). The high numbers of missing EMS data may be due to the emergency setting and population in which these data were collected – patients with a (suspected) stroke in need of urgent care – potentially leading to time constraints when it comes to administrative duties. In order to check for selection bias as a result of the exclusion of patients with no available EMS data, we compared baseline characteristics of included patients to those of patients who were excluded because EMS data were not available. Since baseline characteristics did not differ between groups, except for slightly lower pre-stroke mRS scores among the excluded patients, we did not find any indication of selection bias in this regard. To try to reduce the impact of the missing values on our analyses, we used multiple imputation.

In conclusion, in patients transferred from a PSC for EVT in the Netherlands, median call-to-CSC time was 162 minutes. If the first call to the dispatch center was made by a general practitioner, this was associated with a delay of 34 minutes, although this was the case for only 5% of patients. Dispatching the ambulance for transfer to the CSC with the highest level of urgency was associated with a 28-minute decrease in call-to-CSC time. The general population should be instructed to contact the local emergency phone number directly in case of stroke symptoms, and incorporating a recommended level of urgency for dispatch of ambulances for EVT transfers into stroke care protocols should be considered.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Data collection and analysis was performed by LvM, FR and JC. The first draft of the manuscript was written by LvM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581-1587.
2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723-1731.
3. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, et al. Interhospital Transfer Before Thrombectomy Is Associated With Delayed Treatment and Worse Outcome in the STRATIS Registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke). *Circulation.* 2017;136:2311-2321.
4. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V, et al. Effect of Interhospital Transfer on Endovascular Treatment for Acute Ischemic Stroke. *Stroke.* 2019;50:923-930.
5. Pallesen LP, Winzer S, Barlinn K, Prakapenia A, Siepmann T, Gruener C, et al. Safety of inter-hospital transfer of patients with acute ischemic stroke for evaluation of endovascular thrombectomy. *Scientific reports.* 2020;10:5655.
6. Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ, et al. Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making. *Eur Stroke J.* 2018;3:126-135.
7. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. *JAMA.* 2016;316:1279-1288.
8. Goyal M, Almekhlafi MA, Fan L, Menon BK, Demchuk AM, Yeatts SD, et al. Evaluation of interval times from onset to reperfusion in patients undergoing endovascular therapy in the Interventional Management of Stroke III trial. *Circulation.* 2014;130:265-272.
9. Mehta BP, Leslie-Mazwi TM, Chandra RV, Bell DL, Sun CH, Hirsch JA, et al. Reducing door-to-puncture times for intra-arterial stroke therapy: a pilot quality improvement project. *J Am Heart Assoc.* 2014;3:e000963.
10. Aghaebrahim A, Streib C, Rangaraju S, Kenmuir CL, Giurgiutiu DV, Horev A, et al. Streamlining door to recanalization processes in endovascular stroke therapy. *J Neurointerv Surg.* 2017;9:340-345.
11. Kamal N, Smith EE, Menon BK, Eesa M, Ryckborst KJ, Poppe AY, et al. Improving reperfusion time within the ESCAPE Endovascular Clinical Trial. *Eur Stroke J.* 2017;2:64-69.
12. Psychogios MN, Behme D, Schregel K, Tsogkas I, Maier IL, Leyhe JR, et al. One-Stop Management of Acute Stroke Patients: Minimizing Door-to-Reperfusion Times. *Stroke.* 2017;48:3152-3155.
13. Goldstein ED, Schnusenberg L, Mooney L, Raper CC, McDaniel S, Thorpe DA, et al. Reducing Door-to-Reperfusion Time for Mechanical Thrombectomy With a Multitiered Notification System for Acute Ischemic Stroke. *Mayo Clin Proc Innov Qual Outcomes.* 2018;2:119-128.
14. Helwig SA, Ragoschke-Schumm A, Schwindling L, Kettner M, Roumia S, Kulikovski J, et al. Prehospital Stroke Management Optimized by Use of Clinical Scoring vs Mobile Stroke Unit for Triage of Patients With Stroke: A Randomized Clinical Trial. *JAMA Neurol.* 2019;76:1484-1492.
15. Abilleira S, Perez de la Ossa N, Jimenez X, Cardona P, Cocho D, Purroy F, et al. Transfer to the Local Stroke Center versus Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan

Territory (RACECAT): Study protocol of a cluster randomized within a cohort trial. *Int J Stroke.* 2019;14:734-744.

16. Anadani M, Almallouhi E, Wahlquist AE, Debenham E, Holmstedt CA. The Accuracy of Large Vessel Occlusion Recognition Scales in Telestroke Setting. *Telemed J E Health.* 2019;25:1071-1076.
17. Goyal M, Jadhav AP, Wilson AT, Nogueira RG, Menon BK. Shifting bottlenecks in acute stroke treatment. *J Neurointerv Surg.* 2016;8:1099-1100.
18. Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier C, Guekht A, et al. Action Plan for Stroke in Europe 2018-2030. *Eur Stroke J.* 2018;3:309-336.
19. Dorsch MF, Greenwood JP, Priestley C, Somers K, Hague C, Blaxill JM, et al. Direct ambulance admission to the cardiac catheterization laboratory significantly reduces door-to-balloon times in primary percutaneous coronary intervention. *Am Heart J.* 2008;155:1054-1058.
20. Rathod KS, Jain AK, Firoozi S, Lim P, Boyle R, Nevett J, et al. Outcome of inter-hospital transfer versus direct admission for primary percutaneous coronary intervention: An observational study of 25,315 patients with ST-elevation myocardial infarction from the London Heart Attack Group. *Eur Heart J Acute Cardiovasc Care.* 2020;9:948-957.
21. Mahmoud KD, Gu YL, Nijsten MW, de Vos R, Nieuwland W, Zijlstra F, et al. Interhospital transfer due to failed prehospital diagnosis for primary percutaneous coronary intervention: an observational study on incidence, predictors, and clinical impact. *Eur Heart J Acute Cardiovasc Care.* 2013;2:166-175.
22. Wang TY, Peterson ED, Ou FS, Nallamothu BK, Rumsfeld JS, Roe MT. Door-to-balloon times for patients with ST-segment elevation myocardial infarction requiring interhospital transfer for primary percutaneous coronary intervention: a report from the national cardiovascular data registry. *Am Heart J.* 2011;161:76-83.
23. McTaggart RA, Moldovan K, Oliver LA, Dibiasio EL, Baird GL, Hemendinger ML et al. Door-in-Door-Out Time at Primary Stroke Centers May Predict Outcome for Emergent Large Vessel Occlusion Patients. *Stroke.* 2018;49:2969-2974.
24. Choi PMC, Tsoi AH, Pope AL, Leung S, Frost T, Loh P et al. Door-in-Door-Out Time of 60 Minutes for Stroke With Emergent Large Vessel Occlusion at a Primary Stroke Center. *Stroke.* 2019;50:2829-2834.
25. In 't Veld C, Van Exter P, Rombouts M, De Visser M, De Vos R, Lelieveld K et al. Nationwide Protocol Ambulance Care (in Dutch: Landelijk Protocol Ambulancezorg) [Internet]. 2016 [cited June 1, 2021]. Available from: www.ambulancezorg.nl/themas/kwaliteit-van-zorg/protocollen-en-richtlijnen/landelijk-protocol-ambulancezorg. Dutch.
26. StrokeNet. Regional organization acute stroke care region North-Holland and Flevoland (in Dutch: Regionale inrichting acute beroertezorg regio Noord-Holland en Flevoland) [Internet]. 2018 [cited June 1, 2021]. Available from: https://spoedzorgnet.nl/documenten/beleidsterrein/roaz-3/documenten-type/protocollen-en-afspraken-40/beleidsterrein/traumazorg-1/documenten-type/beleidsdocumenten-6?trefwoord=.
27. Dippel DWJ, Van der Worp HB, Hofmeijer J, Van den Berg-Vos RM, Van Dijk EJ, Geurts M et al. Acute ischemic stroke and acute hemorrhagic stroke (in Dutch: Herseninfarct en hersenbloeding) [Internet]. 2019 [cited June 1, 2021]. Available from: https://richtlijnendatabase.nl/richtlijn/herseninfarct_en_hersenbloeding/startpagina_herseninfarct_-bloeding.html.
28. United Kingdom National Health Service. National Stroke Service Model: Integrated Stroke Delivery Networks [Internet]. 2021 [cited June 1, 2021. Available from: https://www.england.nhs.uk/publication/national-

stroke-service-model-integrated-stroke-delivery-networks/.

29. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Stroke.* 2018;49:e46-e110.
30. Adeoye O, Nystrom KV, Yavagal DR, Luciano J, Nogueira RG, Zorowitz RD, et al. Recommendations for the Establishment of Stroke Systems of Care: A 2019 Update. *Stroke.* 2019;50:e187-e210.
31. Kunte SA, Anderson D, Brown-Espaillat K, Froehler MT. Total Transfer Time for Ground vs. Air Transport for Interhospital and Scene Transfers of Acute Stroke Patients. *J Stroke Cerebrovasc Dis.* 2021;30:105704.

SUPPLEMENTAL MATERIAL

Supplemental Table I. Clinical and workflow-related factors associated with call-to-PSC time

	Univariable model – unadjusted β in minutes (95% CI)	Multivariable model – adjusted β in minutes (95% CI)
Clinical factors		
Age	-0.1 (-0.2 to 0.1)	-0.04 (-0.2 to 0.1)
Previous acute ischemic stroke/TIA[1]	-2.3 (-7.5 to 2.9)	-2.2 (-7.3 to 3.0)
NIHSS on arrival at PSC[2]	0.1 (-0.2 to 0.5)	0.2 (-0.2 to 0.5)
Workflow-related factors		
Onset-to-call time[3]	0.1 (0.1 to 0.2)	0.1 (0.04 to 0.2)
First call to dispatch center outside office hours[4]	3.5 (-2.2 to 9.2)	3.3 (-1.2 to 7.9)
Person making first call to dispatch center, general practitioner[5]	-1.5 (-12.3 to 9.3)	-0.6 (-9.4 to 8.2)
Urgency of first ambulance dispatch, A1[6]	-3.1 (-14.6 to 8.4)	-2.4 (-13.8 to 9.1)

A1 = the A1 ambulance dispatch (most urgent) is used for potentially life threatening situations; target response time is 15 minutes; call-to-PSC time = time between first call to dispatch center and arrival at the PSC; CI = confidence interval; NIHSS = National Institutes of Health Stroke Scale; onset-to-call time = time between symptom onset and first call to dispatch center; PSC = primary stroke center; TIA = transient ischemic attack.

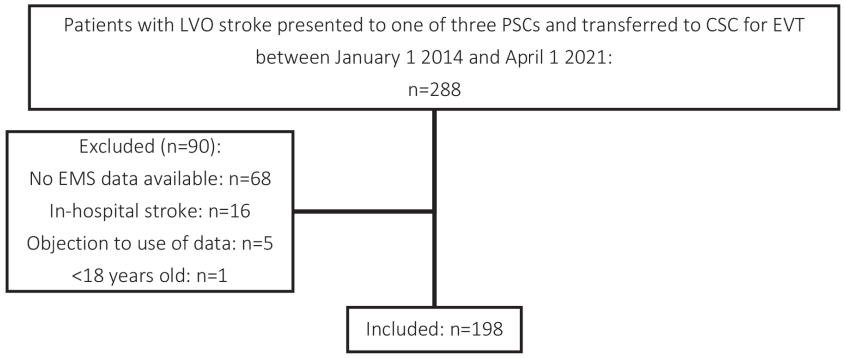
Number of missing values: [1]2; [2]7; [3]35; [4]31; [5]90; [6]31; call-to-PSC time: 32.

[3]β is reported per 10-minute increase in onset-to-call time.

Supplemental Table II. Clinical and workflow-related factors associated with door-in-door-out time

	Univariable model – unadjusted β in minutes (95% CI)	Multivariable model – adjusted β in minutes (95% CI)
Clinical factors		
Age	-0.1 (-0.7 to 0.6)	-0.3 (-1.0 to 0.4)
Previous acute ischemic stroke/TIA[1]	-19.8 (-44.5 to 4.8)	-16.3 (-41.5 to 8.8)
Systolic blood pressure on arrival at PSC[2]	0.5 (0.1 to 0.8)	0.4 (-0.1 to 0.9)
Diastolic blood pressure on arrival at PSC[3]	0.8 (0.2 to 1.4)	0.4 (-0.3 to 1.2)
NIHSS on arrival at PSC[4]	-1.4 (-2.8 to -0.01)	-0.9 (-2.4 to 0.6)
Location of occlusion, anterior circulation	-10.2 (-43.8 to 23.3)	-0.4 (-35.3 to 34.4)
Treatment with IVT	-10.5 (-30.8 to 9.9)	3.3 (-22.2 to 28.8)
Workflow-related factors		
Onset-to-PSC time[5]	0.2 (-0.3 to 0.6)	0.2 (-0.4 to 0.7)
Arrival at PSC outside office hours[6]	7.2 (-12.0 to 26.4)	0.7 (-19.6 to 21.1)
Urgency of second ambulance dispatch, A1[7]	-30.1 (-56.7 to -3.4)	-30.0 (-56.4 to -3.7)

A1 = the A1 ambulance dispatch (most urgent) is used for potentially life threatening situations; target response time is 15 minutes; CI = confidence interval; door-in-door-out time = time between patient arrival at the PSC and time of second ambulance departure from the PSC; ECG = electrocardiography; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; onset-to-PSC time = time between symptom onset and arrival at PSC; PSC = primary stroke center; TIA = transient ischemic attack.
Number of missing values: [1]2; [2]38; [3]39; [4]7; [5]36; [6]31; [7]43; door-in-door-out time: 76.
[5]β is reported per 10-minute increase in onset-to-PSC time



Supplemental Figure I. Inclusion flow chart. CSC = comprehensive stroke center; EMS = emergency medical services; EVT = endovascular thrombectomy; LVO = large vessel occlusion; PSC = primary stroke center.

CHAPTER 3

INTERHOSPITAL TRANSFER VS. DIRECT PRESENTATION OF PATIENTS WITH A LARGE VESSEL OCCLUSION NOT ELIGIBLE FOR IV THROMBOLYSIS

Laura C.C. van Meenen[1], Adrien E. Groot[1], Esmee Venema[2], Bart J. Emmer[3], Martin D. Smeekes[4], Geert Jan Kommer[5], Charles B.L.M. Majoie[3], Yvo B.W.E.M. Roos[1], Wouter J. Schonewille[6], Bob Roozenbeek[7], Jonathan M. Coutinho[1] on behalf of the MR CLEAN Registry Investigators[8]

[1] Department of Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands
[2] Department of Neurology and Department of Public Health, Erasmus MC University Medical Center, Rotterdam, the Netherlands
[3] Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands
[4] Emergency Medical Services North-Holland North, Alkmaar, the Netherlands
[5] National Institute of Public Health and the Environment, Center for Nutrition, Prevention and Health services, Bilthoven, the Netherlands
[6] Department of Neurology, St. Antonius Ziekenhuis, Nieuwegein, the Netherlands
[7] Department of Radiology & Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands
[8] MR CLEAN Registry Investigators - group authors: please see 'Contributing authors and affiliations'

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ABSTRACT

Background and Purpose

Direct presentation of patients with acute ischemic stroke to a comprehensive stroke center (CSC) reduces time to endovascular treatment (EVT), but may increase time to treatment for intravenous thrombolysis (IVT). This dilemma, however, is not applicable to patients who have a contraindication for IVT. We examined the effect of direct presentation to a CSC on outcomes after EVT in patients not eligible for IVT.

Methods

We used data from the MR CLEAN Registry (2014-2017). We included patients who were not treated with IVT and compared patients directly presented to a CSC to patients transferred from a primary stroke center. Outcomes included treatment times and 90-day modified Rankin Scale scores (mRS) adjusted for potential confounders.

Results

Of the 3637 patients, 680 (19%) did not receive IVT and were included in the analyses. Of these, 389 (57%) were directly presented to a CSC. The most common contraindications for IVT were anticoagulation use (49%) and presentation >4.5 hours after onset (26%). Directly presented patients had lower baseline NIHSS scores (median 16 vs. 17, p=0.015), higher onset-to-first-door-times (median 105 vs. 66 min, p<0.001), lower first-door-to-groin-times (median 93 vs. 150 minutes; adjusted β=-51.0, 95%CI:-64.1 to -37.9) and lower onset-to-groin-times (median 220 vs. 230 minutes; adjusted β=-40.0, 95%CI:-61.5 to -18.5). The 90-day mRS score did not differ between groups (adjusted OR:1.23, 95%CI:0.73-2.08).

Conclusions

In patients who were not eligible for IVT, treatment times for EVT were better for patients directly presented to a CSC, but without a statistically significant effect on clinical outcome.

BACKGROUND

Intravenous thrombolysis (IVT) is the standard treatment for patients with acute ischemic stroke (AIS).[1] Patients with a large vessel occlusion (LVO) of the anterior circulation are additionally treated with endovascular treatment (EVT).[2] In most countries, paramedics transport patients with a suspected AIS to the nearest primary stroke center (PSC) for diagnostic work-up and to initiate IVT. Patients who are eligible for EVT are subsequently transferred to a comprehensive stroke center (CSC). Studies show that this 'drip-and-ship' system delays initiation of EVT by 40 to 106 minutes and decreases the chance of a good clinical outcome by approximately 10%.[3-5] Despite this clear disadvantage, the 'drip-and-ship' system is currently the most feasible, because accurately diagnosing an LVO in the pre-hospital setting is challenging. Directly presenting all patients with suspected AIS to a CSC would overburden these hospitals. In addition, due to longer initial travel times, a centralized model could delay initiation of IVT, and thus negatively impact patient outcome in patients who are not eligible for EVT.[5]

Approximately 20% of patients who undergo EVT in routine practice do not receive IVT because of a contraindication for alteplase.[6] Most of these contraindications, such as anticoagulation use and duration of symptoms >4.5 hours, can be easily determined in the ambulance. For patients with such a contraindication for IVT, no valuable time would be lost by bypassing the PSC and going directly to a CSC. In the current study, we analyzed workflow times and clinical outcomes after EVT in patients who were not eligible for IVT, and compared these outcomes between patients who were directly presented to a CSC to those initially presented to a PSC.

METHODS

Data will not be made available to other researchers, as no patient approval was obtained for sharing coded data. However, syntax and output files of statistical analyses may be made available on request.

Study design and population

We used data from the MR CLEAN Registry. The MR CLEAN Registry is a nationwide, prospective cohort study, in which all patients who have undergone EVT for AIS in the Netherlands since completion of the MR CLEAN trial (March 2014) until December 2018 have been registered. Permission to carry out this study was granted by the medical ethics committee of the Erasmus University Medical Center in Rotterdam. Detailed methods of the MR CLEAN Registry have previously been reported.[6] For the current study, we used data collected from March 2014 until November 2017 (Registry part I and II). We included patients who had undergone EVT for AIS, and did not receive IVT. In-hospital strokes were excluded.

Definitions and outcomes

EVT was defined as arterial puncture in the angiography suite, with the objective to perform mechanical thrombectomy with a stent retriever and/or thrombus aspiration, with or without local administration of a thrombolytic agent. The actual EVT strategy was at the discretion of the interventionist. Time of stroke onset was defined as the time of witnessed onset of symptoms or, if this was unknown, the moment that the patient was last known to be well.

Our primary clinical outcome measure was good functional outcome at 90 days post-stroke, defined as a score of 0 to 2 on the modified Rankin Scale (mRS). Other clinical outcome measures were the overall shift in mRS score between groups, occurrence of symptomatic intracranial hemorrhage (sICH) and mortality at 90 days post-stroke. Intracranial hemorrhage was defined as symptomatic if the patient died or deteriorated neurologically (an increase of ≥4 points on the National Institutes of Health Stroke Scale [NIHSS]) as a result of the hemorrhage.[7] Successful reperfusion, defined as a score of ≥2b on the extended thrombolysis in cerebral infarction (eTICI) scale, was used as a radiological outcome measure.

Workflow related outcome measures were: time from stroke onset to arterial puncture (onset-to-groin time [OGT]), which was our main secondary outcome measure, and time from arrival at the first hospital to arterial puncture (first-door-to-groin time [FDGT]).

Transferred patients generally live farther away from a CSC than mothership patients, which makes a direct comparison of treatment times inherently biased in favor of patients directly presented to a CSC. To account for this bias, we calculated adjusted OGT and FDGT, in which we corrected for travel time by subtracting estimated ambulance travel times between the PSC and the CSC from the original treatment times, for all transferred patients. These data were provided by the Dutch National Institute for Public Health and the Environment and calculated using their proprietary model, assuming daytime circumstances outside of rush hour and the ambulance driving with the highest level of emergency.[8]

Statistical analysis

Patients who were directly presented to a CSC were compared to patients who were transferred from a PSC. We compared baseline characteristics using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and χ^2 test for categorical variables. For the regression analyses, we imputed missing data using multiple imputation, using the following covariates: age, sex, previous stroke, previous diabetes, previous atrial fibrillation, previous myocardial infarction, pre-stroke mRS score, baseline blood

pressure (systolic and diastolic), baseline NIHSS score, location of occlusion, collateral status, onset-to-first-door time, OGT, FDGT, onset-to-reperfusion time, eTICI score after EVT, and mRS score at 90 days post-stroke. To analyze the odds of good functional outcome, defined as mRS 0-2 at 90 days, we used binary logistic regression. Ordinal logistic regression was used to assess the overall shift in mRS score between groups. In both analyses, we adjusted for the following pre-specified prognostic variables: age, pre-stroke mRS, anticoagulation use, baseline NIHSS, location of occlusion, collateral status and onset-to-first-door time. For our analyses of sICH and mortality, we also used binary logistic regression, adjusting for age, pre-stroke mRS, anticoagulation use, baseline systolic blood pressure, baseline NIHSS, location of occlusion, collateral status and onset-to-first-door time. For analyzing successful reperfusion rate (eTICI≥2b), we used binary logistic regression and adjusted for the following variables: age, location of occlusion and onset-to-first door time. Linear regression was used for the analyses of OGT and FDGT (with and without correction for travel time). In the OGT analysis, we adjusted for age, pre-stroke mRS, baseline blood pressure, baseline NIHSS, location of occlusion and presentation outside the 4.5 hour time window. In the FDGT analysis, we adjusted for age, pre-stroke mRS, baseline blood pressure, baseline NIHSS, location of occlusion and onset-to-first-door time. In order to explore residual confounding, we performed a secondary analysis in which we stratified for presentation to the first hospital within the 4.5 hour time window. In this analysis, we used all clinical, radiological and workflow related outcomes named above. All analyses were performed using SPSS (version 25; SPSS Inc., Chicago, IL, USA).

RESULTS

Between March 2014 and November 2017, 3637 patients were included in the MR CLEAN Registry (part I and II). We excluded 2957 patients, either because they were treated with IVT (n=2640), because it was unknown whether they were treated with IVT (n=74), or because they had an in-hospital stroke (n=243). Therefore, 680 patients were included in the analysis (Figure 1). Of these, 389 (57%) were directly presented to a CSC and 291 (43%) were transferred from a PSC. Patients who were directly presented to a CSC less often had atrial fibrillation (38% vs. 54%, p<0.001), had lower baseline NIHSS scores (median 16 vs. 17, p=0.015) and had higher collateral scores on baseline CTA (p=0.003) compared to transferred patients. Onset-to-first-door times were longer for the direct group (median 105 vs. 66 minutes, p<0.001 [Table 1]). The median estimated ambulance travel time between PSC and CSC for the transferred group was 17 minutes (IQR: 10-31). Contraindications for IVT are listed in Table 1. Presentation beyond the 4.5 hour time-window was more common in directly presented patients (35% vs. 15%, p<0.001). Use of a vitamin K antagonist was less frequent in directly presented patients (32% vs. 45%, p<0.001), while heparin use (therapeutic dosage) was more common in the direct group (2% vs. 0%, p=0.040). Other contraindications did not differ between the two groups.

Functional outcome was slightly better in patients who were directly presented to a CSC (mRS 0-2: 36 vs. 28%, OR: 1.51, 95% CI 1.06-2.15 [Table 2; Figure 2]). After adjustment, statistical significance was lost (adjusted OR: 1.23, 95% CI 0.73-2.08). When analyzing the shift in overall mRS scores between groups, the results were similar (unadjusted common OR: 1.43, 95% CI 1.07-1.91; adjusted common OR: 1.21, 95% CI 0.80-1.84). Incidence of sICH did not differ between the direct group and the transferred group (5% vs. 5%; adjusted OR: 0.70, 95% CI 0.28-1.75). Other clinical and radiological outcomes also were not different (Table 2).

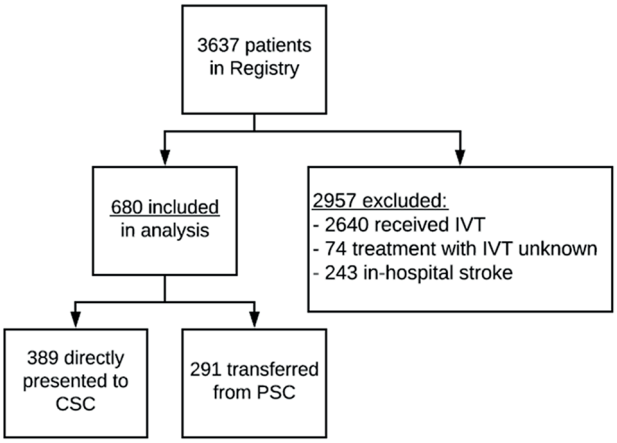

Figure 1. Flow chart of patient selection. CSC = comprehensive stroke center, IVT = intravenous thrombolysis, Registry = the multicenter collaboration for endovascular treatment of acute ischemic stroke in the Netherlands (MR CLEAN Registry)

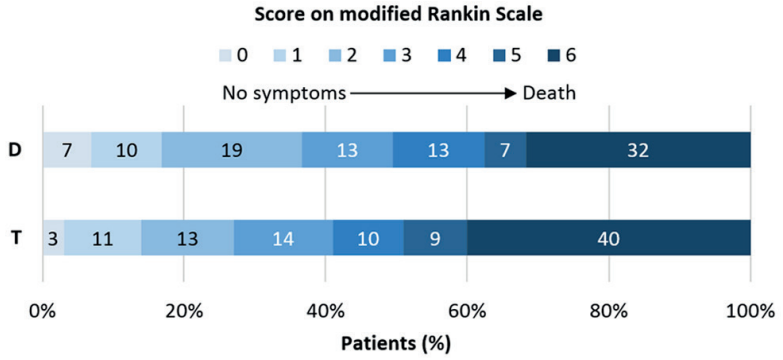

Figure 2. Functional outcome according to modified Rankin Scale score at 90 days post-stroke. D = direct group, T = transferred group.

Table 1. Baseline characteristics

	Direct, n=389	Transfer, n=291	p value
Age, years – mean ± SD	71 ± 14.2	73 ± 12.5	0.053
Male sex – no./total (%)	181/389 (47%)	148/291 (51%)	0.264
Hypertension – no./total (%)	206/380 (54%)	172/287 (60%)	0.140
Diabetes mellitus – no./total (%)	59/386 (15%)	41/289 (14%)	0.691
Atrial fibrillation – no./total (%)	147/384 (38%)	154/286 (54%)	<0.001
Myocardial infarction – no./total (%)	55/385 (14%)	54/278 (19%)	0.078
Previous stroke – no./total (%)	103/387 (27%)	80/287 (28%)	0.667
Pre-stroke mRS score[1] – median (IQR)	0 (0-2)	0 (0-1)	0.180
Systolic blood pressure[2] – mean ± SD	154 ± 28.0	152 ± 26.9	0.395
Diastolic blood pressure[3] – mean ± SD	84 ± 17.0	83 ± 16.7	0.897
NIHSS score[4] – median (IQR)	16 (10-20)	17 (13-21)	0.015
Occlusion site – no./total (%)			0.119
ICA	58/342 (17%)	59/268 (22%)	
M1	169/342 (49%)	138/268 (52%)	
M2	58/342 (17%)	44/268 (16%)	
Anterior cerebral artery	4/342 (1%)	1/268 (0%)	
Posterior circulation	34/342 (10%)	14/268 (5%)	
ASPECTS score on first NCCT[5], – median (IQR)	9 (7-10)	9 (7-10)	0.513
Collateral score on first CTA – no./total (%)			0.003
Grade 0	20/311 (6%)	19/256 (7%)	
Grade 1	100/311 (32%)	105/256 (41%)	
Grade 2	108/311 (35%)	96/256 (38%)	
Grade 3	83/311 (27%)	36/256 (14%)	
Time from stroke onset to door of first hospital, minutes[6] – median (IQR)	105 (51-266)	66 (40-132)	<0.001
Contraindication for IVT – no./total (%)			
Use of vitamin K antagonist	108/336 (32%)	118/262 (45%)	<0.001
Presentation > 4.5 hours	118/336 (35%)	39/262 (15%)	<0.001
Recent clinical event[7]	56/336 (17%)	51/262 (19%)	0.267
Use of DOAC	30/336 (9%)	34/262 (13%)	0.079
Hypertension	10/336 (3%)	10/262 (4%)	0.509
Unfavorable characteristics NCCT	8/336 (2%)	6/262 (2%)	0.996
Use of heparin in therapeutic dosage	6/336 (2%)	0/262 (0%)	0.040[h]
Other	9/336 (3%)	11/262 (4%)	0.263

ASPECTS = Alberta Stroke Program Early CT Score; CTA = computed tomography angiography; DOAC = Direct oral anticoagulant; ICA = intracranial part of internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; M1 = first segment of the middle cerebral artery; M2 = second segment (after first bifurcation) of the middle cerebral artery; mRS = modified Rankin Scale; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale; no. = number; SD = standard deviation.

Number of missing values: [1]14; [2]19; [3]27; [4]12; [5]91; [6]96.

[7]Recent hemorrhagic or ischemic stroke, recent major surgery, recent gastrointestinal or urogenital bleeding or recent head trauma.

[8]Fisher's exact test was used for this analysis.

Table 2. Clinical and radiological outcomes

	Direct, n=389	Transfer, n=291	Unadjusted OR[1] (95% CI)	Adjusted OR[1] (95% CI)
Functional independence at 90 days (mRS 0-2) – no./ total (%)	130/360 (36%)	73/263 (28%)	1.51 (1.06-2.15)	1.23 (0.73-2.08)[2]
mRS score at 90 days[3] – median (IQR)	4 (2-6)	4 (2-6)	1.43 (1.07-1.91)[4]	1.21 (0.80-1.84)[2]
Symptomatic intracranial hemorrhage – no./total (%)	20/388 (5%)	16/291 (5%)	0.93 (0.47-1.83)	0.70 (0.28-1.75)[5]
Mortality at 90 days – no./ total (%)	116/360 (32%)	105/263 (40%)	0.71 (0.51-0.98)	0.90 (0.54-1.50)[5]
Successful reperfusion (eTICI ≥2b) – no./total (%)	186/321 (60%)	156/271 (58%)	0.89 (0.61-1.30)	1.15 (0.78-1.68)[6]

CI = confidence interval; eTICI = extended thrombolysis in cerebral infarction scale; IQR = interquartile range, mRS = modified Rankin Scale; no. = number; OR = odds ratio.
[1]Odds for the direct group.
[2]Adjusted for age, pre-stroke mRS, anticoagulation use, baseline NIHSS, location of occlusion, collateral status and onset-to-first-door time.
[4]Odds of 1-point shift towards a favorable outcome on the mRS for the direct group.
[5]Adjusted for age, pre-stroke mRS, anticoagulation use, baseline systolic blood pressure, baseline NIHSS, location of occlusion, collateral status and onset-to-first-door time.
[6]Adjusted for age, location of occlusion and onset-to-first door time.
Number of missing values: [3]57.

Patients directly presented to a CSC had a median OGT of 220 minutes, compared to 230 minutes for transferred patients (adjusted β=-40.0, 95% CI -61.5 to -18.5 [Table 3]). When the increased travel time for transferred patients was taken into account, adjusted OGT was still 18 minutes shorter for patients directly presented to a CSC, although this was not statistically significant (median 220 vs. 207 minutes; adjusted β=-18.1, 95% CI -39.6 to 3.4). FDGT was also shorter for the direct group (median 93 vs. 150 minutes; adjusted β=-51.0, 95% CI -64.1 to -37.9), even when corrected for increased travel time (median 93 vs. 127 minutes, adjusted β=-28.0, 95% CI -41.3 to -14.7).

We stratified the analysis for presentation to the first hospital within the 4.5 hour time window. Of 476 patients presented within 4.5 hours, 290 (61%) were presented directly to a CSC. Among patients presented outside the 4.5 hour time window, direct presentation was more common, with 90/108 patients (83%) being presented directly to a CSC. Baseline characteristics of the two strata are shown in Supplemental Table I. Patients who were presented within 4.5 hours more often were functionally independent at 90 days (mRS 0-2: 36 vs. 26%, OR: 1.65, 95% CI 1.07-2.56 [Table 4]). After adjustments for potential confounders, this difference was no longer statistically significant (adjusted OR: 1.28, 95% CI 0.74-2.22). We found similar results for the overall shift in mRS between groups among patients presented within 4.5 hours

(unadjusted common OR: 1.47, 95% CI 1.04-2.09; adjusted common OR: 1.17, 95% CI 0.76-1.81). Among patients who were presented >4.5 hours after symptom onset there was no difference in functional outcome (adjusted OR: 0.89, 95% CI 0.18-4.29). Other clinical and radiological outcomes also did not differ (Table 4). In patients presented within 4.5 hours, the difference in OGT remained statistically significant, in favor of the direct group (median 180 vs. 228 minutes; adjusted β=-46.4, 95% CI -66.1 to -26.6). In patients presented after >4.5 hours, OTG did not differ between groups (median 457 vs. 455 minutes; adjusted β=-8.1, 95% CI -115.9 to 99.7). The difference in FDGT in favor of the direct group remained statistically significant in both strata (≤4.5 hours: adjusted β=-50.8, 95% CI -65.7 to -36.2; >4.5 hours: adjusted β=-47.0, 95% CI -71.7 to -22.3). The results of our analyses for both strata of OGT and FDGT corrected for travel time are reported in Supplemental Table II.

Table 3. Treatment times

	Direct, n=389	Transfer, n=291	Unadjusted β (95% CI)	Adjusted β (95% CI)
Onset-to-groin time[1] – median (IQR)	220 (143-360)	230 (283-320)	16.5 (-9.0 to 42.0)	-40.0 (-61.5 to -18.5)[2]
Travel time-corrected onset-to-groin time[3] – median (IQR)	220 (143-360)	207 (163-293)	37.4 (12.0 to 62.8)	-18.1 (-39.6 to 3.4)[2]
First-door-to-groin time[4] – median (IQR)	93 (72-125)	150 (115-186)	-41.7 (-52.1 to -31.4)	-51.0 (-64.1 to -37.9)[5]
Travel time-corrected first-door-to-groin time[6] – median (IQR)	93 (72-125)	127 (96-166)	-20.9 (-31.2 to -10.6)	-28.0 (-41.3 to -14.7)[5]

CI = confidence interval; IQR = interquartile range.

[2]Adjusted for age, pre-stroke mRS, baseline blood pressure, baseline NIHSS, location of occlusion and presentation outside the 4.5 hour time window.

[5]Adjusted for age, pre-stroke mRS, baseline blood pressure, baseline NIHSS, location of occlusion and onset-to-first-door time.

Number of missing values: [1]11; [3]24; [4]95; [6]100.

Table 4. Clinical and radiological outcomes stratified by presentation within 4.5 hour time window

	Presentation ≤ 4.5 hours				Presentation > 4.5 hours			
	Direct, n=290	**Transfer, n=186**	**Unadjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**	**Direct, n=90**	**Transfer, n=18**	**Unadjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**
Functional independence at 90 days (mRS 0-2) – no./ total (%)	95/265 (36%)	46/175 (26%)	1.65 (1.07-2.56)	1.28 (0.74-2.22)[2]	33/87 (38%)	6/16 (38%)	1.12 (0.38-3.36)	0.89 (0.18-4.29)[2]
mRS score at 90 days[3] – median (IQR)	4 (2-6)	4 (2-6)	1.47 (1.04-2.09)[4]	1.17 (0.76-1.81)[2]	4 (2-6)	4 (2-6)	1.20 (0.47-3.11)[4]	1.15 (0.32-4.13)[2]
sICH – no./total (%)	14/290 (5%)	11/186 (6%)	0.81 (0.36-1.82)	0.66 (0.25-1.72)[5]	4/90 (4%)	0/18 (0%)	-	-
Mortality at 90 days – no. (%)	90/265 (34%)	68/175 (39%)	0.76 (0.51-1.12)	0.94 (0.55-1.61)[5]	23/87 (26%)	5/16 (31%)	0.80 (0.25-2.59)	0.56 (0.09-3.50)[5]
Successful reperfusion (eTICI ≥ 2b) – no. (%)	145/240 (60%)	96/174 (55%)	1.07 (0.69-1.68)	1.19 (0.78-1.79)[6]	37/77 (48%)	5/15 (33%)	1.65 (0.54-5.03)	1.26 (0.38-4.18)[6]

CI = confidence interval; eTICI = extended thrombolysis in cerebral infarction scale; IQR = interquartile range, mRS = modified Rankin Scale; no. = number; OR = odds ratio; sICH = symptomatic intracranial hemorrhage.

[1]Odds for the direct group.

[2]Adjusted for age, pre-stroke mRS, anticoagulant use, baseline NIHSS, location of occlusion and collateral status.

[4]Odds of 1-point shift towards a favorable outcome on the mRS at 90 days for the direct group.

[5]Adjusted for age, pre-stroke mRS, anticoagulant use, baseline systolic blood pressure, baseline NIHSS, location of occlusion and collateral status.

[6]Adjusted for age and location of occlusion.

Number of missing values: [3]41.

DISCUSSION

In this nationwide cohort of patients who underwent EVT for AIS, we found that in the subgroup of patients who were not eligible for IVT, treatment times were shorter for patients directly presented to a CSC, compared to patients who were first presented to a PSC. Clinical outcome was also slightly better in directly presented patients, although this was not statistically significant.

Previous post hoc analyses of prospective cohort studies have shown that for patients with an LVO of the anterior circulation, in general, it is beneficial to be directly presented to a CSC, as opposed to being transferred from a PSC. Venema et al., who also used data from the MR CLEAN Registry (part I), found that patients directly presented to a CSC had a 40 minutes shorter OGT and a 57 minutes shorter FDGT than transferred patients.[3] The authors also found a negative effect of inter-hospital transfer on the likelihood of functioning independently at 90 days post-stroke (OR: 0.69, 95% CI 0.54-0.89). A post hoc analysis of data from the STRATIS Registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) showed a similar beneficial effect of direct presentation on functional outcome.[5] However, in a subgroup analysis of patients who were not treated with IVT, the authors found that despite the OGT being almost an hour lower, the chance of good functional outcome did not differ between directly presented and transferred patients (56% vs. 50%, p=0.23). Since previous studies have convincingly shown that earlier initiation of EVT improves clinical outcome, these findings seem discrepant.[4, 9-11] However, the authors did not report if and how their subgroup analysis was adjusted for possible confounders, neither were baseline characteristics reported for the subgroup of patients treated with EVT alone.

In the current study, despite adjustment for baseline imbalances, we found the same discrepancy as did the authors of the STRATIS Registry sub study: a beneficial effect of direct presentation on time to treatment, but no statistically significant difference in functional outcome. A potential explanation for this finding is that our sample size was too small to find a difference in functional outcome, but substantial enough to show the larger differences in time to treatment. Another possible explanation could be residual confounding. Although we tried to adjust for factors that, based on baseline characteristics and clinical experience, may have influenced the hospital choice by ambulance paramedics or the choice of referral for EVT by PSC neurologists, there may be other confounding factors that we did not take into account or that we had no data for. For example, patients with severe comorbidity (e.g. active malignancy, renal failure, congestive heart failure) may be more likely to be directly presented to CSCs, since CSCs are often tertiary care centers. Because data of these severe comorbidities were not available for our study, we could not adjust our analyses for this potential confounder.

There were some baseline imbalances between the direct and the transferred group that warrant mention. First, the transferred group more often had atrial fibrillation. A probable explanation is that this is due to the different distributions of contraindications for IVT over the two groups. Since the transfer group contains relatively few patients in the >4.5 hour time window, other contraindications for IVT are more prevalent in this group. Of these, the most common contraindication is use of anticoagulant medication. Because the indication for anticoagulation use often is atrial fibrillation, this may explain the higher prevalence in this group. Second, the transferred group had higher baseline NIHSS scores. A possible explanation could be that patients with relatively mild neurological deficits were less often referred from a PSC, for instance because the deficits were not considered to be sufficiently severe to warrant EVT. Third, collateral scores were slightly better in directly presented patients. This may be because atrial fibrillation was less common in this group, since this has been associated with worse collaterals.[12] Fourth, time from stroke onset to arrival at the first hospital was significantly longer for directly presented patients. Most likely, this is because ambulance paramedics were inclined to bring patients who were (almost) outside the 4.5 hour time window, who were thus only eligible for EVT, directly to a CSC.

We specifically focused on the effects of interhospital transfer in the subgroup of patients not eligible for IVT. We chose to do so, because of the relevance of this subject for routine clinical practice. In approximately 15-20% of patients with AIS, a contraindication for IVT is present.[2,6] Unlike patients eligible for IVT, in whom direct presentation to a CSC may delay initiation of this treatment, patients ineligible for IVT have no major disadvantage of being presented directly to a CSC. Moreover, the most common contraindications that render patients ineligible for IVT could be identified by ambulance paramedics. For example, anticoagulant use or duration of symptoms could be determined through a patient history. Blood pressure is routinely measured, and an INR could be determined using a point of care test.[13] Further study on this issue is required, for instance to ascertain if determining IVT contraindications negatively influences ambulance response times. However, if such studies do not show any major negative effects, pre-hospital triage of this patient group could relatively easily be implemented.

Some limitations of our study should also be considered. First of all, the Netherlands, where data collection for this study took place, is a relatively small and densely populated country, where hospitals are located relatively close to one another.[14] Therefore, the differences in time to treatment between directly presented and transferred patients that we found in this study, are likely smaller than they would have been in less densely populated areas.[15, 16] Consequently, our findings should be extrapolated to other countries with caution.

Second, it is likely that our data were affected by selection bias. In the MR CLEAN Registry, patients with an LVO that were ultimately deemed ineligible for EVT for whatever reason, were not included. As a consequence, we have no data of patients that could not receive EVT because of time lost by primary transportation to a PSC causing the time window for EVT to exceed.[17] Therefore, the negative effects of interhospital transfer may be larger than shown in this study. Additionally, selection bias is inherent to the manner of hospital selection by ambulance paramedics. Even though the protocol in the Netherlands is to bring patients with a suspected stroke to the nearest stroke center, ambulance paramedics may nonetheless decide to bypass a PSC and bring a patient directly to a CSC. In a similar way, factors affecting the decision of PSC neurologists whether or not to refer a patient for EVT may have influenced our data. By adjusting our analyses for potential confounders, based on clinical experience and baseline imbalances, we have tried to minimize the impact of this issue on our results.

Finally, for some variables we had relatively high numbers of missing values, the most important of which were onset-to-first-door time (14%), FDGT (14%) and mRS score at 90 days post-stroke (8%). We tried to minimize the impact of the missing data on our analyses by using multiple imputation, as described in the methods section.

Further research should focus on finding a triage instrument for prehospital selection of patients eligible for EVT, so that these patients can be brought directly to a CSC, without overburdening these hospitals with patients who can be treated in a PSC. Results of other research toward optimization of prehospital stroke logistics are expected in the coming years: a randomized controlled trial in Spain (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Centre in Acute Stroke Patients With Suspected Large Vessel Occlusion [RACECAT], Clinicaltrials.gov number: NCT02795962) is comparing direct presentation to transfer to a CSC in patients with a high likelihood of an LVO. Until then, directly presenting patients with a suspected stroke and a contraindication for IVT to a CSC may be considered, since there is no obvious disadvantage in bypassing the PSC in this patient population. Implementing this would, however, result in a higher patient load for CSCs. Other studies have shown that approximately 10% of suspected stroke patients have an LVO,[18] and in our cohort, 19% of patients with an LVO had a contraindication for IVT. Assuming that the proportion of patients with a contraindication for IVT is also 19% in the entire population of patients with a suspected AIS, routing these patients directly to a CSC would mean that for every patient with an LVO and a contraindication for IVT, approximately 9 patients without an LVO and with a contraindication for IVT would be presented to a CSC. In addition to the higher patient load, unnecessary transportation of these patients to a CSC may also be a burden on the patients and their families, because it may involve admission to a hospital further from home. To reduce the number of unnecessary direct presentations to a CSC, a triage method applied by paramedics, such as a clinical LVO-detection scale, may be useful.

In conclusion, we showed that in patients with an LVO who were not eligible for IVT, direct presentation to a CSC decreased time to EVT, compared to initial presentation to a PSC. Direct presentation was also associated with a slightly better clinical outcome that was not statistically significant. Since there is no obvious disadvantage in bypassing the PSC in this patient population, directly presenting patients with a suspected stroke and a contraindication for IVT to a CSC, if logistically feasible, may be considered.

DISCLOSURES

Dr. Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation and Stryker, outside the submitted work (paid to institution). In addition, dr. Majoie is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Dr. Roos reports stockholdings from Nico.lab outside the submitted work. Dr. Coutinho reports grants from Medtronic outside the submitted work. Dr. Majoie, dr. Roos and dr. Coutinho are (co-)investigators of the MR-CLEAN-NO IV trial (ISRCTN80619088). The other authors report no conflicts.

ETHICAL STANDARDS

Permission to carry out the MR CLEAN Registry study was granted by the medical ethics committee of the Erasmus University Medical Center in Rotterdam. This study was carried out in accordance with the Declaration of Helsinki.

CONTRIBUTION STATEMENT

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Laura van Meenen, Adrien Groot and Jonathan Coutinho. The first draft of the manuscript was written by Laura van Meenen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Stroke*. 2018;49:e46-e110.
2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731.
3. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V et al. Effect of Interhospital Transfer on Endovascular Treatment for Acute Ischemic Stroke. *Stroke.* 2019;50:923-930.
4. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA.* 2016;316:1279–1288.
5. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP et al; STRATIS Investigators. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS Registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke). *Circulation.* 2017;136:2311–2321.
6. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry Investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949.
7. Von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke.* 2015;46:2981–2986.
8. Kommer GJ, Zwakhals SL, Over E; Dutch National Institute for Public Health and the Environment. Models for the National Ambulance Plan 2016. https://www.rivm.nl/publicaties/modellen-referentiekader-ambulancezorg-2016-ontwikkeling-modellen-voor-dam-b-vervoer-en. Published 20 April 2017.
9. Mulder MJHL, Jansen IGH, Goldhoorn RB, Venema E, Chalos V, Compagne KCJ et al; MR CLEAN Registry Investigators. Time to endovascular treatment and outcome in acute ischemic stroke: MR CLEAN Registry results. *Circulation.* 2018;138:232–240.
10. Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ et al; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands Investigators. Time to reperfusion and treatment effect for acute ischemic stroke: a randomized clinical trial. *JAMA Neurol.* 2016;73:190–196.
11. Nogueira RG, Smith WS, Sung G, Duckwiler G, Walker G, Roberts R et al. Effect of time to reperfusion on clinical outcome of anterior circulation strokes treated with thrombectomy: pooled analysis of the MERCI and Multi MERCI trials. *Stroke.* 2011;42:3144-3149.
12. Guglielmi V, LeCouffe NE, Zinkstok SM, Compagne KCJ, Eker R, Treurniet KM et al; MR CLEAN Registry Investigators. Collateral Circulation and Outcome in Atherosclerotic Versus Cardioembolic Cerebral Large Vessel Occlusion. *Stroke.* 2019;50:3360-3368.
13. Beynon C, Erk AG, Potzy A, Mohr S, Popp E. Point of care coagulometry in prehospital emergency care: an observational study. *Scand J Trauma Resusc Emerg Med.* 2015;23:58.

14. Kommer GJ, van den Broek I, de Bruin-Kooistra M, Deuning C; Dutch National Institute for Public Health and the Environment. Supply and accessibility of emergency hospital care in the Netherlands 2017: analysis of the geographical accessibility of hospitals. https://www.rivm.nl/publicaties/aanbod-en-bereikbaarheid-van-spoedeisende-ziekenhuiszorg-in-nederland-2017-analyse. Published 9 November 2017.
15. Adeoye O, Albright KC, Carr BG, Wolff C, Mullen MT, Abruzzo T et al. Geographic access to acute stroke care in the United States. *Stroke.* 2014;45:3019-3024.
16. Albright KC, Branas CC, Meyer BC, Matherne-Meyer BCm Zivin JA, Lyden PD, et al. ACCESS: acute cerebrovascular care in emergency stroke systems. *Arch Neurol.* 2010;67:1210-1218.
17. Prabhakaran S, Ward E, John S, Lopes DK, Chen M, Temes RE et al. Transfer delay is a major factor limiting the use of intra-arterial treatment in acute ischemic stroke. Stroke. 2011;42:1626-1630.
18. Helwig SA, Ragoschke-Schumm A, Schwindling L, Kettner M, Roumia S, Kulikovski J et al. Prehospital Stroke Management Optimized by Use of Clinical Scoring vs Mobile Stroke Unit for Triage of Patients With Stroke: A Randomized Clinical Trial. JAMA Neurol. 2019;76:1484-1492.

SUPPLEMENTAL MATERIAL

Supplemental Table I. Baseline characteristics stratified by time of presentation within 4.5 hour time window

	Presentation ≤ 4.5 hours			Presentation > 4.5 hours		
	Direct, n=290	Transfer, n=186	p value	Direct, n=90	Transfer, n=18	p value
Age, years – mean ± SD	73 ± 13.0	74 ± 12.0	0.322	66 ± 16.3	65 ± 17.0	0.748
Male sex – no./total (%)	142/290 (49%)	97/186 (52%)	0.498	36/90 (40%)	8/18 (44%)	0.726
Hypertension – no./total (%)	156/283 (55%)	115/184 (63%)	0.114	47/90 (52%)	8/18 (44%)	0.547
Diabetes mellitus – no./total (%)	40/288 (14%)	26/184 (14%)	0.941	18/89 (20%)	1/18 (6%)	0.137
Atrial fibrillation – no./total (%)	130/287 (45%)	109/183 (60%)	0.003	17/88 (19%)	1/18 (6%)	0.156
Myocardial infarction – no./total (%)	43/287 (15%)	31/180 (17%)	0.519	10/89 (11%)	1/18 (6%)	0.469
Previous stroke – no./total (%)	87/290 (30%)	53/184 (29%)	0.781	14/89 (16%)	4/18 (22%)	0.502
Pre-stroke mRS score[1] – median (IQR)	0 (0-2)	0 (0-1)	0.243	0 (0-1)	0 (0-0)	0.171
Systolic blood pressure[2] – mean ± SD	154 ± 28.7	152 ± 26.4	0.510	153 ± 25.9	149 ± 36.8	0.656
Diastolic blood pressure[3] – mean ± SD	84 ± 17.3	85 ± 16.5	0.401	82 ± 15.2	82 ± 21.3	0.971
NIHSS score[4] – median (IQR)	15 (10-20)	17 (12-21)	0.073	16 (12-20)	17 (13-23)	0.228
Occlusion site – no./total (%)			0.156			0.421
ICA	39/290 (13%)	34/186 (18%)		17/89 (19%)	2/18 (11%)	
M1	124/290 (43%)	91/186 (49%)		44/89 (49%)	6/18 (33%)	
M2	47/290 (16%)	29/186 (16%)		10/89 (11%)	5/18 (28%)	
Anterior cerebral artery	4/290 (1%)	1/186 (1%)		0/89 (0%)	0/18 (0%)	
Posterior circulation	22/290 (8%)	7/186 (4%)		8/89 (9%)	2/18 (11%)	
ASPECTS score on first NCCT[5] – median (IQR)	9 (7-10)	9 (8-10)	0.277	8 (6-10)	8 (6-9)	0.614
Collateral score on first CTA – no./total (%)			0.180			0.094
Grade 0	18/231 (8%)	10/160 (6%)		2/77 (3%)	0/15 (0%)	
Grade 1	78/231 (34%)	64/160 (40%)		22/77 (29%)	6/15 (40%)	
Grade 2	83/231 (36%)	63/160 (39%)		24/77 (31%)	8/15 (53%)	
Grade 3	52/231 (23%)	23/160 (14%)		29/77 (38%)	1/15 (7%)	
Time from stroke onset to door of first hospital, minutes – median (IQR)	67 (45-125)	62 (40-111)	0.119	364 (295-517)	316 (295-371)	0.178

ASPECTS = Alberta Stroke Program Early CT Score; CTA = computed tomography angiography; ICA = intracranial part of internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; M1 = first segment of the middle cerebral artery; M2 = second segment (after first bifurcation) of the middle cerebral artery; mRS = modified Rankin Scale; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale; no. = number; SD = standard deviation.

Number of missing values: [1]8; [2]10; [3]15; [4]9; [5]75.

Supplemental Table II. Treatment times stratified by presentation within 4.5 hour time window

	Presentation ≤ 4.5 hours				Presentation > 4.5 hours			
	Direct, n=290	**Transfer, n=186**	**Unadjusted β (95% CI)**	**Adjusted β (95% CI)**	**Direct, n=90**	**Transfer, n=18**	**Unadjusted β (95% CI)**	**Adjusted β (95% CI)**
Onset-to-groin time[1] – median (IQR)	180 (129-255)	228 (180-310)	-38.3 (-56.4 to -20.1)	-46.4 (-66.1 to -26.6)[2]	469 (370-625)	455 (415-590)	7.19 (-91.4 to 105.6)	-8.1 (-115.9 to 99.7)[2]
Travel time-corrected onset-to-groin time[3] – median (IQR)	180 (129-255)	208 (156-279)	-16.3 (-34.4 to 1.7)	-23.7 (-43.3 to -4.1)[2]	469 (370-625)	436 (373-603)	33.6 (-65.1 to 132.3)	19.7 (-88.4 to 127.7)[2]
First-door-to-groin time[1] – median (IQR)	94 (73-125)	150 (116-186)	-47.6 (-61.0 to -34.3)	-50.8 (-65.7 to -36.2)[2]	84 (69-114)	139 (100-191)	-56.7 (-90.0 to -23.5)	-47.0 (-71.7 to -22.3)[2]
Travel time-corrected first-door-to-groin time[3] – median (IQR)	94 (73-125)	128 (97-166)	-25.7 (-39.0 to -12.5)	-28.3 (-43.3 to -13.3)[2]	84 (69-114)	117 (77-168)	-30.3 (-63.5 to 2.8)	-19.2 (-43.7 to 5.3)[2]

CI = confidence interval; IQR = interquartile range.

[2]Adjusted for age, pre-stroke mRS, baseline blood pressure, baseline NIHSS and location of occlusion.

Number of missing values: [1]5; [3]10.

CHAPTER 4

RELATIONSHIP BETWEEN PRIMARY STROKE CENTER VOLUME AND TIME TO ENDOVASCULAR THROMBECTOMY IN ACUTE ISCHEMIC STROKE

Laura C.C. van Meenen, MD, MSc[1], Sanne J. den Hartog, MD, MSc[2-4], Adrien E. Groot, MD, PhD[1], Bart J. Emmer, MD, PhD[5], Martin D. Smeekes, MD, MSc[6], Arjen Siegers, MD, MSc[7], Geert Jan Kommer, MSc[8], Charles B.L.M. Majoie, MD, PhD[5], Yvo B.W.E.M. Roos, MD, PhD[1], Adriaan C.G.M. van Es, MD, PhD[9], Diederik W. Dippel, MD, PhD[2], H. Bart van der Worp, MD, PhD[10], Hester F. Lingsma, MD, PhD[4], Bob Roozenbeek, MD, PhD[2], Jonathan M. Coutinho, MD, PhD[1] on behalf of the MR CLEAN Registry Investigators[11]

[1] Department of Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands
[2] Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[3] Department of Radiology & Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[4] Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[5] Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands
[6] Emergency Medical Services North-Holland North, Alkmaar, the Netherlands
[7] Ambulance Amsterdam, Amsterdam, the Netherlands
[8] National Institute of Public Health and the Environment, Center for Nutrition, Prevention and Health services, Bilthoven, the Netherlands
[9] Department of Radiology and Nuclear Medicine, Leiden University Medical Center, Leiden, the Netherlands
[10] Department of Neurology and Neurosurgery, Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands
[11] MR CLEAN Registry Investigators - group authors: please see 'Contributing authors and affiliations'

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ABSTRACT

Background

We investigated whether the annual volume of patients with acute ischemic stroke referred from a primary stroke center (PSC) for endovascular treatment (EVT) is associated with treatment times and functional outcome.

Methods

We used data from the MR CLEAN Registry (2014-2017). We included patients with acute ischemic stroke of the anterior circulation who were transferred from a PSC to a comprehensive stroke center (CSC) for EVT. We examined the association between EVT referral volume of PSCs and treatment times and functional outcome using multivariable regression modelling. The main outcomes were time from arrival at the PSC to groin puncture (PSC-door-to-groin time), adjusted for estimated ambulance travel times, time from arrival at the CSC to groin puncture (CSC-door-to-groin time), and modified Rankin Scale (mRS) score at 90 days post-stroke.

Results

Of the 3637 patients in the Registry, 1541 patients (42%) from 65 PSCs were included. Mean age was 71 years (SD ±13.3), median National Institutes of Health Stroke Scale score was 16 (IQR: 12-19) and median time from stroke onset to arrival at the PSC was 53 minutes (IQR: 38-90). 83% had received intravenous thrombolysis. EVT referral volume was not associated with PSC-door-to-groin time (adjusted coefficient: -0.49 minutes/annual referral, 95% CI: -1.27 to 0.29), CSC-door-to-groin time (adjusted coefficient: -0.34 minutes/annual referral, 95% CI: -0.69 to 0.01) or 90-day mRS score (adjusted cOR: 0.99, 95% CI: 0.96-1.01).

Conclusions

In patients transferred from a PSC for EVT, higher PSC volumes do not seem to translate into better workflow metrics or patient outcome.

INTRODUCTION

Intravenous thrombolysis with alteplase (IVT) followed by endovascular thrombectomy (EVT) is the standard treatment for patients with acute ischemic stroke caused by a large vessel occlusion of the anterior circulation.[1, 2] While IVT can be given in all hospitals that provide acute stroke care, EVT can only be performed in more specialized hospitals, so-called comprehensive stroke centers (CSCs). In most countries, the majority of patients with a suspected stroke are brought to the nearest primary stroke center (PSC) in order to undergo diagnostic tests and treatment with IVT. Patients with a large vessel occlusion who are potentially eligible for EVT are subsequently transferred to a CSC. The proportion of patients who are treated according to this drip-and-ship paradigm varies between 45% and 83%, depending on the region.[3-6] For both IVT and EVT, timely start of treatment is important, because shorter treatment times improve functional outcome of patients.[7, 8]

For a number of neurological diseases, including glioblastoma, subarachnoid hemorrhage and amyotrophic lateral sclerosis, it has been shown that treatment in high-volume, specialized hospitals improves patient outcomes.[9-11] Regarding treatment of acute ischemic stroke, multiple studies have shown that hospitals with higher annual IVT volumes achieve lower door-to-needle times.[12-14] For EVT, a similar association has been found for the annual number of cases in CSCs.[15-17] However, little is known about the relationship between the volume of EVT eligible patients who present to a PSC (EVT referral volume) and time to treatment. We hypothesized that higher EVT referral volume may positively affect treatment times, because it may be associated with more streamlined care pathways within the PSC, more experienced physicians when it comes to acute stroke treatment, and better facilities for acute stroke imaging. We aimed to investigate the association between the EVT referral volume of PSCs and treatment times and clinical outcomes in patients with an acute ischemic stroke who were transferred from a PSC for EVT.

METHODS AND MATERIALS

Study design and population

We used data from the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands Registry (MR CLEAN Registry), which is a nationwide, prospective cohort study in which data from all adult patients who underwent EVT for an acute ischemic stroke in the Netherlands since completion of the MR CLEAN trial (March 2014) until December 2018 have been registered. Detailed methods of the MR CLEAN Registry have previously been reported.[18] Permission to carry out the Registry was granted by the medical ethics committee of Erasmus MC, University Medical Center in Rotterdam, The Netherlands. The requirement for informed consent was waived.

For the current study, we used data collected from March 2014 until November 2017 (Registry part I and II). We included adult patients with an acute ischemic stroke of the anterior circulation who had initially presented to a PSC and subsequently transferred to a CSC that was a MR CLEAN trial center to undergo EVT. Patients who had primarily presented to a CSC or to a PSC outside the Netherlands were excluded from the analysis. Furthermore, because during the study period EVT was not standard care in the Netherlands for patients with a large vessel occlusion stroke who were presented more than 6 hours after onset and median door-to-groin time in patients transferred for EVT in the Netherlands is approximately 30 minutes,[19] we excluded patients with an onset-to-groin time >390 minutes. In-hospital strokes were also excluded.

Definitions and outcomes

A CSC was defined as a hospital that offers both IVT and EVT. A PSC was defined as a hospital that routinely offers IVT and performs CT angiography (CTA) to identify patients with a large vessel occlusion stroke, but does not provide EVT. To verify whether hospitals provided IVT during the study period, data from the public Health Care Quality registration of the National Health Care Institute (in Dutch: Zorginstituut Nederland) were used.[20] All hospitals are obliged to report IVT-related benchmarks in this annual registration. For hospitals that reported IVT benchmarks only for part of the study period, we assumed that IVT for acute ischemic stroke was only offered in the years in which these benchmarks were reported, and the EVT referral volume was calculated for this period only. For hospitals with multiple locations, each location was treated as a separate PSC. If the specific location of a hospital with multiple locations from which a patient was referred was unknown, we used the patient's postal code to determine which of the hospital locations was located closest to the patient's home, and it was assumed that this was the referring PSC.

The annual EVT referral volume of a PSC was defined as the mean number of patients per year who had primarily presented to that PSC and who ultimately underwent EVT during the study period. For comparison of baseline characteristics and illustrative purposes, we categorized PSCs into low, medium or high-volume. Low annual EVT referral volume was defined as <6 referrals per year, medium as 6-12 referrals per year, and high as >12 referrals per year. For our regression analyses, however, annual EVT referral volume was assessed as a continuous variable. EVT was defined as arterial puncture in the angiography suite, with the objective to perform mechanical thrombectomy. The actual EVT strategy was at the discretion of the interventionist.

Our primary outcome measure was time from PSC arrival to arterial puncture in the CSC (PSC door-to-groin time [PSC DTGT]). Other workflow-related outcome measures were time from arrival at the PSC to arrival at the CSC (door-to-door time) and time from arrival at the CSC to arterial puncture (CSC door-to-groin time [CSC DTGT]). Clinical outcomes were modified Rankin Scale (mRS) score and mortality at 90 days post-stroke.

Statistical analysis

We compared baseline characteristics, treatment times and clinical outcomes of patients referred from low-volume PSCs, medium-volume PSCs and high-volume PSCs, using One way ANOVA for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, and χ^2 test for categorical variables.

We examined the effect of EVT referral volume at the hospital level on treatment times and clinical outcome, using multilevel regression modelling. For these analyses, annual EVT referral volume was assessed as a continuous variable. For our analyses of PSC DTGT and door-to-door time, we used multilevel linear regression, adjusting for the following pre-selected variables on patient-level (unless reported otherwise, baseline characteristics were measured upon arrival at the CSC): referring PSC as a random effect, and age, history of hypertension, pre-stroke mRS, baseline systolic blood pressure, baseline NIHSS, location of occlusion on CTA, treatment with IVT, onset-to-first-door time, estimated time of travel by ambulance from PSC to CSC, and the receiving CSC as fixed effects. The estimated ambulance travel times were provided by the Dutch National Institute for Public Health and the Environment and calculated using their proprietary model, assuming the ambulance driving with the highest level of emergency and daytime circumstances outside of rush hour.[21] When analyzing CSC DTGT, we also used multilevel linear regression, adjusting for the following patient-level variables: referring PSC as a random effect and age, history of hypertension, pre-stroke mRS, baseline systolic blood pressure, baseline NIHSS, location of occlusion on CTA, time from onset to arrival at the CSC, and the receiving CSC as fixed effects. For our analysis of the 90-day mRS score we used multilevel ordinal logistic regression, and for our analysis of mortality we used multilevel binary logistic regression. Both analyses were adjusted for the following variables on patient-level: referring PSC as a random effect and age, history of hypertension, pre-stroke mRS, baseline systolic blood pressure, baseline NIHSS, location of occlusion on CTA, treatment with IVT, onset-to-first-door time, and the receiving CSC as fixed effects. For all regression analyses, we imputed missing data using multiple imputation, using the following covariates: age, sex, history of stroke, history of hypertension, history of diabetes mellitus, history of atrial fibrillation, pre-stroke mRS, baseline blood pressure (systolic and diastolic), baseline NIHSS, location of occlusion on CTA, treatment with IVT, onset-to-first-door time, estimated time of travel by ambulance from PSC to CSC, PSC DTGT, door-to-door time, CSC DTGT, expanded Treatment In Cerebral Ischemia (eTICI) score after EVT, symptomatic intracranial hemorrhage and 90-day mRS. All analyses were performed using SPSS (version 25; SPSS Inc., Chicago, IL, USA).

Data availability statement

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

RESULTS

Between March 2014 and November 2017, 3637 patients were included in the MR CLEAN Registry. We excluded 2096/3637 patients (58%) because they had not primarily presented to a PSC (n=1474), underwent EVT in a CSC that did not participate in the MR CLEAN trial (n=177), had an acute ischemic stroke of the posterior circulation (n=172), had an in-hospital stroke (n=149), had an onset-to-groin time of >390 minutes (n=99) or had presented to a PSC outside the Netherlands (n=16; Figure 1). Therefore, 1541/3637 patients (42%) were included in the study.

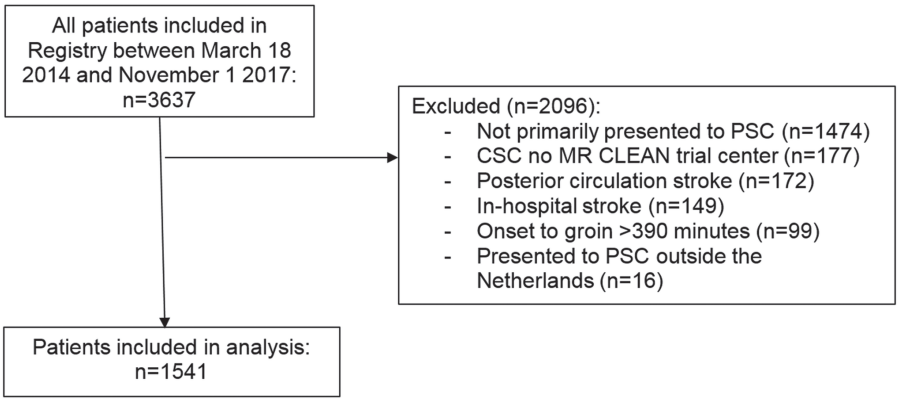

Figure 1. Flow chart patient inclusion. CSC = comprehensive stroke centers; PSC = primary stroke center; Registry = MR CLEAN Registry.

Patients had primarily presented to one of 65 PSCs and treated with EVT in one of 16 CSCs. Annual EVT referral volume was low (<6 per year) for 35/65 PSCs (54%), medium (6-12 per year) for 20/65 PSCs (31%) and high (>12 per year) for 10/65 PSCs (15%). Of all patients, 435/1541 (28%) had presented to a low-volume PSC, 583/1541 (38%) to a medium-volume PSC, and 523/1541 (34%) to a high-volume PSC. For one patient, it was unknown which of two hospital locations was the referring PSC, so the hospital location located closest to the patient's postal code was assumed to be the referring PSC.

Baseline characteristics categorized by low, medium and high PSC volume are reported in Table 1. Patients presented to high-volume PSCs more often had a history of hypertension (low: 48%, medium: 54%, high: 57%; p=0.03) and had slightly lower NIHSS scores at baseline (low: median 16 [IQR 12-20], medium: 16 [IQR 12-20], high: 15 [IQR 11-19]; p=0.01). Estimated ambulance travel times between PSC and receiving CSC were shorter for patients presented to high-volume PSCs (low: median 22 minutes [IQR 15-28], medium: 22 minutes [IQR 15-33], high: 17 minutes [IQR 9-30]; p<0.01). Other baseline characteristics did not differ between groups.

When comparing treatment times between low-, medium- and high-volume PSCs, we found that patients who had presented to high- and medium-volume PSCs had shorter PSC DTGT (low: median 150 [IQR 123-186], medium: 145 [IQR 120-173], high: 146 [IQR 124-178]; p=0.03) and lower door-to-door times (low: median 109 [IQR 84-135], medium: 102 [IQR 83-124], high: 106 [IQR 85-128]; p<0.01), compared to patients presented to low-volume PSCs (Table 2). However, when we analyzed EVT referral volume as a continuous variable and adjusted for potential confounders, there was no association between annual EVT referral volume and PSC DTGT (Figure 2A) or door-to-door time (Figure 2B). CSC DTGT also did not differ between groups (Table 2) and there was no statistically significant association between EVT referral volume as a continuous variable and CSC DTGT after adjustment (Figure 2C).

The mRS score and mortality at 90 days post-stroke did not differ between patients presented to low-, medium- and high-volume PSCs (Table 2). After adjustment, there was also no association between annual EVT referral volume and 90-day mRS score (unadjusted cOR: 0.98 [95% CI: 0.96-1.01]; adjusted cOR: 0.99 [95% CI: 0.96-1.01]) or mortality (unadjusted OR: 1.02 [95% CI: 0.99-1.04]; adjusted OR: 1.02 [95% CI: 0.98-1.06]).

Table 1. Baseline characteristics

Characteristic[1]	All patients	Annualized EVT referral volume			p-value[7]
		Low (<6)	Medium (6-12)	High (>12)	
No. of hospitals (no. of patients)	65 (1541)	35 (435)	20 (583)	10 (523)	NA
Age, years – mean ± SD	70.8 ± 13.3	70.0 ± 13.3	71.4 ± 13.5	70.9 ± 13.1	0.27
Male sex – no./total (%)	795/1541 (52%)	220/435 (51%)	301/583 (52%)	274/523 (52%)	0.86
History of hypertension – no./total (%)	798/1502 (53%)	205/426 (48%)	304/566 (54%)	289/510 (57%)	0.03
Diabetes mellitus – no./total (%)	241/1528 (16%)	70/430 (16%)	86/578 (15%)	85/520 (16%)	0.76
Atrial fibrillation – no./total (%)	366/1519 (24%)	105/430 (24%)	143/571 (25%)	118/518 (23%)	0.67
Previous stroke – no./total (%)	236/1524 (15%)	68/429 (16%)	96/576 (17%)	72/519 (14%)	0.43
Pre-stroke mRS score[2] – median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0.07
Systolic blood pressure[3] – mean ± SD	150 (132-166)	148 (131-166)	150 (134-168)	150 (132-165)	0.34
Diastolic blood pressure[4] – mean ± SD	80 (71-91)	80 (71-90)	81 (72-92)	80 (70-90)	0.13
NIHSS score[5] – median (IQR)	16 (12-19)	16 (12-20)	16 (12-20)	15 (11-19)	0.01
Intracranial occlusion site on CTA – no./total (%)					0.21
Intracranial ICA	406/1468 (28%)	113/419 (27%)	165/545 (30%)	128/504 (25%)	
M1	876/1468 (60%)	267/419 (64%)	311/545 (57%)	298/504 (59%)	
M2	177/1468 (12%)	37/419 (9%)	68/545 (12%)	72/504 (14%)	
A1	2/1468 (0%)	0/419 (0%)	1/545 (0%)	1/504 (0%)	
Other	4/1468 (0%)	1/419 (0%)	0/545 (0%)	3/504 (1%)	
None	3/1468 (0%)	1/419 (0%)	0/545 (0%)	2/504 (0%)	
Presentation outside office hours – no./total (%)	1030/1541 (67%)	284/435 (65%)	387/583 (66%)	359/523 (69%)	0.52
Time from stroke onset to arrival at PSC, minutes[6] – median (IQR)	53 (38-90)	53 (40-94)	50 (36-83)	56 (37-90)	0.38
Estimated ambulance travel time between PSC and receiving CSC – median (IQR)	19 (12-32)	22 (15-28)	22 (15-33)	17 (9-30)	<0.01
Treatment with IVT – no./total (%)	1280/1533 (83%)	353/434 (81%)	489/577 (85%)	438/522 (84%)	0.52

A1 = first segment of anterior cerebral artery; CSC = comprehensive stroke center; CTA = CT angiography; EVT = endovascular thrombectomy; ICA = internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; M1 = first segment of the middle cerebral artery; M2 = second segment of the middle cerebral artery; mRS = modified Rankin Scale; NA = not applicable; NIHSS = National Institutes of Health Stroke Scale; no. = number; PSC = primary stroke center; SD = standard deviation.

[1]All baseline characteristics were measured on arrival at the CSC, unless reported otherwise. Number of missing values: [2]44; [3]55; [4]60; [5]19; [6]438.

[7]p-value for comparison between patients who were referred from low, medium and high annual referral volume PSCs.

Table 2. Treatment times and clinical outcomes for patients presented to low-, medium- and high-volume PSCs

		Annualized EVT referral volume			
	All patients (n=1541)	**Low (<6) (n=435)**	**Medium (6-12) (n=583)**	**High (>12) (n=523)**	**p-value[5]**
PSC DTGT, minutes[1] – median (IQR)	146 (122-178)	150 (123-186)	145 (120-173)	146 (123-177)	0.03
Door-to-door time, minutes[2] – median (IQR)	105 (84-129)	109 (84-135)	102 (83-124)	106 (85-128)	<0.01
CSC DTGT, minutes[3] – median (IQR)	39 (27-57)	36 (25-55)	40 (27-56)	40 (28-60)	0.18
mRS score at 90 days[4] – median (IQR)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	0.19
Mortality at 90 days[4] – no./total (%)	445/1541 (29%)	121/435 (28%)	162/583 (28%)	162/532 (30%)	0.37

CI = confidence interval; CSC DTGT = time from arrival at the comprehensive stroke center to arterial puncture; door-to-door time = time from arrival at the PSC to arrival at the CSC; EVT = endovascular thrombectomy, IQR = interquartile range; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; PSC DTGT = time from arrival at the primary stroke center to arterial puncture.

Number of imputed values: [1]432, [2]481, [3]71, [4]138.

Numbers of imputed values did not differ between groups for the time intervals ([†]p=0.12, [‡]p=0.18, [§]p=0.97).

[5]p-value for comparison between patients who were referred from low, medium and high annual referral volume PSCs.

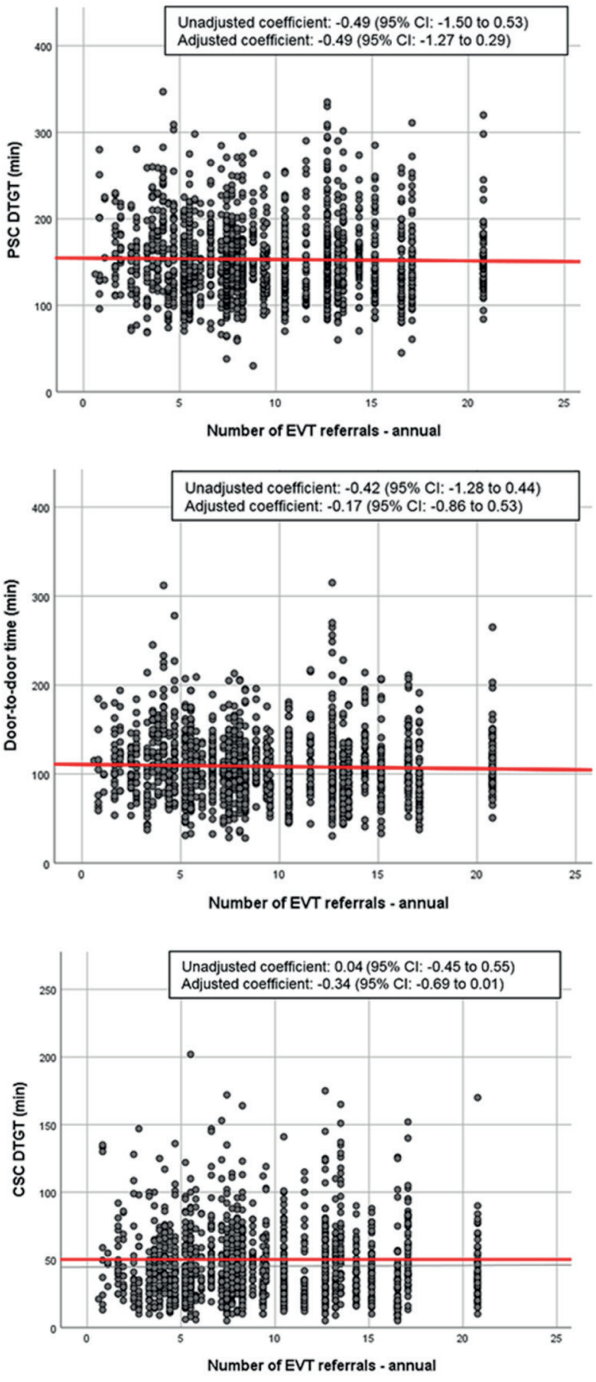

Figure 2. Plots of treatment times by annual EVT referral volumes. The treatment times (y-axis) and the annual EVT referral volume (x-axis) are shown for each patient (imputed data). Each dot represents a single patient. Vertically aligned dots represent the data of a single hospital with the corresponding number of annual EVT referrals. In case multiple hospitals had the same annual EVT referral volume, they were plotted on the same vertical axis. Both the adjusted and unadjusted coefficients are shown. For adjustment variables, see the Methods section. A. PSC DTGT. B. Door-to-door-time. C. CSC DTGT. CI = confidence interval; CSC = comprehensive stroke center; CSC DTGT = time from arrival at the comprehensive stroke center to arterial puncture; door-to-door time = time from arrival at the PSC to arrival at the CSC; EVT = endovascular thrombectomy; PSC = primary stroke center; PSC DTGT = time from arrival at the primary stroke center to arterial puncture.

DISCUSSION

In this cohort study, we examined the relationship between the EVT referral volume of PSCs and treatment times and clinical outcomes. We observed that PSCs with high or medium EVT referral volume had shorter PSC DTGT compared to low-volume PSCs. However, after adjustment, there was no association between PSC volume and workflow times or functional outcome of patients.

The consonance of previous studies when it comes to the benefits of treatment in high-volume, specialized hospitals has led many to plead for increasing centralization of care for several neurological diseases,[9-11] including acute ischemic stroke.[12-17, 22-25] In light of this, it is somewhat surprising that our findings indicate that high PSC volumes do not translate into better workflow metrics or patient outcome. We defined 'high PSC volume' as >12 EVT referrals per year based on the distribution of our data: only 15% of PSCs had >12 annual EVT referrals. Although few previous studies have reported on EVT referral volumes, average PSC volumes in our study seem relatively high compared to those found in regions in Germany and Australia (6 annual EVT referrals per PSC in our study vs. 4 in both Germany and Australia).[26, 27] Nonetheless, it is possible that for even higher EVT referral volumes, an association with shorter time to treatment would exist. Bray et al. found a similar trend for the association between hospital volume and time to initiation of IVT: only hospitals with >50 IVT cases per year achieved lower door-to-needle times, while no difference was found between hospitals with <25 annual cases and hospitals with 25-50 annual cases.[13] However, because the number of PSCs with very high EVT referral volumes was low in our cohort, we could not test this hypothesis.

Another potential explanation for the absence of an association between PSC volume and treatment times in our study could be the fact that the Netherlands has a well-developed health care system. Stroke workflow in the Netherlands, including Emergency Medical Services, PSC and CSC logistics, is generally well-organized, resulting in relatively short treatment times.[19] Within such a system it may be more difficult to discern potential effect modifying variables, such as PSC volume.

Two baseline imbalances should be noted. First, estimated ambulance travel times between PSC and receiving CSC were shorter for patients presented to high-volume PSCs. PSCs that are located in an area with low population density, and therefore have lower annual patient volumes, are likely located further away from the nearest CSC than PSCs in densely populated regions. This makes a comparison of treatment times inherently biased in favor of patients presented to a PSC in a more densely populated area, and thus in favor of high-volume PSCs. To account for this bias, we adjusted our analyses of treatment times for the estimated ambulance travel time between the PSC and the receiving CSC. Second, patients presented to high-volume PSCs had

slightly lower NIHSS scores upon arrival at the CSC. A potential explanation for this could be that low-volume PSCs, due to possible lack of around-the-clock availability of stroke imaging facilities, may not have routinely performed CT angiography in patients with a suspected stroke and mild neurological deficits, causing these patients to less often be referred for EVT. Alternatively, more distal location occlusions, such as M2 occlusions, may have been overlooked more often in low-volume PSCs because of less experienced readers.

There are several limitations to our study. First, the analysis of hospital performance is inherently influenced by variation by chance across hospitals, which especially affects low-volume hospitals. We used multilevel regression analysis, because such models can take clustering effects and variation by chance into account, contrary to regular fixed effects models. However, it is possible that the effects of PSC volume were slightly underestimated by our random effects model, because the observed variation across the hospitals may have been diluted, especially for low-volume PSCs.[28-30] Second, data collection for our study took place in the Netherlands, which is a densely populated country in which hospitals are located relatively close to one another and there is overall good infrastructure.[31] Furthermore, in our study, the median PSC DTGT was short (144 minutes) compared to existing literature, in which median PSC DTGTs ranging from 153 to 191 minutes have been reported.[3, 32-34] This was also the case for ambulance travel times: median ambulance travel time in our study was 19 minutes, compared to 23 to 95 minutes in other studies.[3, 5, 32, 33, 35] Our median CSC DTGT (39 minutes) was within the range, although on the lower end, of previously reported median CSC DTGTs for transferred patients (35 to 81 minutes).[3, 7, 33] As data for this study were collected in a country with an advanced health care system and time intervals were relatively short compared to those found in other countries, our findings should be extrapolated to other countries with caution. Third, we did not have data of patients who were referred to a CSC for EVT and were ultimately deemed ineligible for EVT, because these patients were not included in the MR CLEAN Registry. The true annual number of patients referred from the PSCs for EVT therefore may have been higher than reported in our study and the frequency with which futile transfers occurred could not be assessed. Finally, we had relatively high numbers of missing values for three variables: door-to-door time (31%), PSC DTGT (28%) and time from stroke onset to arrival at the PSC (28%). To minimize the impact of these missing values on our analyses, we used multiple imputation. Time between arrival at the PSC and departure from the PSC (door-in-door-out time), which would have been an outcome measure of interest in our study, was not available in our dataset.

In conclusion, we did not observe an association between the EVT referral volume of PSCs and the PSC-door-to-groin time or the 90-day mRS score of patients who were transferred from a PSC for EVT. Based on the data in our study, PSC volumes do not seem to translate into better overall workflow metrics or patient outcome.

DISCLOSURES

Bart Emmer reports funding from ZonMW (Leading The Change) and Health Holland paid to institution and has received grants paid to institution from Stryker Neurovascular in the past and personal fees from Dekra and from Novartis outside the submitted work in the past. Charles Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation, Stryker, and Health Evaluation Netherlands, all outside the submitted work (paid to institution), and is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Yvo Roos is a minor shareholder of Nico.lab. Bart van der Worp has received speaker's fees Boehringer Ingelheim, has served as a consultant to Boehringer Ingelheim, and is the recipient of unrestricted grants from Dutch Heart Foundation and the European Union for the conduct of trials on acute treatment for stroke, all outside the submitted work. Diederik Dippel reports fees for consultations by Stryker and Bracco Imaging; grants from Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, The Netherlands Organisation for Health Research and Development, and Health Holland Top Sector Life Sciences & Health; and unrestricted grants from AngioCare BV, Covidien/EV3, MEDAC Gmbh/LAMEPRO, Top Medical/Concentric, Stryker, Stryker European Operations BV, Penumbra Inc, Medtronic, Thrombolytic Science, LLC and Cerenovus, all paid to institution. Jonathan Coutinho received unrelated research support from the Dutch Heart Foundation, Bayer, Boehringer, and Medtronic. All fees were paid to his employer. The other authors report no conflicts.

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REFERENCES

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731
3. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311-2321
4. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V, et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923-930
5. Pallesen LP, Winzer S, Barlinn K, Prakapenia A, Siepmann T, Gruener C, et al. Safety of inter-hospital transfer of patients with acute ischemic stroke for evaluation of endovascular thrombectomy. *Scientific reports*. 2020;10:5655
6. Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ, et al. Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making. *Eur Stroke J*. 2018;3:126-135
7. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
8. Goyal M, Almekhlafi M, Dippel DW, Campbell BCV, Muir K, Demchuk AM, et al. Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions. *Stroke*. 2019;50:645-651
9. Zhu P, Du XL, Zhu JJ, Esquenazi Y. Improved survival of glioblastoma patients treated at academic and high-volume facilities: A hospital-based study from the national cancer database. *J Neurosurg*. 2019;132:491-502
10. Rush B, Romano K, Ashkanani M, McDermid RC, Celi LA. Impact of hospital case-volume on subarachnoid hemorrhage outcomes: A nationwide analysis adjusting for hemorrhage severity. *J Crit Care*. 2017;37:240-243
11. Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy C, et al. A multidisciplinary clinic approach improves survival in als: A comparative study of als in ireland and northern ireland. *J Neurol Neurosurg Psychiatry*. 2015;86:496-501
12. Groot AE, van Schaik IN, Visser MC, Nederkoorn PJ, Limburg M, Aramideh M, et al. Association between i.V. Thrombolysis volume and door-to-needle times in acute ischemic stroke. *J Neurol*. 2016;263:807-813
13. Bray BD, Campbell J, Cloud GC, Hoffman A, Tyrrell PJ, Wolfe CD, et al. Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke*. 2013;44:3129-3135
14. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: Patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*. 2011;123:750-758

15. Saber H, Navi BB, Grotta JC, Kamel H, Bambhroliya A, Vahidy FS, et al. Real-world treatment trends in endovascular stroke therapy. *Stroke*. 2019;50:683-689
16. Rinaldo L, Brinjikji W, Rabinstein AA. Transfer to high-volume centers associated with reduced mortality after endovascular treatment of acute stroke. *Stroke*. 2017;48:1316-1321
17. Shim DH, Kim Y, Roh J, Kang J, Park KP, Cha JK, et al. Hospital volume threshold associated with higher survival after endovascular recanalization therapy for acute ischemic stroke. *J Stroke*. 2020;22:141-149
18. Jansen IGH, Mulder M, Goldhoorn RB, investigators MCR. Endovascular treatment for acute ischaemic stroke in routine clinical practice: Prospective, observational cohort study (mr clean registry). *BMJ*. 2018;360:k949
19. Van Meenen LCC, Riedijk F, Stolp J, van der Veen B, Halkes PHA, van der Ree TC et al. Pre- and Interhospital Workflow Times for Patients With Large Vessel Occlusion Stroke Transferred for Endovascular Thrombectomy. *Front Neurol*. 2021;12:730250.
20. Public data Hospitals and Treatment Centers / Medical Specialist Care (in Dutch: Open data Ziekenhuizen en Zelfstandige Behandelcentra / Medisch-specialistische zorg). National Health Care Institute (in Dutch: Zorginstituut Nederland). https://www.zorginzicht.nl. Accessed December 7, 2020.
21. Kommer GJ, Zwakhals SL, Over E. Models for the national ambulance plan 2016 (in Dutch: Modellen referentiekader ambulancezorg 2016). https://www.rivm.nl/publicaties/modellen-referentiekader-ambulancezorg-2016-ontwikkeling-modellen-voor-dam-b-vervoer-en. Published April 20, 2017. Accessed December 7, 2020.
22. Hastrup S, Johnsen SP, Terkelsen T, Hundborg HH, von Weitzel-Mudersbach P, Simonsen CZ, et al. Effects of centralizing acute stroke services: A prospective cohort study. *Neurology*. 2018;91:e236-e248
23. Turner S, Ramsay A, Perry C, Boaden R, McKevitt C, Morris S, et al. Lessons for major system change: Centralization of stroke services in two metropolitan areas of england. *J Health Serv Res Policy*. 2016;21:156-165
24. Elameer M, Price C, Flynn D, Rodgers H. The impact of acute stroke service centralisation: A time series evaluation. *Future Healthc J*. 2018;5:181-187
25. Takagi T, Yoshimura S, Sakai N, Iihara K, Oishi H, Hirohata M, et al. Distribution and current problems of acute endovascular therapy for large artery occlusion from a two-year national survey in japan. *Int J Stroke*. 2020;15:289-298
26. Edwards LS, Blair C, Cordato D, McDougall A, Manning N, Cheung A et al. Impact of interhospital transfer on patients undergoing endovascular thrombectomy for acute ischaemic stroke in an Australian setting. *BMJ Neurol Open*. 2020;2:e000030.
27. Stefanou MI, Stadler V, Baku D, Hennersdorf F, Ernemann U, Ziemann U et al. Optimizing Patient Selection for Interhospital Transfer and Endovascular Therapy in Acute Ischemic Stroke: Real-World Data From a Supraregional, Hub-and-Spoke Neurovascular Network in Germany. *Front Neurol*. 2020;11:600917.
28. Fischer C, Lingsma HF, van Leersum N, Tollenaar RA, Wouters MW, Steyerberg EW. Comparing colon cancer outcomes: The impact of low hospital case volume and case-mix adjustment. *Eur J Surg Oncol*. 2015;41:1045-1053
29. Glance LG, Dick A, Osler TM, Li Y, Mukamel DB. Impact of changing the statistical methodology on hospital and surgeon ranking: The case of the new york state cardiac surgery report card. *Med Care*. 2006;44:311-319
30. Austin PC, Alter DA, Tu JV. The use of fixed- and random-effects models for classifying

hospitals as mortality outliers: A monte carlo assessment. *Med Decis Making*. 2003;23:526-539

31. Kommer GJ, Van den Broek I, de Bruin-Kooistra M, Deuning C. Supply and accessibility of emergency hospital care in the Netherlands 2017: analysis of the geographical accessibility of hospitals (in Dutch: Aanbod en bereikbaarheid van de spoedeisende ziekenhuiszorg in Nederland 2017: Analyse gevoelige ziekenhuizen 2017). https://www.rivm.nl/publicaties/aanbod-en-bereikbaarheid-van-spoedeisende-ziekenhuiszorg-in-nederland-2017-analyse. Published November 9, 2017. Accessed December 7, 2021.
32. Sablot D, Dumitrana A, Leibinger F, Khlifa K, Fadat B, Farouil G, et al. Futile inter-hospital transfer for mechanical thrombectomy in a semi-rural context: Analysis of a 6-year prospective registry. *J Neurointerv Surg*. 2019;11:539-544
33. Liang JW, Stein L, Wilson N, Fifi JT, Tuhrim S, Dhamoon MS. Timing of vessel imaging for suspected large vessel occlusions does not affect groin puncture time in transfer patients with stroke. *J Neurointerv Surg*. 2018;10:22-24
34. Cappellari M, Bonetti B, Forlivesi S, Sajeva G, Naccarato M, Caruso P, et al. Acute revascularization treatments for ischemic stroke in the stroke units of triveneto, northeast italy: Time to treatment and functional outcomes. *J Thromb Thrombolysis*. 2021;51:159-167
35. Fuentes B, Alonso de Lecinana M, Ximenez-Carrillo A, Martinez-Sanchez P, Cruz-Culebras A, Zapata-Wainberg G, et al. Futile interhospital transfer for endovascular treatment in acute ischemic stroke: The madrid stroke network experience. *Stroke*. 2015;46:2156-2161

CHAPTER 5

VALUE OF REPEATED IMAGING IN PATIENTS WITH A STROKE WHO ARE TRANSFERRED FOR ENDOVASCULAR TREATMENT

Laura C.C. van Meenen, MSc[1], Nerea Arrarte Terreros, MSc[2,3], Adrien E. Groot, MSc[1], Manon Kappelhof, MSc[3], Ludo F.M. Beenen, MSc[3], Henk A. Marquering, PhD[2,3], Bart J. Emmer, PhD[3], Yvo B.W.E.M. Roos, PhD[1], Charles B.L.M. Majoie, PhD[3], Jonathan M. Coutinho, PhD[1]

[1] Department of Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands
[2] Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, the Netherlands
[3] Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands

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ABSTRACT

Background

Stroke patients who are transferred to a comprehensive stroke center for endovascular treatment (EVT) often undergo repeated neuroimaging prior to EVT. We evaluated the yield of repeating imaging and its effect on treatment times.

Methods

We included adult patients with a large vessel occlusion (LVO) stroke who were referred to our hospital for EVT by primary stroke centers (2016-2019). We excluded patients who underwent repeated imaging because primary imaging was unavailable, incomplete or of insufficient quality. Outcomes included treatment times and repeated imaging findings.

Results

Of 677 transferred LVO stroke patients, 551 were included. Imaging was repeated in 165/551 patients (30%), mostly because of clinical improvement (86/165 [52%]) or deterioration (40/165 [24%]). Repeated imaging patients had higher door-to-groin-times than patients without repeated imaging (median 43 vs. 27 minutes, adjusted time difference: 20 minutes, 95% CI:15-25). Among patients who underwent repeated imaging because of clinical improvement, the LVO had resolved in 50/86 (58%). In patients with clinical deterioration, repeated imaging led to refrainment from EVT in 3/40 (8%). No symptomatic intracranial hemorrhages (sICH) were identified. Ultimately, 75/165 (45%) of repeated imaging patients underwent EVT, versus 326/386 (84%) of patients without repeated imaging ($p<0.01$).

Conclusions

Neuroimaging was repeated in 30% of LVO stroke patients and resulted in a median treatment delay of 20 minutes. In patients with clinical deterioration, no sICH were detected and repeated imaging rarely changed the indication for EVT. However, in more than half of patients with clinical improvement, the LVO had resolved, resulting in refrainment from EVT.

INTRODUCTION

Endovascular treatment (EVT) is routine care for patients with anterior circulation large vessel occlusion (LVO) acute ischemic stroke (AIS).[1-3] EVT can only be performed in specialized hospitals, so called comprehensive stroke centers (CSC). In most countries, paramedics transport patients with a suspected stroke to the nearest hospital for diagnostic work-up and initiation of intravenous thrombolysis (IVT). Usually, this nearest hospital is not a CSC, but a primary stroke center (PSC). Thus, patients who are eligible for EVT must subsequently be transferred to a CSC.

Upon arrival at the CSC, neuroimaging is often repeated, albeit in varying frequencies.[4-8] Repeated imaging may provide information on change in Alberta Stroke Program Early CT Score (ASPECTS),[6 9 10] thrombus migration, recanalization, and intracranial hemorrhage after IVT. Such findings can be clinically relevant and may result in the decision to refrain from EVT. Repeating imaging may thus reduce the number of futile diagnostic angiographies, and the associated risks of these procedures, such as femoral artery dissections, thromboembolic complications, and anesthesia complications.[11] In addition, avoiding unnecessary EVT procedures reduces healthcare costs. On the other hand, repeating imaging itself also adds healthcare costs and increases contrast medium exposure for patients. Moreover, performing additional imaging delays treatment, which can negatively affect the prognosis of patients.[12] With our study, we aimed to evaluate the diagnostic yield and the treatment delay caused by repeating imaging in LVO stroke patients who are transferred from a PSC for EVT.

MATERIALS AND METHODS

Data will not be made available to other researchers, as no patient approval was obtained for sharing coded data. However, syntax and output files of statistical analyses can be made available on request.

Study design and population

We performed a single-center cohort study, using data of our prospective stroke registry. Our hospital receives EVT referrals from 11 nearby PSCs and has a catchment area for EVT of approximately 3.3 million inhabitants. We included adult patients with AIS due to an LVO, who were primarily presented to a PSC and subsequently referred to our hospital for EVT. We used data of patients referred between January 2016 and June 2019. We excluded patients who underwent repeated imaging because imaging from the referring hospital was unavailable, of insufficient quality, or incomplete, including the necessity to perform CT perfusion in patients who presented more than 6 hours after symptom onset. The study was approved by the medical ethics committee of the Amsterdam UMC, location AMC. The procedures followed were all in accordance with institutional guidelines. All patients eligible for inclusion were sent

a letter with detailed information about the study. The patient or legal representative had the opportunity to deny permission for use of their data via an opt-out form, in accordance with the European Union General Data Protection Regulation.

Definitions, procedures and outcomes

EVT was defined as arterial puncture in the angiography suite, with the objective to perform mechanical thrombectomy with a stent retriever and/or thrombus aspiration. The exact EVT strategy was at the discretion of the interventionist. Time of stroke onset was defined as the time of witnessed symptom onset or, if this was unknown, the time that the patient was last known to be well. All imaging was assessed as part of standard clinical practice.

The National Institutes of Health Stroke Scale (NIHSS) was used to quantify the severity of neurological deficit. If no NIHSS score was reported by the treating physician, it was scored retrospectively as previously published.[13]

Our primary outcome was time from arrival at the CSC to groin puncture (CSC DTGT). Other workflow related outcomes were time from stroke onset to groin puncture (OGT) and time from arrival at the PSC to groin puncture (PSC DTGT). Clinical outcome measures were good functional outcome at 90 days post-stroke, defined as a score of 0-2 on the modified Rankin Scale (mRS), overall shift in mRS score between groups, occurrence of symptomatic intracranial hemorrhage (sICH), and mortality at 90 days post-stroke. Repeated imaging findings were scored separately for non-contrast CT (NCCT) and CT angiography (CTA). On NCCT, the presence or absence of intracranial hemorrhage (ICH) was scored. ICH was defined as symptomatic if the patient died or deteriorated neurologically (an increase of ≥4 points on the NIHSS) as a result of the hemorrhage.[14] On CTA, the presence or absence of an LVO was scored, and its location was compared to PSC imaging (vascular territory and segment). LVO was defined as an occlusion of the intracranial part of the internal carotid artery (ICA), the first segment of the middle cerebral artery (M1), the proximal part of the second segment (after first bifurcation) of the middle cerebral artery (proximal M2), the first segment of the anterior cerebral artery, or the basilar artery. A persistent LVO was defined as an LVO in the same vascular territory on repeated imaging, even if the vascular segment had changed.

Statistical analysis

We compared patients in whom neuroimaging (NCCT and/or CTA) was repeated on arrival at the CSC with patients who did not undergo repeated imaging. Baseline characteristics were compared using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and χ^2 test for categorical variables. Multivariable linear

regression was used for the analyses of treatment times. The analysis of CSC DTGT was adjusted for the following potential confounders (unless reported otherwise, baseline characteristics were measured on arrival at the CSC): age, previous stroke, NIHSS score, location of occlusion on first CTA and presentation outside office hours. For the analyses of OGT and PSC DTGT, we adjusted for age, previous stroke, NIHSS score, location of occlusion on first CTA, presentation outside office hours, and treatment with intravenous thrombolysis (IVT). Binary logistic regression was used for the analyses of good functional outcome, sICH and mortality. Ordinal logistic regression was used to assess the overall shift in mRS score between groups. These regression analyses were adjusted for age, blood pressure, previous stroke, NIHSS score, location of occlusion on first CTA, time of presentation (within or outside office hours), treatment with IVT, and treatment with EVT. For all regression analyses, we imputed missing data using multiple imputation for variables with more than 10% missing values, using the following covariates: age, sex, previous stroke, diabetes, atrial fibrillation, coronary artery disease, blood pressure, baseline NIHSS, location of occlusion, treatment with IVT, treatment with EVT, OGT, PSC DTGT, expanded Treatment In Cerebral Ischemia (eTICI) score after EVT and 90-day mRS. Analyses were performed using SPSS (version 25; SPSS Inc., Chicago, IL, USA).

RESULTS

Within the study period, 677 patients with LVO stroke were transferred from one of the PSCs to our hospital for EVT. Of these, 126 were excluded for the following reasons: primary imaging unavailable, incomplete or of poor quality (n=109), objection to use of data (n=14), and age <18 years (n=3). Therefore, we included 551 patients in the current analysis (Figure 1). Repeated imaging was performed in 165/551 (30%) of these patients. The change in proportion of patients who underwent repeated imaging over time is depicted in Supplemental Figure I. The most common reasons for repeating imaging were clinical improvement (86/165 [52%]) and clinical deterioration (40/165 [24%]). Other reasons are reported in Table 1.

Baseline characteristics for patients with and without repeated imaging are shown in Table 1. In the repeated imaging group, patients more often had received IVT (82% vs. 72%, p=0.01) and presentation outside office hours was less common (49% vs. 64%, p<0.01). Coronary artery disease was less prevalent in the repeated imaging group (9% vs. 21%, p<0.01). There were slightly less ICA and M1 occlusions and slightly more proximal M2 occlusions in the repeated imaging group, although this difference was not statistically significant (Table 1). Patients who underwent repeated imaging because of clinical improvement (86/165 [52%]), had a median change in NIHSS score of -5 between PSC and CSC (IQR: -8 to -2). In patients with clinical deterioration (40/165 [24%]), NIHSS scores had increased by a median of 6 points on arrival at the CSC (IQR: 3 to 9).

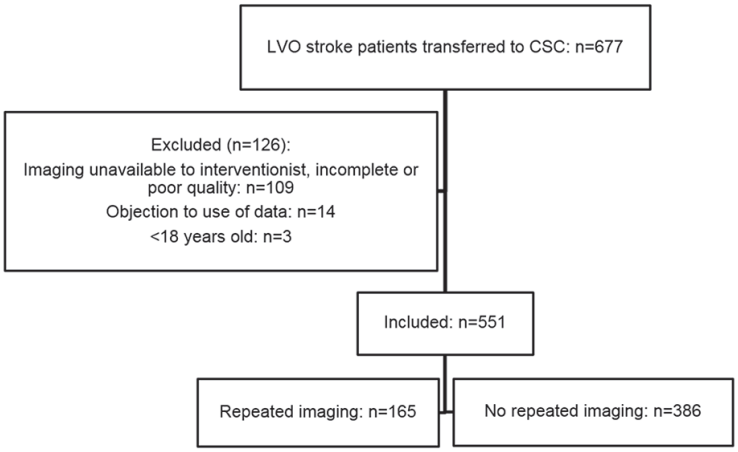

Figure 1. Flow chart patient inclusion. CSC = comprehensive stroke center; LVO = large vessel occlusion.

Patients who underwent repeated imaging had longer CSC DTGT (median 43 vs. 27 minutes, adjusted time difference: 20 minutes, 95% CI: 15-25) and PSC DTGT (median 147 vs. 124 minutes, adjusted time difference: 27 minutes, 95% CI: 14-40). The OGT did not differ between groups (Table 2). The odds of good functional outcome at 90 days post-stroke (mRS 0-2) were higher for the repeated imaging group, but this association dissipated after adjusting for potential confounders (unadjusted OR: 1.57, 95% CI: 1.01-2.44; adjusted OR: 1.10, 95% CI: 0.61-1.99; Supplemental Table I). Symptomatic ICH was numerically less frequent in the repeated imaging group, but this was not statistically significant after adjustment (1% vs. 8%; unadjusted OR: 0.15, 95% CI 0.03-0.62; adjusted OR: 0.29, 95% CI: 0.07-1.31). Other clinical outcomes did not differ between groups (Supplemental Table I).

Among patients with repeated imaging, NCCT was redone at the CSC in 73% and CTA in 75% of patients (both in 48%). The diagnostic yield of repeated imaging is shown in Table 3. Among all patients with a repeated NCCT, only one ICH was found, which was asymptomatic and did not occur in a patient with clinical deterioration. Of all patients with a repeated CTA, 67/124 (54%) had a persistent LVO, 11/67 (16%) of which had migrated to a more distal segment. One LVO was found in a new vascular territory. In 57/124 (46%) of patients, the LVO had resolved. In patients with clinical improvement, i.e. with a decrease in NIHSS, the LVO had resolved more often on repeated imaging ($p<0.01$; Supplemental Figure II). When analyzed separately, in patients who underwent repeated CTA because of clinical improvement, the LVO had resolved in 50/86 (58%) of patients. In patients who underwent repeated CTA because of clinical deterioration, CTA showed that the LVO had resolved in 3/13 (23%) of patients (Table 3). In the remaining 27 patients with clinical deterioration, CTA was not repeated.

Table 1. Baseline characteristics

Characteristic[1]	Repeated imaging (n=165)	No repeated imaging (n=386)	p value
Age, years – mean ± SD	71 ± 15.3	70 ± 13.3	0.40
Male sex – no./total (%)	79/165 (48%)	200/386 (52%)	0.40
Hypertension – no./total (%)	68/164 (41%)	150/382 (39%)	0.63
Diabetes mellitus – no./total (%)	21/164 (13%)	56/382 (15%)	0.57
Atrial fibrillation – no./total (%)	34/164 (21%)	95/382 (25%)	0.30
Coronary artery disease – no./total (%)	14/164 (9%)	80/382 (21%)	<0.01
Previous stroke – no./total (%)	30/164 (18%)	66/382 (17%)	0.78
Pre-stroke mRS score[2] – median (IQR)	1 (0-1)	1 (0-1)	0.72
Systolic blood pressure – mean ± SD	150 ± 28.1	148 ± 23.9	0.37
Diastolic blood pressure – mean ± SD	83 ± 17.0	82 ± 16.5	0.65
NIHSS score at PSC arrival[3] – median (IQR)	11 (7-15)	13 (9-17)	<0.01
NIHSS score at CSC arrival[4] – median (IQR)	9 (4-17)	16 (10-20)	<0.01
Intracranial occlusion site (on PSC imaging) – no./total (%)			0.07
ICA	26/164 (16%)	76/386 (20%)	
M1	90/164 (55%)	228/386 (59%)	
Proximal M2	31/164 (19%)	38/386 (10%)	
Anterior cerebral artery	0/164 (0%)	1/386 (0%)	
Basilar artery	13/164 (8%)	31/386 (8%)	
No LVO (misread by radiologist at PSC)	4/164 (2%)	12/386 (3%)	
Reason for repeating imaging – no./total (%)			
Clinical improvement	86/165 (52%)	NA	-
Clinical deterioration	40/165 (24%)	NA	-
Additional imaging characteristics for assessing indication for EVT[5]	11/165 (7%)	NA	-
Other	6/165 (4%)	NA	-
Reason not recorded	22/165 (13%)	NA	-
Presentation outside office hours – no./total (%)	74/150 (49%)	233/365 (64%)	<0.01
Time from stroke onset to arrival at PSC, minutes[6] – median (IQR)	50 (30-81)	58 (32-95)	0.14
Treatment with IVT – no./total (%)	135/165 (82%)	276/386 (72%)	0.01

ASPECTS = Alberta Stroke Program Early CT Score; CSC = comprehensive stroke center; CTA = computed tomography angiography; EVT = endovascular treatment; ICA = intracranial part of internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; LVO = large vessel occlusion; M1 = first segment of the middle cerebral artery; M2 = proximal part of the second segment (after first bifurcation) of the middle cerebral artery; mRS = modified Rankin Scale; NA = not applicable; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale; no. = number; PSC = primary stroke center; SD = standard deviation.

[1]All baseline characteristics were measured on arrival at the CSC, unless reported otherwise.

[5]E.g. ASPECTS, collaterals, core/penumbra ratio <6 hours.

Number of missing values: [2]350; [3]28; [4]4; [6]178.

Table 2. EVT related outcomes

	Repeated imaging (n=165)	No repeated imaging (n=386)	p value
Groin puncture – no./total (%)	75/165 (45%)	326/386 (84%)	<0.01
Persistent LVO, ≥1 MT attempt(s)	57/165 (35%)	261/386 (68%)	<0.01
Persistent LVO, no access to occlusion location	12/165 (7%)	35/386 (9%)	0.49
LVO resolved, angiography only[1]	6/165 (4%)	29/386 (8%)	0.09

Subgroup: patients who underwent groin puncture

	Repeated imaging (n=75)	No repeated imaging (n=326)	Unadjusted β (95% CI)	Adjusted β (95% CI)
CSC door-to-groin time[2] – median (IQR)	43 (35-59)	27 (19-37)	19.9 (14.7 - 25.1)	20.0 (14.8-25.3)[5]
PSC door-to-groin time[3] – median (IQR)	147 (118-190)	124 (104-154)	22.6 (9.6-35.6)	26.9 (14.2-39.6)[6]
Onset-to-groin time[4] – median (IQR)	198 (167-261)	195 (156-249)	11.1 (-9.6 to 31.9)	15.0 (-6.0 to 35.9)[6]

ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; CSC = comprehensive stroke center; CTA = computed tomography angiography; EVT = endovascular treatment; IQR = interquartile range; LVO = large vessel occlusion; MT = mechanical thrombectomy; no. = number; PSC = primary stroke center.

[1]Among patients who underwent a cerebral angiography only, one periprocedural complication was reported (femoral pseudoaneurysm, in the repeated imaging group).

[5]Adjusted for: age, previous stroke, NIHSS score, location of occlusion on first CTA, presentation outside office hours.

[6]Adjusted for: age, previous stroke, NIHSS score, location of occlusion on first CTA, presentation outside office hours, treatment with intravenous thrombolysis.

Number of missing values: [2]27; [3]55; [4]17.

Table 3. Repeated imaging findings

Imaging modality	All patients (n=165)	Clinical improvement[1] (n=86)	Clinical deterioration[2] (n=40)
NCCT[3]			
Symptomatic ICH	0/120 (0%)	0/50 (0%)	0/38 (0%)
Asymptomatic ICH	1/120 (1%)	0/50 (0%)	0/38 (0%)
CTA[4]			
Persistent LVO	67/124 (54%)	36/86 (42%)	10/13 (77%)
Same segment	55/124 (44%)	28/86 (33%)	8/13 (62%)
Distal migration	11/124 (9%)	8/86 (9%)	2/13 (15%)
New vascular territory	1/124 (1%)	0/86 (0%)	0/13 (0%)
LVO resolved	57/124 (46%)	50/86 (58%)	3/13 (23%)

CTA = computed tomography angiography; ICH = intracranial hemorrhage; IQR = interquartile range; LVO = large vessel occlusion; NCCT = non-contrast computed tomography.
[1]Median Δ NIHSS score between PSC and CSC: -5 (-8 to -2)
[2]Median Δ NIHSS score between PSC and CSC: 6 (3 to 9)
[3]NCCT was repeated in 120/165 patients (73%); 50/86 (58%) of patients with clinical improvement and 38/40 (95%) of patients with clinical deterioration.
[4]CTA was repeated in 124/165 patients (75%); all patients with clinical improvement and 13/40 (33%) of patients with clinical deterioration.

Ultimately, 75/165 (45%) of the repeated imaging group underwent EVT, versus 326/386 (84%) of patients without repeated imaging. In the repeated imaging group, less patients underwent a cerebral angiography only, although this difference was not statistically significant (4% vs. 8%, p=0.09; Table 2). Among patients who underwent an angiography only (n=35), one periprocedural complication (2.9%) was reported, which occurred in the repeated imaging group. This complication was a femoral pseudoaneurysm, which was treated with an ultrasound-guided thrombin injection and was resolved without sequelae. Reasons for refraining from groin puncture are reported for both groups in Supplemental Table II. In 61/165 (37%) of patients who underwent repeated imaging, the findings on repeated imaging resulted in, or contributed to the decision to refrain from EVT. This was the case for 49/86 (57%) of patients with clinical improvement and 3/40 (8%) of patients with clinical deterioration.

DISCUSSION

In this single-center cohort study of LVO stroke patients who were transferred for EVT, neuroimaging was repeated in 30% of patients on arrival at the CSC, resulting in a median treatment delay of 20 minutes. In patients with clinical deterioration, repeated imaging rarely resulted in the decision to refrain from EVT and no sICH was detected. On the other hand, in more than half of patients with clinical improvement, the LVO had resolved, abolishing the need for EVT altogether.

Reports on the frequency with which imaging is repeated in patients transferred for EVT vary substantially. Venema et al. reported that in CSCs in the Netherlands, on average, NCCT is repeated in 6% and CTA in 5% of transferred patients prior to EVT.[7] However, this study excluded transferred patients in whom EVT was ultimately not performed, probably leading to an underestimation of the true frequency of repeating imaging in LVO stroke patients. Other studies report repeated imaging rates of up to 86% of patients, or even in all transferred patients as standard practice.[4-6 8] Little has been reported about the diagnostic yield of repeated imaging in patients transferred for EVT or its effects on workflow. Several previous studies have found that presentation of patients directly to the angiography suite, instead of to the emergency room, substantially reduces DTGT.[15-17] For instance, Jadhav et al. found that in patients transferred for EVT, DTGT was reduced by 59 minutes when the emergency room was bypassed.[17] The authors hypothesized that this was partly due to a reduction in repeating imaging. However, presenting patients directly to the angiography suite requires around-the-clock availability of an angiography suite and personnel, which is often not feasible and increases healthcare costs. Compared to previous literature, the percentage of patients who ultimately did not undergo EVT was relatively low in our population. Two previous studies have reported 41% and 45% of futile interhospital transfers,[4 8] while in our study this was the case for 27% of patients. Potential explanations for this finding could be longer travel times or different selection methods for transferring patients for EVT.

We found several baseline imbalances that should be noted. First, NIHSS scores on arrival at the CSC were lower for the repeated imaging patients. Most likely, this is because clinical improvement was a common reason for CSC physicians to repeat imaging. Interestingly, NIHSS scores at the PSC were also lower for the repeated imaging group. This could be because the repeated imaging group contained slightly more patients with an M2 occlusion, which are associated with less severe neurological deficits than more proximally located LVOs, and which more often show early recanalization after IVT[18]. Another possible explanation is that CSC physicians may have been more inclined to repeat imaging in patients with less severe neurological deficits, independent of the change in NIHSS score. Second, the percentage of patients that received IVT was higher in the repeated imaging group.

It seems plausible that this is because IVT caused part of the LVOs to resolve, resulting in clinical improvement, which again was a common reason for CSC physicians to repeat imaging. Third, a history of coronary artery disease was less prevalent in the repeated imaging group. A possible explanation for this finding could be that patients with coronary artery disease, and thus atherosclerosis, more often have an atherosclerotic etiology of their stroke. Previous studies have reported that atherosclerotic stroke is more often refractory to IVT,[19 20] which may have resulted in less clinical improvement and therefore less often repeated imaging.

Several limitations to our study warrant mentioning. First, imaging was not assessed by a core lab, but only assessed as part of standard clinical practice. Some imaging characteristics, such as ASPECTS score, collateral score, and core/penumbra volumes on CT perfusion therefore were not systematically scored. These imaging characteristics may have influenced decision making on whether or not to perform EVT. Although CT perfusion volumes are strictly only indicated for patients in the 'late' time window - who were excluded from our analyses if the necessity of obtaining CT perfusion imaging was the sole reason for repeating imaging - we cannot exclude the possibility that CT perfusion characteristics nonetheless affected treatment decisions. However, if these imaging characteristics were reported as a reason for refraining from EVT, we included this in our results. Second, it is important to note that this study took place in the Netherlands, which is a densely populated country in which hospitals are located relatively close to one another and which has an overall good infrastructure. As a result, both transfer times and times between acquisition of primary imaging and repeated imaging were relatively short. Consequently, our findings should be extrapolated with caution to hospital systems with longer travel times between centers. Finally, for three variables, we had relatively high numbers of missing values: pre-stroke mRS (64%), mRS at 90 days post-stroke (32%) and time of patient arrival at the PSC (23%). We tried to minimize the impact of the missing data on our analyses by using multiple imputation.

Future research on this topic may focus on developing a prediction model for early recanalization, in order to help avoid futile interhospital transfer.

In conclusion, patients transferred to our CSC for EVT underwent repeated neuroimaging in 30% of cases. Repeating imaging delayed treatment by approximately 20 minutes. In patients with clinical deterioration, the yield of repeating imaging was low and no sICH prior to EVT were identified. In patients with clinical improvement, repeated imaging showed that the LVO had resolved in 58% of cases and thereby resulted in refrainment from EVT. Based on our findings, repeating neuroimaging does not seem beneficial in patients with clinical deterioration, but is very useful in patients with clinical improvement, since it helps avoid futile diagnostic angiographies in more than half of this population

DISCLOSURES

Charles Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation and Stryker, outside the submitted work (paid to institution). In addition, Charles Majoie is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Yvo Roos reports stockholdings from Nico.lab outside the submitted work. Henk Marquering is co-founder and shareholder of Nico.lab. Jonathan Coutinho reports grants from Medtronic outside the submitted work. The other authors report no conflicts.

CONTRIBUTION STATEMENT

All authors contributed to the study conception and design. Material preparation, data collection and analyses were performed by Laura van Meenen and Jonathan Coutinho. The first draft of the manuscript was written by Laura van Meenen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11-20
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/ american stroke association. *Stroke*. 2018;49:e46-e110
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731
4. Fuentes B, Alonso de Lecinana M, Ximenez-Carrillo A, Martinez-Sanchez P, Cruz-Culebras A, Zapata-Wainberg G, et al. Futile interhospital transfer for endovascular treatment in acute ischemic stroke: The madrid stroke network experience. *Stroke*. 2015;46:2156-2161
5. Sun CH, Connelly K, Nogueira RG, Glenn BA, Zimmermann S, Anda K, et al. Aspects decay during inter-facility transfer predicts patient outcomes in endovascular reperfusion for ischemic stroke: A unique assessment of dynamic physiologic change over time. *J Neurointerv Surg*. 2015;7:22-26
6. Boulouis G, Siddiqui KA, Lauer A, Charidimou A, Regenhardt RW, Viswanathan A, et al. Immediate vascular imaging needed for efficient triage of patients with acute ischemic stroke initially admitted to nonthrombectomy centers. *Stroke*. 2017;48:2297-2300
7. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V, et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923-930
8. Sablot D, Dumitrana A, Leibinger F, Khlifa K, Fadat B, Farouil G, et al. Futile inter-hospital transfer for mechanical thrombectomy in a semi-rural context: Analysis of a 6-year prospective registry. *J Neurointerv Surg*. 2019;11:539-544
9. Mokin M, Gupta R, Guerrero WR, Rose DZ, Burgin WS, Sivakanthan S. Aspects decay during inter-facility transfer in patients with large vessel occlusion strokes. *J Neurointerv Surg*. 2017;9:442-444
10. Purrucker JC, Mattern N, Herweh C, Mohlenbruch M, Ringleb PA, Nagel S, et al. Electronic alberta stroke program early ct score change and functional outcome in a drip-and-ship stroke service. *J Neurointerv Surg*. 2020;12:252-255
11. Kaufmann TJ, Huston J, 3rd, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: Evaluation of 19,826 consecutive patients. *Radiology*. 2007;243:812-819
12. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
13. Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the nih stroke scale. *Stroke*. 2000;31:858-862
14. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The heidelberg bleeding classification: Classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981-2986
15. Mendez B, Requena M, Aires A, Martins N, Boned S, Rubiera M, et al. Direct transfer to angio-suite to reduce workflow times and increase favorable clinical outcome. *Stroke*. 2018;49:2723-2727

16. Ribo M, Boned S, Rubiera M, Tomasello A, Coscojuela P, Hernandez D, et al. Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke. *J Neurointerv Surg*. 2018;10:221-224
17. Jadhav AP, Kenmuir CL, Aghaebrahim A, Limaye K, Wechsler LR, Hammer MD, et al. Interfacility transfer directly to the neuroangiography suite in acute ischemic stroke patients undergoing thrombectomy. *Stroke*. 2017;48:1884-1889
18. Zangerle A, Kiechl S, Spiegel M, Furtner M, Knoflach M, Werner P, et al. Recanalization after thrombolysis in stroke patients: Predictors and prognostic implications. *Neurology*. 2007;68:39-44
19. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabin J. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke*. 2004;35:486-490
20. Forlivesi S, Bovi P, Tomelleri G, Micheletti N, Carletti M, Moretto G, et al. Stroke etiologic subtype may influence the rate of hyperdense middle cerebral artery sign disappearance after intravenous thrombolysis. *J Thromb Thrombolysis*. 2017;43:86-90

SUPPLEMENTAL MATERIAL

Supplemental Table I. Clinical outcomes

	Repeated imaging, n=165	No repeated imaging, n=386	Unadjusted OR (95% CI)	Adjusted OR[3] (95% CI)
Functional independence (90 day mRS 0-2) – no./total (%)	45/95 (47%)	113/279 (41%)	1.57 (1.01 – 2.44)	1.10 (0.61 – 1.99)
mRS score at 90 days[1] – median (IQR)	3 (1-6)	3 (1-6)	1.55[2] (0.95 – 2.54)	1.14[2] (0.70 – 1.88)
Symptomatic ICH – no./ total (%)	2/164 (1%)	30/383 (8%)	0.15 (0.03 – 0.62)	0.29 (0.07 – 1.31)
Mortality at 90 days – no./ total (%)	31/95 (33%)	78/279 (28%)	0.94 (0.61 – 1.46)	0.82 (0.45 – 1.50)

CI = confidence interval; ICH = intracranial hemorrhage; IQR = interquartile range; mRS = modified Rankin scale; OR = odds ratio.

Number of missing values: [1]177.

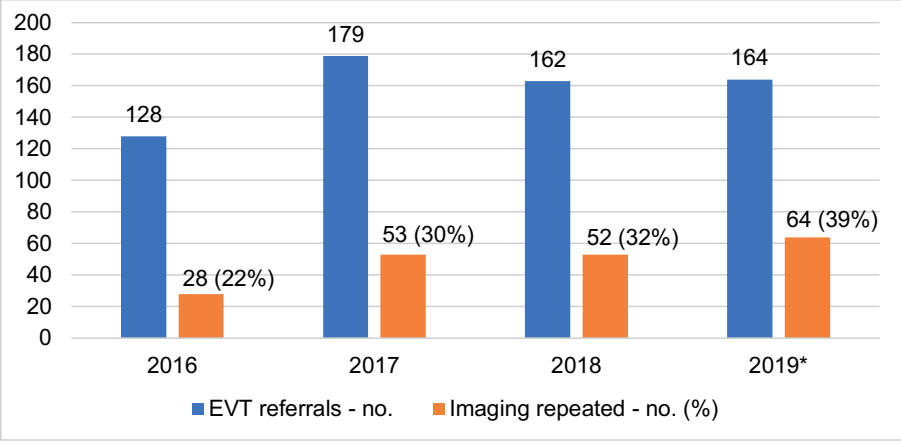
[2]Odds of 1-point shift towards a favorable outcome on the mRS for the repeated imaging group.

[3]All analyses were adjusted for: age, blood pressure, previous stroke, NIHSS score, location of occlusion on first CTA, time of presentation (within or outside office hours), treatment with IVT, treatment with EVT.

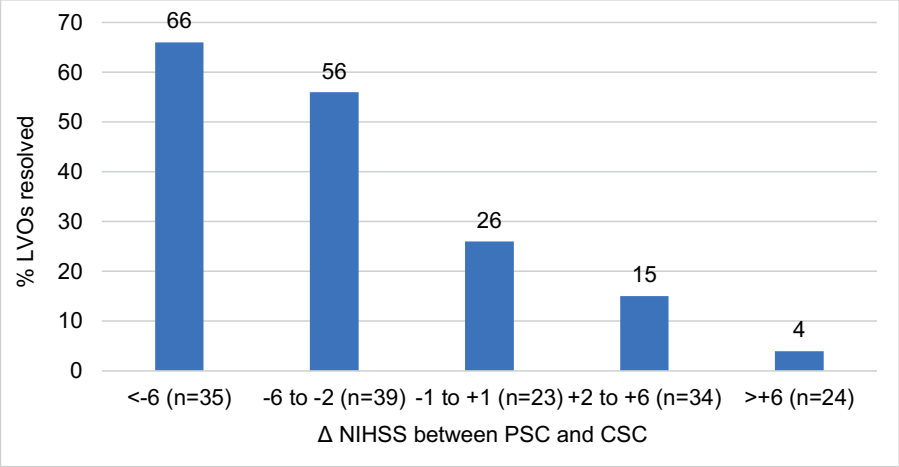
Supplemental Table II. Reasons for refraining from EVT

	Repeated imaging (n=90)	No repeated imaging (n=60)	p value
Reason for refraining from EVT			<0.01
Clinical characteristics – no./total (%)	21/90 (23%)	37/60 (62%)	
Combination of clinical and radiological characteristics – no./total (%)	6[1]/90 (7%)	9/60 (15%)	
Radiological characteristics – no./total (%)	63[2]/90 (70%)	13/60 (22%)	
LVO resolved	55/90 (61%)	0/60 (0%)	
No LVO on PSC imaging[3]	0/90 (0%)	10/60 (17%)	
Unfavorable imaging characteristics[4]	3/90 (3%)	2/60 (3%)	
EVT not technically feasible	3/90 (3%)	1/60 (2%)	
Other	2/90 (2%)	1/60 (2%)	

ASPECTS = Alberta stroke program early CT score; EVT = endovascular treatment; LVO = large vessel occlusion; no. = number; PSC = primary stroke center.
[1]In 3/6 patients, repeated imaging contributed to the decision to refrain from EVT; in the other 3/6 patients, the imaging factors contributing to the decision to refrain from EVT were (also) visible on PSC imaging.
[2]In 58/63 patients, repeated imaging contributed to the decision to refrain from EVT; in the other 5/63 patients, the imaging factors contributing to the decision to refrain from EVT were (also) visible on PSC imaging.
[3]Upon reassessment by the neuro-interventional radiologist at the CSC
[4]Low ASPECTS, poor collateral status and/or unfavorable CT perfusion characteristics.



Supplemental Figure I. Referrals for EVT per year during the study period. Number of referrals (blue) and number and percentage of patients with repeated imaging (red) are reported for our hospital during the study period (January 2016 – June 2019). *For 2019, data were extrapolated for the remainder of the year. EVT = endovascular treatment; no. = number.



Supplemental Figure II. Percentage of resolved LVOs per Δ NIHSS sub group. The percentage of LVOs that were resolved on repeated CTA related to the change in NIHSS score between PSC and CSC. A negative Δ NIHSS value signifies clinical improvement; a positive value means clinical deterioration. The lower the Δ NIHSS, the higher the percentage of patients with a resolved LVO on repeated imaging ($p<0.01$). CSC = comprehensive stroke center; CTA = computed tomography angiography; LVO = large vessel occlusion; NIHSS = National Institutes of Health Stroke Scale; PSC = primary stroke center.

PART II

FUTURE WORKFLOW

CHAPTER 6

DETECTION OF LARGE VESSEL OCCLUSION STROKE IN THE PREHOSPITAL SETTING: ELECTROENCEPHALOGRAPHY AS A POTENTIAL TRIAGE INSTRUMENT

Laura C.C. van Meenen, MD, MSc[1]*, Maritta N. van Stigt, MSc[2]*, Arjen Siegers, MD, MSc[3], Martin D. Smeekes, MD, MSc[4], Joffry A.F. van Grondelle, BSc[3], Geertje Geuzebroek, BSc[3], Henk A. Marquering, PhD[5,6], Charles B.L.M. Majoie, MD, PhD[6], Yvo B.W.E.M. Roos, MD, PhD[1], Johannes H.T.M. Koelman, MD, PhD[2], Wouter V. Potters, PhD[1,2], Jonathan M. Coutinho, MD, PhD[1]

1. Department of Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands
2. Department of Clinical Neurophysiology, Amsterdam UMC, University of Amsterdam, the Netherlands
3. Ambulance Amsterdam, Amsterdam, the Netherlands
4. Emergency Medical Services North-Holland North, Alkmaar, the Netherlands
5. Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, the Netherlands
6. Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands

*These authors contributed equally to the manuscript.

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ABSTRACT

A reliable and fast instrument for prehospital detection of large vessel occlusion (LVO) stroke would be a game-changer in stroke care, because it would enable direct transportation of LVO stroke patients to the nearest comprehensive stroke center for endovascular treatment. This strategy would substantially improve treatment times, and thus clinical outcomes of patients. Here, we outline our view on the requirements of an effective prehospital LVO detection method, namely: high diagnostic accuracy; fast application and interpretation; user-friendliness; compactness; and low costs. We argue that existing methods for prehospital LVO detection, including clinical scales, mobile stroke units and transcranial Doppler, do not fulfill all criteria, hindering broad implementation of these methods. Instead, electroencephalography (EEG) may be suitable for prehospital LVO detection, since in-hospital studies have shown that quantification of hypoxia-induced changes in the EEG signal have good diagnostic accuracy for LVO stroke. Although performing EEG measurements in the prehospital setting comes with challenges, solutions for fast and simple application of this method are available. Currently, the feasibility and diagnostic accuracy of EEG in the prehospital setting are being investigated in clinical trials.

INTRODUCTION

Acute ischemic stroke (AIS) is one of the leading causes of death and disability, affecting around 9 million people per year worldwide.[1] Approximately a quarter to a third of AIS patients has a large vessel occlusion (LVO) and is thus potentially eligible for endovascular treatment (EVT).[2,3] It is of vital importance that EVT is initiated as soon as possible, especially in patients in the early time window.[4-6] In most countries, patients with a suspected stroke are transported by paramedics to the nearest hospital for diagnostic work-up and, if indicated, initiation of IVT. If this nearest hospital is a primary stroke center (PSC) and the patient is diagnosed with an LVO stroke, the patient must again be transferred by paramedics to a comprehensive stroke center (CSC) for EVT. This so-called 'drip-and-ship' model, which is schematically depicted in Figure 1A, delays initiation of EVT by 40 to 106 minutes, thereby substantially decreasing the chance of good functional outcome.[7,8] Despite the clear disadvantages of the drip-and-ship model, it is widely used because directly presenting all patients with a suspected stroke to a CSC – the so-called mothership model – would overburden these hospitals. Moreover, centralizing all stroke care would lead to longer initial travel times, which puts a strain on ambulance services and, importantly, could delay the start of IVT. This latter effect would be particularly harmful for AIS patients without an LVO.[10]

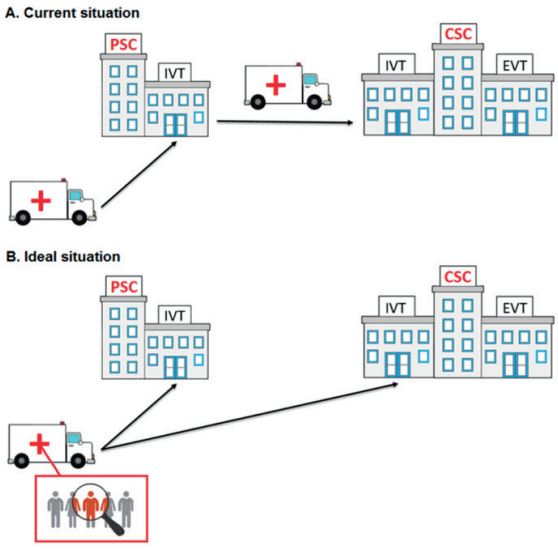

Figure 1. Illustrations of the 'drip-and-ship' model and the 'ideal' model. A. The 'drip-and-ship' model: suspected stroke patients are transported to the nearest PSC, and patients eligible for EVT are subsequently transferred to a CSC. B. The 'ideal' model: patients with a large vessel occlusion are identified in the prehospital setting and brought directly to a CSC, while all other suspected stroke patients are brought to a PSC. CSC = comprehensive stroke center; EVT = endovascular treatment; IVT = intravenous thrombolysis; PSC = primary stroke center.

Ideally, patients with an LVO stroke can be identified in the prehospital setting, so that these patients can be transported directly to the nearest CSC for EVT, while all other suspected stroke patients are brought to a PSC, where IVT can be initiated (Figure 1B). Toward future development and implementation of an effective prehospital LVO detection instrument, we describe our views on the required characteristics of such an instrument, lessons that can be learned from cardiology, and review previously studied LVO detection methods. Finally, we discuss ongoing research and future directions in this field, and propose that electroencephalography (EEG) may be suitable for prehospital LVO detection.

REQUIREMENTS OF AN EFFECTIVE PREHOSPITAL LVO DETECTION METHOD

Our views on the requirements of an effective prehospital LVO detection method are summarized in Table 1. First and foremost, a high diagnostic accuracy is essential. Both sensitivity and specificity are important in this respect. A high sensitivity is required because a false negative result would mean that a patient with an LVO stroke is not directly transported to a CSC, resulting in time loss and worse clinical outcome. A high specificity is also important, because false positive cases would put an unnecessary burden on CSCs and ambulance services, and delay initiation of IVT for these patients. Furthermore, with a triage method with high specificity, a positive result would warrant the operating team to be alerted and the angiography suite to be prepared before patient arrival, which in itself could further lower time to treatment. Second, a prehospital LVO detection method must be applicable fast. Inevitably, triaging will take up time, but the time saved by accurate patient selection should outweigh this short prehospital delay. Third, it is important that the method is user-friendly. Since only approximately 3% of all emergency ambulance transports concerns neurological emergencies,[11, 12] ambulance paramedics have a relatively low exposure to this population. As a result, elaborate triage strategies are difficult to implement and a relatively simple method should be pursued. Fourth, a prehospital LVO detection instrument should be sufficiently compact that it can be stored in every ambulance. Ambulance paramedics should also be able to take the instrument out of the ambulance, for example inside a patient's house, since that is where the triage often takes place. Finally, the instrument should be relatively affordable, so that broad implementation is feasible in all countries where endovascular treatment is available.

LESSONS FROM CARDIOLOGY

In selecting or developing a method suitable for prehospital LVO detection, we may learn from interventional cardiology, which has dealt with similar logistical dilemmas in the past. Electrocardiography (ECG) is widely used by ambulance paramedics as a triage instrument in patients with suspected myocardial infarction Patients with a

high likelihood of requiring percutaneous coronary intervention (PCI) are transported directly to the nearest PCI capable hospital.[13] On arrival, the emergency department is bypassed and the patient is brought directly to the catheterization room to initiate treatment. This model drastically improves treatment times and thereby clinical outcome.[14, 15] ECG can be performed in the prehospital setting in minutes and can be interpreted by ambulance paramedics with high sensitivity and specificity.[16, 17] Furthermore, it can be implemented in every ambulance and is relatively affordable.

Table 1. Requirements of an effective prehospital LVO detection method

	Requirement	Purpose
1	High diagnostic accuracy	Limiting the number of false positives and false negatives
2	Fast application and interpretation	Limiting the treatment delay caused by application of the triage method
3	User-friendly	Enabling paramedics with low exposure to stroke population to correctly apply instrument and interpret results
4	Compact	Permitting storage in every ambulance
5	Relatively affordable	Enabling broad implementation in all countries where endovascular treatment is available

PREVIOUSLY STUDIED LVO DETECTION METHODS

The need for a prehospital instrument for LVO detection has been recognized worldwide and several research groups have previously examined different methods for this purpose. Advantages and disadvantages of these methods are discussed below and are summarized in Table 2.

Clinical scales

Multiple clinical scales, containing items for scoring the severity of neurological deficit, have been developed for the purpose of LVO detection. Clinical scales tick off some of the requirements for an effective prehospital LVO detection method, since they are compact and can be applied fast (requirements 4 and 2; Table 1). However, the diagnostic accuracy of clinical scales is relatively low. Most scales either have high sensitivity or high specificity, depending on the cut-off value that is used, but not both.[18-21] Several detailed overviews of diagnostic accuracy of clinical scales have been published previously.[18-20] Most of these scales have also only been validated in an in-hospital setting,[18-20] and thus the external validity for a prehospital setting has not been properly assessed. Furthermore, several studies that have examined the accuracy of clinical scales for LVO detection have excluded patients with an eventual diagnosis other than AIS, such as stroke-mimicking conditions or intracerebral hemorrhage, which makes their findings difficult to extrapolate to a population of suspected stroke patients.[20] Scales that have been tested in the prehospital setting often have low specificity for LVO stroke.[20] This could be explained by the relatively low exposure of ambulance paramedics to patients

with suspected stroke, which makes it difficult to reliably apply clinical scales. As a result, development of a clinical scale with high diagnostic accuracy in the prehospital setting is challenging, and training ambulance paramedics in the correct application of such a clinical scale is time consuming and costly. Altogether, clinical scales fail to meet two essential requirements for an effective prehospital LVO detection method: high diagnostic accuracy and user-friendliness (requirements 1 and 3; Table 1).

Table 2. Advantages and disadvantages of previously studied LVO detection methods

	1. High diagnostic accuracy	2. Fast application and interpretation	3. User-friendly	4. Compact	5. Affordable	Other advantages/ disadvantages
Clinical scales	–	+	–	+	+	
Mobile stroke units	+	+	–	–	–	- Specifically trained team - Futile deployment common
Telemedicine	?	+	+	+	+	- Privacy and security issues
Transcranial Doppler	+[1]	–	–	+	+	- Prehospital validation lacking
VIPS	?	+	+	+	?	- Prehospital validation lacking
EEG						
Wet electrode EEG	?	–	–	+	+	- Prehospital validation lacking
Dry electrode EEG	+[2]	+	+	+	+	- Prehospital validation lacking

EEG = electroencephalography; VIPS = volumetric impedance phase shift spectroscopy; + = yes; – = no; ? = unknown.

[1]Diagnostic accuracy has only been examined in an in-hospital setting.

[2]Diagnostic accuracy has only been examined in an in-hospital setting, and was only high when combined with clinical data.

Mobile stroke units

Another method for prehospital LVO detection that has been explored, is equipping selected ambulances – so called 'mobile stroke units' (MSUs) - with an imaging system for performing non-contrast CT and CT angiography to diagnose LVO stroke and, in some studies, initiate IVT.[23] Obviously, this method has an optimal diagnostic accuracy. A recent study also found that deployment of MSUs was associated with lower time to EVT.[24] However, there are substantial concerns regarding the efficacy and cost-effectiveness of this method. MSUs require a team of specifically trained personnel, often including a CT technician and a vascular neurologist.[23] If remote assessment of the imaging is used, wireless connectivity may be problematic, especially in rural

areas.[25] Furthermore, since only approximately half of suspected stroke patients have an AIS, [26] deployment of an MSU is often futile. The costs of equipping one MSU are estimated between US $497,604 and $955,666, and the annual costs of one operational unit have been estimated at $946,818.[27] The high costs and personnel requirements make broad implementation of MSUs practically impossible. Since this method is expensive, complex and cannot be implemented in every ambulance, it fails to meet three important requirements for an effective prehospital LVO detection method (requirements 3, 4 and 5; Table 1).

Telemedicine

Telemedicine enables evaluation of suspected stroke patients by a remote physician, often using audio and video connection and/or transfer of clinical data.[28] Several telemedicine techniques have been shown to be feasible in the prehospital setting and are widely accepted by ambulance paramedics and physicians.[29, 30] However, there is limited data on the accuracy of prehospital identification of AIS by telemedicine.[29, 30] More importantly, the diagnostic accuracy of telemedicine for detection of LVO stroke is unknown. Therefore, at this time, telemedicine does not meet the most essential requirement for an effective LVO detection method: high diagnostic accuracy (requirement 1; Table 1). Although studies have shown a decrease in time to IVT, [30, 31] little is known about the effect of telemedicine on EVT treatment times.[28] One observational study found that clinical outcome after EVT for patients selected with telemedicine was comparable to the outcome of patients directly admitted to a CSC.[32] However, the absence of a between-group difference in clinical outcome in this study may also be due to its relatively small sample size. Implementation of a triage method using telemedicine may further be complicated due to privacy and security issues.[33]

Transcranial Doppler

Transcranial Doppler (TCD), which uses ultrasound waves for direct measurement of the cerebral blood flow, has been proposed as a method for prehospital LVO detection. Preliminary in-hospital studies have shown that TCD can detect LVO stroke with high sensitivity and specificity in suspected AIS patients.[34-36] A TCD device is also relatively compact and affordable,[35, 36] ticking off some important requirements (requirements 1, 4 and 5; Table 1). However, feasibility of using TCD in the prehospital setting is limited due to long measurement times and user-dependence in both application and interpretation.[34-36] Therefore, this method is currently not fast nor user-friendly (requirements 2 and 3; Table 1). To minimize these issues, new TCD devices have been developed, using automated algorithms for occlusion detection. The SONAS (BURL Concepts Inc., USA) device utilizes ultrasound microbubbles as acoustic tracers to evaluate asymmetry in cerebral perfusion.[37] Its accuracy for LVO detection and technical and logistical feasibility are currently being investigated in an in-hospital clinical trial (clinicaltrials.gov: NCT03897153). The Lucid Robotic System

(Neural Analytics Inc., USA) is designed to be a fully autonomous TCD device for diagnosis of neurovascular diseases including stroke. Interim, non-peer reviewed results suggest a high sensitivity and specificity for LVO stroke in suspected stroke patients.[38] However, its efficacy and feasibility for LVO detection in the prehospital setting are currently unknown.

Volumetric impedance phase shift spectroscopy

Volumetric impedance phase shift spectroscopy (VIPS), which detects asymmetry in the cerebral bioimpedance pattern, has also been proposed as a prehospital LVO detection method, although it has not yet been evaluated in the prehospital setting. The VIPS device is compact, fast and user-friendly (requirements 2, 3 and 5; Table 1).[39] Data from a preliminary study showed that VIPS could be used to identify severe strokes within a group of suspected stroke patients with high sensitivity and specificity, but it did not discriminate between ischemic and hemorrhagic stroke.[39] However, little is known about the diagnostic accuracy of VIPS for LVO stroke (requirement 1; Table 1). Additionally, the future cost of the device is unknown (requirement 4; Table 1).[39]

Electroencephalography

Electroencephalography (EEG) measures electrical brain activity through electrodes placed on the scalp. Because of its sensitivity to cerebral hypoxia, it is used for monitoring during carotid endarterectomy surgery. Multiple studies have shown that unilateral hemispheric hypoxia almost immediately results in EEG signal changes that predict intraoperative stroke with high specificity.[40, 41] Research of EEG in patients with AIS has mainly focused on prediction of functional outcome and differentiation between AIS patients and healthy controls. For the latter, several quantitative EEG (qEEG) measures have been proposed. First, slowing of the EEG signal has been described as a sign of hemispheric hypoxia (i.e. a decrease in higher frequencies and an increase in lower frequencies; Figure 2A).[42] EEG slowing can be quantified by measures sensitive to the power of the low frequency delta band relative to higher frequency bands. Multiple case-control studies found a higher delta/alpha ratio – indicating a slower EEG – in AIS patients compared to healthy controls.[43-45] Changes in the power spectrum can also be compared between the affected and unaffected hemisphere (Figure 2B). The Brain Symmetry Index (BSI) quantifies the difference in mean hemispheric power, and has been shown to discriminate between AIS patients and healthy controls.[46, 47] Another qEEG measure for cerebral hypoxia is functional brain connectivity, which can be quantified by the degree of phase synchronization between pairs of EEG signals.[49, 50] One case-control study found reduced synchronization – indicating lower connectivity – in both the ipsi- and contralesional hemispheres of AIS patients compared to healthy controls.[45] Besides differentiation between AIS patients and healthy subjects, one study also reported differences between the EEG signal of AIS patients and patients with a transient ischemic

attack.[48] However, whether EEG can be used to discriminate between old and new infarcts, between ischemic and hemorrhagic stroke, and between stroke mimicking conditions, is currently uncertain. A small diagnostic accuracy study of 24 patients with suspected stroke in the emergency department found good discriminative power for several frequency band power ratios between patients with and without an AIS with a large infarct volume.[51] Recently, in a larger diagnostic accuracy study by Erani et al., dry electrode EEG registrations were performed in 100 patients with suspected or definite stroke in an in-hospital setting, after reperfusion therapy. Multiple frequency band powers combined could predict LVO stroke with an area under the curve of 69, and 86 when combined with clinical data.[52] These findings, although preliminary, indicate the possible potential of EEG as an instrument for prehospital LVO detection.

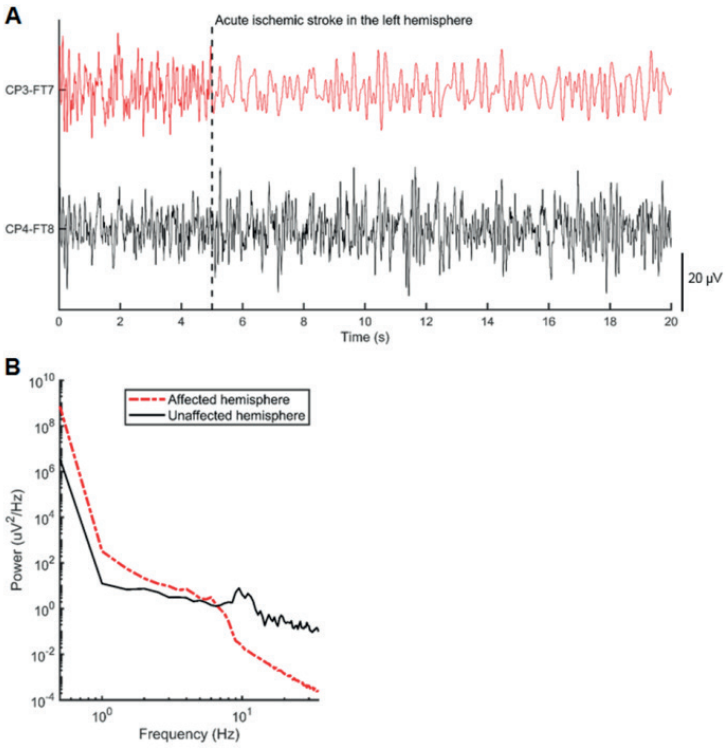

Figure 2. Illustration of slowing of the EEG signal caused by unihemispheric hypoxia. A. EEG signal of the left (CP3-FT7) and right (CP4-FT8) hemisphere. At t=5s, the left hemisphere is affected by an acute ischemic stroke (simulated). B. The corresponding mean power spectra of the affected and the unaffected hemisphere. Lower frequencies are more common in the affected hemisphere, while higher frequencies are decreased.

Although EEG may have high diagnostic accuracy for LVO detection (requirement 1; Table 1),[51, 52] performing EEG measurements in the prehospital setting comes with challenges. First, a traditional EEG measurement requires time-consuming preparation, including skin abrasion and application of a conductive gel or paste. Second, extensive training is needed for correct application of the electrodes and skin-electrode impedance optimization.[53] To overcome these issues, faster and more user-friendly methods for performing an EEG measurement have been proposed. Dry electrodes, for example, require no skin preparation or conductive paste and thus decrease EEG preparation time to at least one-third of its original duration.[54, 55] One type of dry electrodes is the multipin electrode coated with silver-silver chloride, which is designed to pass the hair layer and make direct contact with the scalp (Figure 3A).[56] When integrated into a cap, these electrodes are easy to apply, even by relatively unexperienced users (Figure 3B). Erani et al. reported that the average total preparation time required for a dry electrode EEG measurement – including electrode application and adjustments – was 13 minutes.[52] At the end of the study, experienced users achieved an average preparation time of approximately 5 minutes. EEG measurement time was 3 minutes, which resulted in a total EEG acquisition time 8 minutes at the end of the study. However, this study used an EEG setup with 17 electrodes. To decrease preparation time and complexity, the number of electrodes may be reduced.[46, 57] EEG setups with less electrodes (e.g. 8 electrodes, Figure 3A) are available. The time it takes to interpret the EEG measurement depends on whether this is done visually or using an algorithm. To the best of our knowledge, there is currently no literature available on visual or automatic interpretation times of EEG for LVO-detection. However, automatic interpretation of EEG - including artefact detection - for other classification tasks usually takes less than a second.[58, 59] A downside of dry electrodes is their increased electrode impedance, resulting in lower signal quality. Multiple studies, nonetheless, have shown that by excluding EEG channels with low signal quality, similar performance to regular wet EEG can be obtained.[54, 55] It is important to note that obtaining high quality EEG data in the relatively uncontrolled prehospital setting is probably more challenging, increasing the risk of artifacts in the EEG signal. While automated methods to detect and remove these artifacts are available, future studies that properly address this issue are required.[60] Another challenge in using EEG as a prehospital LVO detection method is the interpretation of the EEG signal. In current standard practice, EEGs are interpreted by a neurologist in a non-acute setting. In the acute, prehospital setting, EEG data may be interpreted automatically by an artificial intelligence-based algorithm. Based on the performance of EEG-based algorithms for other classification tasks, e.g. in epilepsy, such an algorithm may be able to accurately diagnose LVO stroke without human interference.[61, 62] If not, visual interpretation by a remote neurologist on call, in all cases or only in case of the algorithm being inconclusive, is also a possible solution. Furthermore, EEG equipment can be made compact (Figure 3C), portable (Figure 3D) and relatively affordable, ticking off requirements 4 and 5 (Table 1).[63]

Worldwide, several research groups are working towards an EEG based prehospital instrument for LVO detection. Forest Devices (Pittsburgh, USA) has developed *AlphaStroke*, a portable device that should automatically determine the likelihood of the presence of an LVO stroke based on asymmetry in both EEG and evoked potential measurements. This device has not yet been validated in a clinical trial.[64] The ELECTRA-STROKE study (Amsterdam, the Netherlands; clinicaltrials.gov: NCT03699397) is an ongoing trial investigating the diagnostic accuracy of dry electrode cap EEG for LVO detection, performed by ambulance paramedics in the prehospital setting, in a population of suspected stroke patients. The EEG setup used in this study is shown in Figure 3. The SPIDER study (Brisbane, Australia), investigates the accuracy and feasibility of wet electrode EEG for LVO detection in the prehospital setting. In this study, EEGs are performed by specifically trained research paramedics.[65]

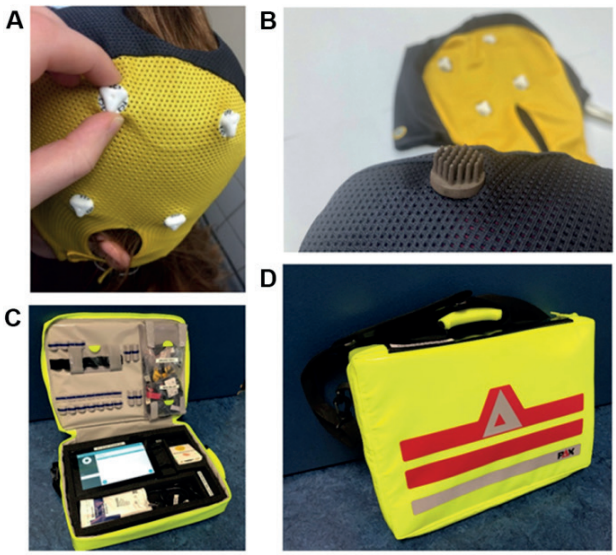

Figure 3. An example of a dry electrode EEG system. A. A dry electrode EEG cap. B. The inside of the cap, showing a multipin dry electrode. C/D. Portable and lightweight EEG equipment, including the dry electrode EEG cap (Waveguard touch, Eemagine, Berlin, Germany), as used in the ELECTRA-STROKE study.

CONCLUSIONS

An effective instrument for prehospital LVO detection would allow patients with an LVO stroke to be brought directly to a CSC. This would save precious time to treatment and thus improve patient outcome. LVO detection methods that have previously been studied do not seem suitable for this purpose. Based on available data, EEG is a promising technique for LVO detection and is currently being investigated in clinical trials in the prehospital setting.

DISCLOSURES

Charles Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation, Dutch Health Evaluation Program and Stryker, outside the submitted work (paid to institution). In addition, Charles Majoie is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Yvo Roos reports stockholdings from Nico.lab outside the submitted work. Henk Marquering is co-founder and shareholder of Nico.lab. Wouter Potters reports grants from Dutch Heart Foundation and grants from Topconsortia for Knowledge and Innovation outside the submitted work. Jonathan Coutinho reports grants from Medtronic and Boehringer outside the submitted work. The other authors report no conflicts.

REFERENCES

1. Collaborators GBDS. Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the global burden of disease study 2016. *Lancet Neurol*. 2019;18:439-458
2. Malhotra K, Gornbein J, Saver JL. Ischemic strokes due to large-vessel occlusions contribute disproportionately to stroke-related dependence and death: A review. *Front Neurol*. 2017;8:651
3. Dozois A, Hampton L, Kingston CW, Lambert G, Porcelli TJ, Sorenson D. Plumber study (prevalence of large vessel occlusion strokes in mecklenburg county emergency response). *Stroke*. 2017;48:3397-3399
4. Mulder M, Jansen IGH, Goldhoorn RB, Venema E, Chalos V, Compagne KCJ et al. Time to endovascular treatment and outcome in acute ischemic stroke: Mr clean registry results. *Circulation*. 2018;138:232-240
5. Menon BK, Sajobi TT, Zhang Y, Rempel JL, Shuaib A, Thornton J et al. Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (escape) randomized, controlled trial. *Circulation*. 2016;133:2279-2286
6. Albers GW. Late window paradox. *Stroke*. 2018;49:768-771
7. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311-2321
8. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V, Zinkstok SM et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923-930
9. Helwig SA, Ragoschke-Schumm A, Schwindling L, Kettner M, Roumia S, Kulikovski J et al. Prehospital stroke management optimized by use of clinical scoring vs mobile stroke unit for triage of patients with stroke: A randomized clinical trial. *JAMA Neurol*. 2019
10. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929-1935
11. Magnusson C, Axelsson C, Nilsson L, Stromsoe A, Munters M, Herlitz J et al. The final assessment and its association with field assessment in patients who were transported by the emergency medical service. *Scand J Trauma Resusc Emerg Med*. 2018;26:111
12. Christensen EF, Bendtsen MD, Larsen TM, Jensen FB, Lindskou TA, Holdgaard HO et al. Trends in diagnostic patterns and mortality in emergency ambulance service patients in 2007-2014: A population-based cohort study from the north denmark region. *BMJ Open*. 2017;7:e014508
13. Kawecki D, Gierlotka M, Morawiec B, Hawranek M, Tajstra M, Skrzypek M et al. Direct admission versus interhospital transfer for primary percutaneous coronary intervention in st-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2017;10:438-447
14. Bagai A, Jollis JG, Dauerman HL, Peng SA, Rokos IC, Bates ER et al. Emergency department bypass for st-segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: A report from the american heart association mission: Lifeline program. *Circulation*. 2013;128:352-359

15. Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE, Jr., Messenger JC et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: A retrospective study. *Lancet*. 2015;385:1114-1122

16. Wilson RE, Kado HS, Percy RF, Butterfield RC, Sabato J, Jr., Strom JA et al. An algorithm for identification of st-elevation myocardial infarction patients by emergency medicine services. *Am J Emerg Med*. 2013;31:1098-1102

17. Le May MR, Dionne R, Maloney J, Trickett J, Watpool I, Ruest M et al. Diagnostic performance and potential clinical impact of advanced care paramedic interpretation of st-segment elevation myocardial infarction in the field. *CJEM*. 2006;8:401-407

18. Turc G, Maier B, Naggara O, Seners P, Isabel C, Tisserand M et al. Clinical scales do not reliably identify acute ischemic stroke patients with large-artery occlusion. *Stroke*. 2016;47:1466-1472

19. Anadani M, Almallouhi E, Wahlquist AE, Debenham E, Holmstedt CA. The accuracy of large vessel occlusion recognition scales in telestroke setting. *Telemed J E Health*. 2019;25:1071-1076

20. Antipova D, Eadie L, Macaden A, Wilson P. Diagnostic accuracy of clinical tools for assessment of acute stroke: A systematic review. *BMC Emerg Med*. 2019;19:49

21. Lima FO, Mont'Alverne FJA, Bandeira D, Nogueira RG. Pre-hospital assessment of large vessel occlusion strokes: Implications for modeling and planning stroke systems of care. *Front Neurol*. 2019;10:955

22. Noorian AR, Sanossian N, Shkirkova K, Liebeskind DS, Eckstein M, Stratton SJ et al. Los angeles motor scale to identify large vessel occlusion: Prehospital validation and comparison with other screens. *Stroke*. 2018;49:565-572

23. Fassbender K, Grotta JC, Walter S, Grunwald IQ, Ragoschke-Schumm A, Saver JL. Mobile stroke units for prehospital thrombolysis, triage, and beyond: Benefits and challenges. *Lancet Neurol*. 2017;16:227-237

24. Zhao H, Coote S, Easton D, Langenberg F, Stephenson M, Smith K et al. Melbourne mobile stroke unit and reperfusion therapy: Greater clinical impact of thrombectomy than thrombolysis. *Stroke*. 2020;51:922-930

25. Shuaib A, Jeerakathil T, Alberta Mobile Stroke Unit I. The mobile stroke unit and management of acute stroke in rural settings. *CMAJ*. 2018;190:E855-E858

26. Gibson LM, Whiteley W. The differential diagnosis of suspected stroke: A systematic review. *J R Coll Physicians Edinb*. 2013;43:114-118

27. Gyrd-Hansen D, Olsen KR, Bollweg K, Kronborg C, Ebinger M, Audebert HJ. Cost-effectiveness estimate of prehospital thrombolysis: Results of the phantom-s study. *Neurology*. 2015;84:1090-1097

28. Lumley HA, Flynn D, Shaw L, McClelland G, Ford GA, White PM et al. A scoping review of pre-hospital technology to assist ambulance personnel with patient diagnosis or stratification during the emergency assessment of suspected stroke. *BMC Emerg Med*. 2020;20:30

29. Bergrath S, Reich A, Rossaint R, Rörtgen D, Gerber J, Fischermann H et al. Feasibility of prehospital teleconsultation in acute stroke--a pilot study in clinical routine. *PLoS One*. 2012;7:e36796

30. Belt GH, Felberg RA, Rubin J, Halperin JJ. In-transit telemedicine speeds ischemic stroke treatment: Preliminary results. *Stroke*. 2016;47:2413-2415

31. Ziegler V, Rashid A, Müller-Gorchs M, Kippnich U, Hiermann E, Kögerl C et al. Mobile computing systems in preclinical care of stroke. Results of the stroke angel initiative within the bmbf project percomed. *Anaesthesist*. 2008;57:677-685

32. Moustafa H, Barlinn K, Prakapenia A, Winzer S, Gerber J, Pallesen LP et al. Endovascular therapy for anterior circulation large vessel

occlusion in telestroke. *J Telemed Telecare*. 2019:1357633X19867193

33. Kruse CS, Frederick B, Jacobson T, Monticone DK. Cybersecurity in healthcare: A systematic review of modern threats and trends. *Technol Health Care*. 2017;25:1-10
34. Dorn A, Thorpe SG, Jalaleddini K, Wilk SJ, Hamilton RB. Feasibility study in the combination of non-contrast computed tomography and transcranial doppler for large vessel occlusion detection. *Neuro Neurosurg* 2020;3
35. Brunser AM, Lavados PM, Hoppe A, Lopez J, Valenzuela M, Rivas R. Accuracy of transcranial doppler compared with ct angiography in diagnosing arterial obstructions in acute ischemic strokes. *Stroke*. 2009;40:2037-2041
36. Demchuk AM, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC et al. Accuracy and criteria for localizing arterial occlusion with transcranial doppler. *J Neuroimaging*. 2000;10:1-12
37. Sonas® – portable ultrasound device for brain diagnostics and treatment monitoring. BURL Concepts. https://burlconcepts.com/our-new-device/. Accessed October 12, 2020.
38. EXPEDITE Study Evaluates Neural Analytics' Portable Transcranial Doppler Technology to Measure Early Strokes. Endovascular today. https://evtoday.com/news/expedite-study-evaluates-neural-analytics-portable-transcranial-doppler-technology-to-measure-early-strokes. Accessed October 12, 2020.
39. Kellner CP, Sauvageau E, Snyder KV, Fargen KM, Arthur AS, Turner RD et al. The vital study and overall pooled analysis with the vips non-invasive stroke detection device. *Journal of neurointerventional surgery*. 2018;10:1079-1084
40. Lam AM, Manninen PH, Ferguson GG, Nantau W. Monitoring electrophysiologic function during carotid endarterectomy: A comparison of somatosensory evoked potentials and conventional electroencephalogram. *Anesthesiology*. 1991;75:15-21
41. Thirumala PD, Thiagarajan K, Gedela S, Crammond DJ, Balzer JR. Diagnostic accuracy of eeg changes during carotid endarterectomy in predicting perioperative strokes. *J Clin Neurosci*. 2016;25:1-9
42. Foreman B, Claassen J. Quantitative eeg for the detection of brain ischemia. *Critical care (London, England)*. 2012;16:216
43. Finnigan SP, Walsh M, Rose SE, Chalk JB. Quantitative eeg indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2007;118:2525-2532
44. Finnigan S, Wong A, Read S. Defining abnormal slow eeg activity in acute ischaemic stroke: Delta/alpha ratio as an optimal qeeg index. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2016;127:1452-1459
45. Van Kaam RC, van Putten M, Vermeer SE, Hofmeijer J. Contralesional brain activity in acute ischemic stroke. *Cerebrovascular diseases (Basel, Switzerland)*. 2018;45:85-92
46. Gottlibe M, Rosen O, Weller B, Mahagney A, Omar N, Khuri A et al. Stroke identification using a portable eeg device - a pilot study. *Neurophysiologie clinique = Clinical neurophysiology*. 2020;50:21-25
47. van Putten MJ, Tavy DL. Continuous quantitative eeg monitoring in hemispheric stroke patients using the brain symmetry index. *Stroke*. 2004;35:2489-2492
48. Sheorajpanday RV, Nagels G, Weeren AJ, van Putten MJ, De Deyn PP. Reproducibility and clinical relevance of quantitative eeg parameters in cerebral ischemia: A basic approach. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2009;120:845-855

49. Dacosta-Aguayo R, Grana M, Iturria-Medina Y, Fernandez-Andujar M, Lopez-Cancio E, Caceres C et al. Impairment of functional integration of the default mode network correlates with cognitive outcome at three months after stroke. *Human brain mapping*. 2015;36:577-590

50. Zhu Y, Bai L, Liang P, Kang S, Gao H, Yang H. Disrupted brain connectivity networks in acute ischemic stroke patients. *Brain imaging and behavior*. 2017;11:444-453

51. Shreve L, Kaur A, Vo C, Wu J, Cassidy JM, Nguyen A et al. Electroencephalography measures are useful for identifying large acute ischemic stroke in the emergency department. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2019;28:2280-2286

52. Erani F, Zolotova N, Vanderschelden B, Khoshab N, Sarian H, Nazarzai L et al. Electroencephalography might improve diagnosis of acute stroke and large vessel occlusion. *Stroke*. 2020:Strokeaha120030150

53. Teplan M. Fundementals of eeg measurement. *Measurement Science Review*. 2002;2:1-11

54. Fiedler P, Pedrosa P, Griebel S, Fonseca C, Vaz F, Supriyanto E et al. Novel multipin electrode cap system for dry electroencephalography. *Brain Topogr*. 2015;28:647-656

55. di Fronso S, Fiedler P, Tamburro G, Haueisen J, Bertollo M, Comani S. Dry eeg in sports sciences: A fast and reliable tool to assess individual alpha peak frequency changes induced by physical effort. *Frontiers in neuroscience*. 2019;13:982

56. Fiedler P, Griebel S, Pedrosa P, Fonseca C, Vaz F, Zentner L et al. Multichannel eeg with novel ti/tin dry electrodes. *Sensors and Actuators A: Physical*. 2015;221:139-147

57. Aminov A, Rogers JM, Johnstone SJ, Middleton S, Wilson PH. Acute single channel eeg predictors of cognitive function after stroke. *PLoS One*. 2017;12:e0185841

58. Fang W, Wang K, Fahier N, Ho Y, Huang Y. Development and validation of an eeg-based real-time emotion recognition system using edge ai computing platform with convolutional neural network system-on-chip design. 2019;9:645-657

59. Zhu G, Li Y, Wen P, Wang S, Zhong N. Unsupervised classification of epileptic eeg signals with multi scale k-means algorithm. 2013:158-167

60. Islam MK, Rastegarnia A, Yang Z. Methods for artifact detection and removal from scalp eeg: A review. *Neurophysiologie clinique = Clinical neurophysiology*. 2016;46:287-305

61. Daoud H, Bayoumi MA. Efficient epileptic seizure prediction based on deep learning. *IEEE Trans Biomed Circuits Syst*. 2019;13:804-813

62. Rim B, Sung NJ, Min S, Hong M. Deep learning in physiological signal data: A survey. *Sensors (Basel)*. 2020;20

63. Michel CM, Murray, MM. Towards the utilization of eeg as a brain imaging tool. *Neuroimage*. 2012;61:371-385

64. Forest devices. https://www.forestdevices.com/. Accessed October 12, 2020.

65. Finnigan S, Loudon W, Wong A, Tippett V. Stroke prehospital informed decision-making using eeg recordings (spider). *Prehospital and Disaster Medicine*. 2019;34:s87-s88

CHAPTER 7

DETECTION OF LARGE VESSEL OCCLUSION STROKE WITH ELECTROENCEPHALOGRAPHY IN THE EMERGENCY ROOM: FIRST RESULTS OF THE ELECTRA-STROKE STUDY

Laura C.C. van Meenen, MD, MSc[1]*, Maritta N. van Stigt, MSc[2]*, Henk A. Marquering, PhD[3,4], Charles B.L.M. Majoie, MD, PhD[4], Yvo B.W.E.M. Roos, MD, PhD[1], Johannes H.T.M. Koelman, MD, PhD[1,2], Wouter V. Potters, PhD[1,2], Jonathan M. Coutinho, MD, PhD[1]

1. Department of Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands
2. Department of Clinical Neurophysiology, Amsterdam UMC, University of Amsterdam, the Netherlands
3. Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, the Netherlands
4. Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands

*These authors contributed equally to the manuscript.

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ABSTRACT

Background

Prehospital detection of large vessel occlusion stroke of the anterior circulation (LVO-a) would enable direct transportation of these patients to an endovascular thrombectomy (EVT) capable hospital. The ongoing ELECTRA-STROKE study investigates the diagnostic accuracy of dry electrode electroencephalography (EEG) for LVO-a stroke in the prehospital setting. To determine which EEG-features are most useful for this purpose and assess EEG-data quality, EEGs are also performed in the emergency room (ER). Here, we report data of the first 100 patients included in the ER.

Methods

Patients presented to the ER with a suspected stroke or known LVO-a stroke underwent a single EEG prior to EVT. Diagnostic accuracy for LVO-a stroke of frequency band power, brain symmetry and phase synchronization measures were evaluated by calculating receiver operating characteristic curves. Optimal cut-offs were determined as the highest sensitivity at a specificity of ≥80%.

Results

EEG data were of sufficient quality for analysis in 65/100 included patients. Of these, 35/65 (54%) had an acute ischemic stroke, of whom 9/65 (14%) had an LVO-a stroke. Median onset-to-EEG-time was 266 minutes (IQR 121-655) and median EEG-recording-time was 3 minutes (IQR 3-5). The EEG feature with the highest diagnostic accuracy for LVO-a stroke was theta-alpha ratio (AUC 0.83; sensitivity 75%; specificity 81%). Combined, weighted phase lag index and relative theta-power best identified LVO-a stroke (sensitivity 100%; specificity 84%).

Conclusion

Dry electrode EEG is a promising tool for LVO-a stroke detection, but data quality needs to be improved and validation in the prehospital setting is necessary. (TRN: NCT03699397, registered October 9 2018.)

BACKGROUND

Endovascular thrombectomy (EVT) is standard treatment for patients with an acute ischemic stroke (AIS) caused by a large vessel occlusion of the anterior circulation (LVO-a).[1] It is important that EVT is performed as soon as possible, in particular in the early time window, since time delay decreases the chance of patient recovery.[2, 3] In most countries, paramedics transport a patient with a suspected stroke to the nearest hospital for diagnostic work-up and, if indicated, initiation of intravenous thrombolysis (IVT).[4] In 45-83% of cases,[5-8] this nearest hospital is a primary stroke center (PSC), where EVT cannot be performed. In these situations, a patient with an LVO-a stroke requires a second transfer to a comprehensive stroke center (CSC) in order to undergo EVT. This 'drip-and-ship' model delays initiation of EVT by 40 to 106 minutes,[5, 6] which theoretically decreases the chance of a good functional outcome by up to 10%.[9, 10]

In an ideal situation, paramedics would be able to identify patients with an LVO-a stroke in the prehospital setting, so that these patients can be immediately transported to the nearest CSC. Multiple clinical scales, containing items for scoring the severity of neurological deficit, have been developed for the purpose of prehospital LVO-a stroke detection. However, none of these scales have both high sensitivity and high specificity for LVO-a stroke in the prehospital setting.[11-15] A recent study in which eight clinical scales for LVO-a stroke detection were validated in the prehospital setting found that the Rapid Arterial Occlusion Evaluation scale (RACE) and the Gaze-Face-Arm-Speech-Time scale (G-FAST) had the highest diagnostic accuracy, with an area under the receiver operating characteristic curve of 0.83 and 0.80, sensitivity of 67% and 50%, and specificity of 87% and 89%, respectively.[14]

Electroencephalography (EEG) may be an alternative to boost diagnostic accuracy of prehospital LVO-a stroke identification. Recently, two small studies performed in an emergency department setting have provided preliminary data that suggest that EEG could be a feasible instrument for detection of LVO-a stroke.[16, 17] Although traditional EEG measurement requires long preparation times, solutions for faster and easier application are available. For example, dry electrodes require no skin preparation or conductive paste and can reduce EEG preparation time to less than 5 minutes.[17] ELECTRA-STROKE is an ongoing study with the primary aim to determine the diagnostic accuracy of dry electrode EEG for LVO-a stroke detection in the prehospital setting. In order to gain insight into which EEG features are most useful for LVO-a stroke detection in the ambulance and to assess and improve EEG data quality in an emergency setting, the ELECTRA-STROKE study also performs dry electrode EEGs in patients with a suspected stroke or a known LVO-a stroke in the emergency room (ER). Here, we describe our first experiences with dry electrode EEG in an emergency setting and report the results of the first 100 patients in the study in whom an EEG was performed in the ER.

METHODS

Study design and population

ELECTRA-STROKE (EEG controlled triage in the ambulance for acute ischemic stroke; NCT03699397) is an ongoing, multicenter, prospective, single-arm, clinical study that evaluates the diagnostic accuracy of dry electrode EEG for detection of LVO-a stroke. The study consists of four different phases. In phases 1 and 2, dry electrode EEGs were performed in controlled in-hospital settings: healthy subjects in the outpatient clinic (phase 1, n=8) and patients admitted to the stroke unit (phase 2, n=7). These two phases were not intended for data acquisition, but only to assess technical and logistical feasibility of performing dry electrode EEGs. In phase 3, we aim to include 250 patients who are presented to the ER of our hospital with a suspected stroke or with a known LVO-a stroke (after being transferred from a PSC to our hospital to undergo EVT). Patients with a known LVO-a stroke were included to 'enrich' our study population, i.e. to increase the incidence of LVO-a stroke compared to the primary target population in order to improve the reliability of the EEG-analysis. In the fourth and final phase, ambulance paramedics (Ambulance Amsterdam and Witte Kruis Alkmaar, both in the Netherlands) perform dry electrode EEGs in the prehospital setting in 222 patients with a suspected stroke. The full study protocol of ELECTRA-STROKE is available at www.clinicaltrials.gov, NCT03699397).

Patient enrollment for ELECTRA-STROKE started in October 2018. Phases 1 and 2 of the study were completed in October 2018 and December 2018, respectively. Recruitment in phases 3 and 4 has started in December 2018 and August 2020, respectively, and is currently ongoing.

In the current study, we report the results of the first 100 patients who were included in the ER, between January 2019 and October 2020. Patients were eligible if they were presented to the ER of our hospital (Amsterdam UMC, location AMC) either with a suspected stroke or with a known LVO-a stroke that was diagnosed in a referring PSC, with symptom onset less than 24 hours before acquisition of the EEG. Patients with a wound or active infection of the scalp in the dry electrode cap placement area were excluded. As of February 2020, we also excluded patients with a (suspected) COVID-19 infection.

Study procedures

In every patient, a single EEG was performed in the ER using a dry electrode cap with 8 electrodes, in positions FC3, FC4, CP3, CP4, FT7, FT8, TP7 and TP8 (Waveguard touch, Eemagine, Berlin, Germany; Supplemental Figure I). These electrode positions were selected to achieve optimal coverage of the vascular territory of the middle cerebral artery, while trying to minimize the risk of EEG artifacts. All EEG recordings were

acquired with an EEG amplifier (eego amplifier EE-411, Eemagine, Berlin, Germany) at a sample frequency of 500 Hz, using clinical EEG software (Clinical Science Systems, Leiden, The Netherlands). EEG recordings were stored in a 16-bit EDF format prior to 12 December 2019 and afterwards in a 32-bit EDF format to avoid incidental clipping of the stored signal. EEG recordings were performed by research personnel who were instructed to perform a recording with a duration of approximately 3 minutes as soon as logistically feasible after patient arrival and before initiation of EVT. All patients underwent a non-contrast CT and, if indicated, CT angiography and CT perfusion. All imaging was evaluated by neuro- or acute radiologists with extensive experience with acute stroke imaging. LVO-a stroke diagnoses were established using CT angiography and all final diagnoses were established by a board-certified neurologist; these were used as the gold standard.

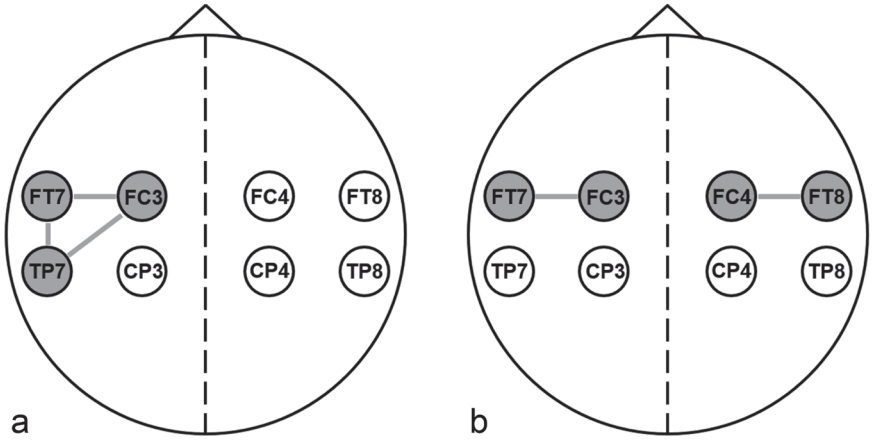

Figure. 1 Example of bipolar derivations as used in the EEG feature analysis. a. For analysis of single hemispheres, 3 unilateral bipolar derivations were used (e.g. FC3-FT7, FC3-TP7 and FT7-TP7) b. For the brain symmetry analysis, 2 symmetric bipolar derivations were used (e.g. FC3-FT7 and FC4-FT8).

Definitions and outcomes

Time of stroke onset was defined as the time of witnessed onset of symptoms or, if this was unknown, the moment that the patient was last known to be well. LVO-a was defined as an occlusion of the intracranial part of the internal carotid artery (ICA), the first segment of the middle cerebral artery (M1), the proximal part of the second segment of the middle cerebral artery (proximal M2), or the first segment of the anterior cerebral artery (A1).

Diagnostic accuracy for LVO-a stroke was calculated for each of the following EEG features: relative delta power, relative theta power, relative alpha power, delta-alpha ratio, theta-alpha ratio, pairwise derived Brain Symmetry Index (pdBSI),[18] and weighted phase lag index (WPLI).[19] For the definitions of these measures as used in the current study, please see the Supplemental Material (Expanded Methods). Additionally, diagnostic accuracy for LVO-a stroke was calculated for the combinations of each frequency band power measure with the WPLI.

Data analysis

For all analyses, we compared patients with an LVO-a stroke to those with any other diagnosis (stroke or stroke mimic). We analyzed baseline characteristics and EEG acquisition times using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test for categorical variables.

EEG preprocessing consisted of artifact rejection, re-referencing and epoch selection. Loose electrodes and major movement or muscle activity artifacts were automatically detected and rejected for each channel (Supplemental Table I). Subsequently, all channels were re-referenced to a 12-channel bipolar montage consisting of 6 bipolar derivations located at each hemisphere (Supplemental Figure I). An EEG recording was considered to be of sufficient quality for analysis if, after artifact rejection, at least 10 seconds of EEG signal remained in either ≥3 unilateral bipolar derivations simultaneously and/or ≥2 symmetric bipolar derivations simultaneously (Figure 1).

EEG features were calculated per 10-second epoch with a 5-second overlap using 3 unilateral bipolar derivations for analysis of single hemispheres and 2 symmetric bipolar derivations for analysis of the brain symmetry (Figure 1). For single hemispheres, we determined the relative delta power (1-4 Hz), relative theta power (4-8 Hz), relative alpha power (8-12 Hz), delta-alpha ratio and theta-alpha ratio for each bipolar derivation separately and averaged them thereafter. As a measure for phase synchronization within a single hemisphere, we determined the WPLI in the frequency range of 4-18 Hz. As a measure for brain symmetry, we determined the pdBSI in the frequency range of 4-18 Hz. Frequency bands were selected using a third order Butterworth band pass filter and mean power spectral densities were obtained for each epoch using Welch's method with a Hamming window of 2 seconds and 50% overlap.

EEG features were compared between patients with an LVO-a stroke and all patients with another diagnosis using the Mann-Whitney U test. For data from single hemispheres, the EEG features were compared between the affected hemispheres of LVO-a stroke patients and both hemispheres (if data were of sufficient quality) of patients without an LVO-a stroke. For all single EEG features, a receiver operating characteristic (ROC) analysis for LVO-a stroke diagnosis was performed and the

AUC was calculated. Confidence intervals for the AUCs were determined using the standard normal distribution with standard errors calculated using the method of Hanley and McNeil.[20] For combined measures, the presence of an LVO-a stroke was scored as present if at least one individual measure was above (if higher values were associated with LVO-a stroke) or below (if lower values were associated with LVO-a stroke) the cut-off value. For all single and combined measures, the optimal cut-off value was determined as the highest sensitivity at a specificity of ≥80% for LVO-a stroke detection and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the optimal cut-off value were calculated. Confidence intervals for all diagnostic accuracy measures were calculated using the Wilson method.[21]

All analyses were performed offline in MATLAB (R2019B, The MathWorks Inc., Natick, USA).

RESULTS

We performed a dry electrode EEG in 105 patients presented to the ER of our hospital, of whom five patients were excluded because they did not give informed consent (Figure 2). Of the remaining 100 patients, we had to exclude 35 patients from the EEG analysis because of insufficient data quality due to EEG artifacts (n=34) or because of a corrupted EDF file (n=1). Baseline characteristics of all 100 included patients are reported in Supplemental Table II. Patients with EEG data of insufficient quality for analysis more often had an LVO-a stroke (40% vs. 14%, $p<0.01$), more often were women (75% vs. 28%, $p<0.01$), and more often had long hair (31% vs. 8%; $p<0.01$) compared to patients with EEG data of sufficient quality. The EEG data quality improved over the course of the study: of the last 50 included patients, 72% had EEG data of sufficient quality for analysis compared to 58% of the first 50 included patients, although this difference was not statistically significant (72% vs. 58%, $p=0.21$). EEG recordings stored in the 32-bit EDF format were more often of sufficient quality than recordings stored in the 16-bit EDF format, although this was also not a statistically significant difference (72% vs. 55%, $p=0.09$). For the 32-bit data (n=58), more EEG recordings were useable if performed by a more experienced user (≤10 recordings vs. >10 recordings performed: 61% vs. 88%; $p=0.03$).

Of the 65 patients with EEG data of sufficient quality for analysis, 35/65 had an AIS (54%) and 9/65 (14%) had an LVO-a stroke. Of the 9 LVO-a strokes, 7 were M1 occlusions and 2 were intracranial ICA occlusions. In the other 26 patients with an AIS, the AIS was located in the vascular territory of the anterior circulation in 19 and in the posterior circulation in 7 patients. There were no patients with an LVO of the posterior circulation. The remaining 30 suspected stroke patients who did not have an AIS had the following final diagnoses: transient ischemic attack (n=8), seizure (n=6),

hemorrhagic stroke (n=5), acute peripheral vestibular syndrome (n=3), or another stroke mimic (n=8). Baseline characteristics of the 65 patients included in the EEG analysis are reported in Table 1. LVO-a stroke patients were slightly older (78 vs. 72 years, p=0.26) and more often were women (56% vs 23%, p=0.10) compared to patients without an LVO-a stroke (Table 1). None of the LVO-a stroke patients had a history of ischemic stroke, compared to 14 patients without an LVO-a stroke. Patients with an LVO-a stroke had more severe neurological deficits (median NIHSS 18 vs. 1; p<0.01). IVT was initiated prior to the EEG recording in 5/9 (56%) of LVO-a stroke patients and in 8/56 (14%) of patients without an LVO-a stroke. Median time from symptom onset to start of the EEG recording was 266 minutes (IQR: 121-655). Median time from arrival at the emergency room to start of the EEG recording was 46 minutes (IQR: 35-62), and median time from EEG cap placement to start of the EEG recording was 2 minutes (IQR: 2-3). The EEG recordings had a median duration of 3 minutes (IQR: 3-5). The median duration of the entire process of EEG acquisition was 6 minutes (IQR: 5-7). EEG recording times did not differ between patients with and without an LVO-a stroke (Table 1).

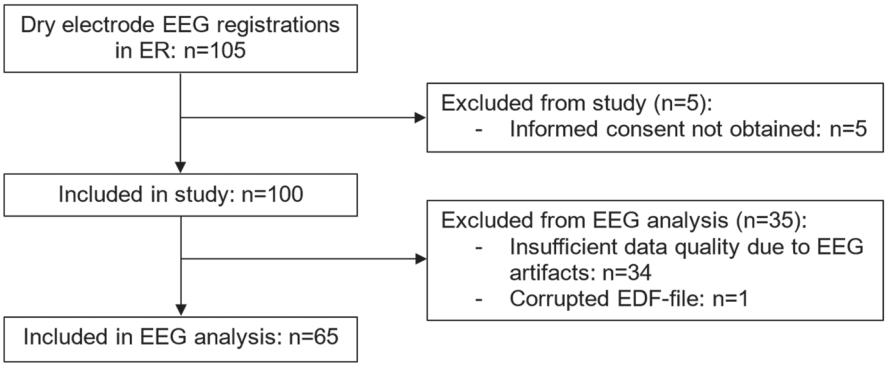

Figure. 2 Inclusion flow chart. EEG = electroencephalography; ER = emergency room; EDF = European Data Format.

The relative theta power and the theta-alpha ratio were higher in the affected hemispheres of LVO-a stroke patients, compared to the hemispheres of patients without an LVO-a stroke (0.63 vs. 0.49, p=0.01 and 0.45 vs. 0.26, p<0.01, respectively; Table 2). The relative alpha power was lower in the affected hemispheres of patients with an LVO-a stroke (0.19 vs. 0.28, p<0.01). There was no statistically significant between-group difference for any of the other EEG features (Table 2).

The diagnostic accuracy with 95% confidence intervals of all single EEG features for diagnosis of LVO-a stroke are reported in Table 3. The theta-alpha ratio had the highest diagnostic accuracy for LVO-a stroke, with an AUC of 0.83 (95% CI: 0.72-0.94),

and, at optimal cut-off, a sensitivity of 75% (95% CI: 41%-93%), specificity of 81% (95% CI: 69%-89%), PPV of 25% (95% CI: 12%-45%) and NPV of 97% (95% CI: 90%-99%) (Figure 3). For the relative alpha power, we found an AUC of 0.80 (95% CI: 0.67-0.93), and, at optimal cut-off, a sensitivity of 75% (95% CI: 41%-93%), specificity of 87% (95% CI: 76%-94%), PPV of 33% (95% CI: 16%-56%) and NPV of 98% (95% CI: 92%-100%). ROC curves of all single EEG features are reported in the Supplemental Material (Supplemental Figure II-VIII). The diagnostic accuracy of the combined measures is reported in Supplemental Table III. Of these measures, the combination of relative theta power and WPLI best identified LVO-a stroke with a sensitivity of 100% (95% CI: 68%-100%), specificity of 84% (95% CI: 72%-91%), PPV of 35% (95% CI: 19%-55%) and NPV of 100% (95% CI: 95%-100%).

Table 1. Baseline characteristics

	All patients (n=65)	LVO-a stroke (n=9)	No LVO-a stroke (n=56)	p value[1]
Age – mean ± SD	73 ± 15	78 ± 6	72 ± 15	0.26
Sex – no. of males/total (%)	47/65 (72%)	4/9 (44%)	43/56 (77%)	0.10
Medical history – no./total (%)				
Ischemic stroke	14/65 (22%)	0/9 (0%)	14/56 (25%)	0.19
Hemorrhagic stroke	2/65 (3%)	0/9 (0%)	2/56 (4%)	1.00
Epilepsy	2/65 (3%)	0/9 (0%)	2/56 (4%)	1.00
NIHSS[2] – median (IQR)	2 (0-6)	18 (12-22)	1 (1-4)	<0.01
Transferred from PSC – no./total (%)	11/65 (17%)	8/9 (89%)	3/56 (5%)	<0.01
Treatment – no./total (%)				
IVT	18/65 (28%)	6/9 (67%)	12/56 (21%)	0.01
Prior to start EEG[3]	13/65 (20%)	5/9 (56%)	8/56 (14%)	0.01
EVT	6/65 (9%)	6/9 (67%)	0/56 (0%)	<0.01
Timeline, minutes – median (IQR)				
Symptom onset to start EEG[4]	266 (121-655)	333 (126-966)	262 (120-641)	0.59
ER arrival to start EEG[5]	46 (35-62)	28 (21-76)	48 (38-62)	0.07
Cap placement to start EEG[6]	2 (2-3)	2 (1-3)	2 (2-3)	0.53
IVT to start EEG[7]	25 (7-71)	75 (61-137)	10 (3-22)	<0.01

EEG = electroencephalography; ER = emergency room; EVT = endovascular thrombectomy; IQR = interquartile ranges; IVT = intravenous thrombolysis; LVO-a = large vessel occlusion of the anterior circulation; NIHSS = National Institutes of Health Stroke Scale; no. = number; PSC = primary stroke center; SD = standard deviation.

[1]p-value for the difference between patients with and without an LVO-a stroke.

[7]Time from start of initiation of IVT to start of the EEG recording is reported for the 13 patients in whom IVT was initiated prior to start of the EEG recording.

Number of missing values: [2]4; [3]1; [4]15; [5]4; [6]4.

Table 2. EEG features

	LVO-a stroke (n=9)	No LVO-a stroke (n=56)	p values
Single hemispheres[1]			
Relative delta	0.85 (0.77-0.88)	0.80 (0.72-0.85)	0.24
Relative theta	0.63 (0.55-0.69)	0.49 (0.40-0.58)	0.01
Relative alpha	0.19 (0.19-0.24)	0.28 (0.23-0.32)	<0.01
Delta-alpha ratio	0.90 (0.87-0.92)	0.84 (0.72-0.89)	0.02
Theta-alpha ratio	0.45 (0.42-0.58)	0.26 (0.10-0.40)	<0.01
WPLI	0.08 (0.05-0.15)	0.10 (0.08-0.14)	0.27
Brain asymmetry[2]			
pdBSI	0.31 (0.23-0.32)	0.33 (0.26-0.43)	0.33

Data are expressed as median (interquartile range). EEG = electroencephalography; LVO-a = large vessel occlusion of the anterior circulation; NIHSS = National Institutes of Health Stroke Scale; pdBSI = pairwise derived Brain Symmetry Index; WPLI = weighted phase lag index.
[1]EEG recordings of 63 patients were available for analysis, with at least 10 seconds of EEG signal remaining after artifact rejection in ≥3 unilateral bipolar derivations simultaneously, of whom 8 patients had an LVO-a stroke.
[2]EEG recordings of 53 patients were available for analysis, with at least 10 seconds of EEG signal remaining after artifact rejection in ≥2 symmetric bipolar derivations simultaneously, of whom 6 patients had an LVO-a stroke.

Table 3. Diagnostic accuracy of EEG features for LVO-a stroke diagnosis

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
Single hemispheres (n=63)					
Relative delta[1]	50% (22%-78%)	82% (70%-90%)	19% (8%-40%)	95% (88%-98%)	0.63 (0.44-0.82)
Relative theta[2]	63% (31%-87%)	87% (76%-94%)	29% (13%-53%)	96% (89%-99%)	0.77 (0.63-0.91)
Relative alpha[3]	75% (41%-93%)	87% (76%-94%)	33% (16%-56%)	98% (92%-100%)	0.80 (0.67-0.93)
Delta-alpha ratio[4]	38% (14%-93%)	90% (79%-95%)	25% (9%-53%)	94% (87%-97%)	0.76 (0.62-0.90)
Theta-alpha ratio[5]	75% (41%-93%)	81% (69%-89%)	25% (12%-45%)	97% (90%-99%)	0.83 (0.72-0.94)
WPLI[6]	50% (22%-78%)	85% (73%-92%)	22% (9%-45%)	95% (88%-98%)	0.61 (0.42-0.80)
Brain asymmetry (n=53)					
pdBSI[7]	0% (0%-39%)	100% (92%-100%)	NA	89% (78%-95%)	0.38 (0.13-0.63)

AUC = area under the receiver operating characteristic curve; CI = confidence interval; EEG = electroencephalography; LVO-a = large vessel occlusion of the anterior circulation; NA = not available; NPV = negative predictive value; pdBSI = pairwise derived Brain Symmetry Index; PPV = positive predictive value; WPLI = weighted phase lag index.
The presence of an LVO-a stroke was indicated if the EEG features were: [1]>0.88; [2]>0.62; [3]<0.21; [4]>0.92; [5]>0.43; [6]<0.07, [7]>0.67.

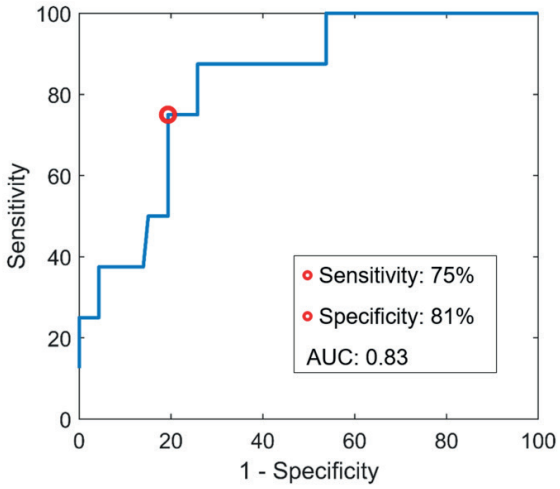

Figure. 3 ROC curve for LVO-a stroke detection by the theta-alpha ratio. The red circle is located at a cut-off value of 0.43, with a sensitivity of 75% and a specificity of 81% for LVO-a stroke.

DISCUSSION

We found that in a population of patients with a suspected stroke who were presented to the emergency room, dry electrode EEG could identify LVO-a stroke with high diagnostic accuracy. Single EEG features with the highest accuracy were the theta-alpha ratio (AUC 0.83) and relative alpha-power (AUC 0.80). The combination of relative theta power and WPLI best identified LVO-a stroke, with a sensitivity of 100% and a specificity of 84%. An important limitation was that the EEG data were of insufficient quality for analysis in 35% of patients.

Several previous cohort studies have shown that interhospital transfer of patients with an LVO-a stroke delays EVT by 40 to 106 minutes and is associated with worse clinical outcome.[5, 6] The RACECAT trial (NCT02795962), in which patients with a suspected LVO-a stroke were randomized between primary presentation to a PSC and direct presentation to a CSC, also found that interhospital transfer prior to EVT was associated with a treatment delay of approximately an hour, although no difference in clinical outcome was found.[22] A prehospital LVO-a stroke detection method with high diagnostic accuracy, however, would not only save time by enabling direct transportation of patients with an LVO-a stroke to the nearest CSC, but with high specificity, a positive result would also warrant the angiography suite to be prepared and the operating team to be alerted before patient arrival, which could further lower time to treatment. Several prehospital LVO-a stroke detection methods

that have previously been proposed, do not seem suitable for this purpose at this time.[23] Multiple clinical scales have been studied in the prehospital setting and some can reach a relatively high diagnostic accuracy,[14] comparable to the diagnostic accuracy of several single EEG features in our study. However, while diagnostic accuracy of EEG may be drastically improved in the future by the further development of LVO-a detection algorithms and new EEG acquisition techniques, it seems unlikely that the diagnostic accuracy of clinical scales can be substantially improved. The relatively low exposure of ambulance paramedics to the population of suspected stroke patients combined with the complexity of the neurological examination makes reliable application of clinical scales in the prehospital setting difficult. Nonetheless, it is important that – once the technique of dry electrode EEG in the ambulance has matured – future studies appropriately assess the added value of EEG measurement on top of clinical scales for triage of patients with a suspected stroke.

Recently, two small studies performed in the ER have provided data that suggest that EEG could be suitable for LVO-a stroke detection. A previous small study of 24 suspected stroke patients found that the alpha-delta ratio, the (delta*theta)/(alpha*beta) ratio, delta power and lower beta power discriminated between patients with and without an AIS with a large infarct volume, in a population of suspected stroke patients in the ER.[16] In another study, dry electrode EEGs were performed in 100 patients with suspected or definite stroke in the ER.[17] In this study, the relative theta power and relative alpha power combined identified LVO-a stroke with an AUC of 0.69. When combined with clinical data, the AUC improved to 0.86. This suggests that combining the EEG with a clinical scale may further improve its diagnostic accuracy, although in our study, relatively high diagnostic accuracy was achieved without use of clinical data. Contrary to the study by Erani et al., we acquired all EEGs prior to EVT, with a substantially lower median time from symptom onset to EEG acquisition (4.4 vs. 9.4 hours). As cellular mechanisms change rapidly during the first hours after AIS onset,[24, 25] this difference in timing of EEG acquisition is important to consider when interpreting the findings of both studies and when assessing their generalizability.

An important limitation to our study is the high number of patients with EEG data that were of insufficient quality for analysis. Although lower channel reliability is a known disadvantage of dry electrode EEG, average channel reliability has previously been reported to be approximately 80%.[25] In our study, however, only 65% of patients had EEG data of sufficient quality. A possible explanation for this discrepancy could be that our EEG preparation times were relatively short and the fact that the EEGs were performed in an emergency setting. We chose to use dry electrode EEG because it requires a substantially decreased preparation time compared to wet electrode EEG.[26, 27] Since EEGs were performed prior to EVT, we wanted to take as little time as logistically feasible and therefore aimed for a total EEG acquisition time of approximately 5 minutes. When comparing our study to that of Erani et al., in which

EEG data of 95% of measured patients were used for analysis, our EEG preparation times were substantially lower (2 minutes vs. 9 minutes).[17] These low preparation times could also explain why patients with EEG data of insufficient quality more often had an LVO-a stroke (40% vs. 14%), since there was more of a time constraint in these patients, especially in those who were transferred from a PSC directly to the angiography suite. Additionally, in our study, compared to that of Erani et al., more EEG recordings were performed by inexperienced users (70% vs. 90%), which may also have contributed to the high number of low quality EEGs. Another possible explanation for our low data quality is that with the EEG recording software that was used, electrode impedance could not be visualized for dry electrodes. Therefore, the researcher performing the EEG was unable to ensure sufficient electrode-skin contact. Because having a lot of hair on the scalp makes sufficient electrode-skin contact more difficult to achieve,[28] this may also explain why patients with EEG data of insufficient quality were more often women and more often had long hair. Since poor electrode skin-contact increases the power of lower frequencies and dry electrode recordings are known to have increased power in the lower frequencies until 3 Hz compared to wet electrode EEG, related to increased electrode drift and a higher offset potential,[28] our results regarding the delta frequency band should be interpreted with caution. Finally, the limited number of electrodes in our dry electrode cap may have contributed to the high number of patients with EEG data of insufficient quality, since with less electrodes, the chances of obtaining good quality EEG data may be lower. Over the course of our study, the EEG quality did improve, as we found that recordings were more often of sufficient quality for analysis if they were stored in a 32-bit file format and were performed by a more experienced user. Other possibilities to improve data quality include: providing feedback of the electrode-skin contact to the user prior to the EEG recording; enforcing better electrode-skin contact by increasing the tightness of the cap fit; increasing the electrode surface area to improve electrode stability and electrode-skin contact; and improving the training of the users of the EEG equipment. Although automated methods for detection and removal of EEG artifacts are available, these have not yet been studied in the prehospital setting.[29]

Another limitation of our study is the relatively small sample size of patients with an LVO-a stroke (n=9). As a result, the estimates of diagnostic accuracy had fairly broad confidence intervals and validation in a larger sample in the prehospital setting is necessary.

Finally, a challenge for future use of EEG for prehospital LVO-a stroke detection is the interpretation of the signal. Ideally, EEG data would be interpreted automatically by an artificial intelligence-based algorithm. Previous studies have shown that for other classification tasks, e.g. in epilepsy, EEG-based algorithms can obtain high diagnostic accuracy.[30, 31] Another possible solution could be visual interpretation of the EEG by a remote neurologist on call, either in every suspected stroke case or only if the

outcome of the algorithm is inconclusive.
In conclusion, dry electrode EEG can identify LVO-a stroke among patients with a suspected stroke with high diagnostic accuracy in an emergency setting. Towards future use of dry electrode EEG in the prehospital setting, data quality needs to be improved and prehospital validation is necessary.

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CONTRIBUTION STATEMENT

All authors contributed to the study conception and design. Data collection and analysis was performed by LvM, MvS, WP and JC. The first draft of the manuscript was written by LvM and MvS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

Charles Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation, Stryker, and Dutch Health Evaluation Program, all outside the submitted work (paid to institution), and is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Yvo Roos is a minor shareholder of Nico.lab. Henk Marquering is co-founder and shareholder of Nico.lab. Jonathan Coutinho received related research support from the Dutch Heart Foundation and Medtronic and unrelated research support from Bayer and Boehringer. All fees were paid to his employer. The other authors report no conflicts.

AVAILABILITY OF DATA AND MATERIAL

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data, even in coded form.

CODE AVAILABILITY

All syntax files and output of statistical analyses will be made available upon reasonable request.

ETHICS APPROVAL AND CONSENT

Permission to carry out ELECTRA-STROKE was granted by the medical ethics committee of the Amsterdam UMC, location AMC. All enrolled patients or their legal representatives provided written informed consent. A deferred consent procedure was approved by the ethical review board, meaning that informed consent was asked after acquisition of the EEG, as soon as logistically feasible (preferably within 72 hours after arrival at the hospital or at discharge).

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731
2. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
3. Albers GW. Late window paradox. *Stroke*. 2018;49:768-771
4. Maas WJ, Lahr MMH, Buskens E, van der Zee DJ, Uyttenboogaart M, Investigators C. Pathway design for acute stroke care in the era of endovascular thrombectomy: A critical overview of optimization efforts. *Stroke*. 2020;51:3452-3460
5. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311-2321
6. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V, et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923-930
7. Pallesen LP, Winzer S, Barlinn K, Prakapenia A, Siepmann T, Gruener C, et al. Safety of inter-hospital transfer of patients with acute ischemic stroke for evaluation of endovascular thrombectomy. *Scientific reports*. 2020;10:5655
8. Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ, et al. Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making. *Eur Stroke J*. 2018;3:126-135
9. Mulder M, Jansen IGH, Goldhoorn RB, Venema E, Chalos V, Compagne KCJ, et al. Time to endovascular treatment and outcome in acute ischemic stroke: Mr clean registry results. *Circulation*. 2018;138:232-240
10. Menon BK, Sajobi TT, Zhang Y, Rempel JL, Shuaib A, Thornton J, et al. Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (escape) randomized, controlled trial. *Circulation*. 2016;133:2279-2286
11. Heldner MR, Hsieh K, Broeg-Morvay A, Mordasini P, Buhlmann M, Jung S, et al. Clinical prediction of large vessel occlusion in anterior circulation stroke: Mission impossible? *J Neurol*. 2016;263:1633-1640
12. Turc G, Maier B, Naggara O, Seners P, Isabel C, Tisserand M, et al. Clinical scales do not reliably identify acute ischemic stroke patients with large-artery occlusion. *Stroke*. 2016;47:1466-1472
13. Antipova D, Eadie L, Macaden A, Wilson P. Diagnostic accuracy of clinical tools for assessment of acute stroke: A systematic review. *BMC Emerg Med*. 2019;19:49
14. Duvekot MHC, Venema E, Rozeman AD, Moudrous W, Vermeij FH, Biekart M, et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (presto): A prospective observational study. *Lancet Neurol*. 2021;20:213-221
15. Nguyen TTM, van den Wijngaard IR, Bosch J, van Belle E, van Zwet EW, Dofferhoff-Vermeulen T, et al. Comparison of prehospital scales for predicting large anterior vessel occlusion in the ambulance setting. *JAMA Neurol*. 2020;78:157-164

16. Shreve L, Kaur A, Vo C, Wu J, Cassidy JM, Nguyen A, et al. Electroencephalography measures are useful for identifying large acute ischemic stroke in the emergency department. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2019;28:2280-2286
17. Erani F, Zolotova N, Vanderschelden B, Khoshab N, Sarian H, Nazarzai L, et al. Electroencephalography might improve diagnosis of acute stroke and large vessel occlusion. *Stroke*. 2020:Strokeaha120030150
18. Sheorajpanday RV, Nagels G, Weeren AJ, van Putten MJ, De Deyn PP. Reproducibility and clinical relevance of quantitative eeg parameters in cerebral ischemia: A basic approach. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2009;120:845-855
19. Vinck M, Oostenveld R, van Wingerden M, Battaglia F, Pennartz CM. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage*. 2011;55:1548-1565
20. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143:29-36
21. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Statistical Science*. 2001;16:101-133
22. Perez de la Ossa N, Ribo M. Transfer to closest stroke center vs. Direct transfer to endovascular stroke-center of acute stroke patients with suspected large vessel occlusion in catalonia(racecat): Final results (abstract).European Stroke Organisation - World Stroke Organization Conference 2020.
23. Lee VH, Thakur G, Nimjee SM, Youssef PP, Lakhani S, Heaton S, et al. Early neurologic decline in acute ischemic stroke patients receiving thrombolysis with large vessel occlusion and mild deficits. *J Neurointerv Surg*. 2020;12:1085-1087
24. Maas MB, Furie KL, Lev MH, Ay H, Singhal AB, Greer DM, et al. National institutes of health stroke scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. *Stroke*. 2009;40:2988-2993
25. Lumley HA, Flynn D, Shaw L, McClelland G, Ford GA, White PM, et al. A scoping review of pre-hospital technology to assist ambulance personnel with patient diagnosis or stratification during the emergency assessment of suspected stroke. *BMC Emerg Med*. 2020;20:30
26. di Fronso S, Fiedler P, Tamburro G, Haueisen J, Bertollo M, Comani S. Dry eeg in sports sciences: A fast and reliable tool to assess individual alpha peak frequency changes induced by physical effort. *Frontiers in neuroscience*. 2019;13:982
27. Fiedler P, Pedrosa P, Griebel S, Fonseca C, Vaz F, Supriyanto E, et al. Novel multipin electrode cap system for dry electroencephalography. *Brain Topogr*. 2015;28:647-656
28. Fiedler P, Pedrosa P, Griebel S, Fonseca C, Vaz F, Zanow F, et al. Novel flexible dry pu/tin-multipin electrodes: First application in eeg measurements. *Annu Int Conf IEEE Eng Med Biol Soc*. 2011;2011:55-58
29. Jiang X, Bian GB, Tian Z. Removal of artifacts from eeg signals: A review. *Sensors (Basel, Switzerland)*. 2019;19
30. Gao Y, Gao B, Chen Q, Liu J, Zhang Y. Deep convolutional neural network-based epileptic electroencephalogram (eeg) signal classification. *Front Neurol*. 2020;11:375
31. Daoud H, Bayoumi MA. Efficient epileptic seizure prediction based on deep learning. *IEEE Trans Biomed Circuits Syst*. 2019;13:804-813

SUPPLEMENTAL MATERIAL

Expanded methods

The relative delta, theta and alpha power were calculated by dividing the power in the delta (1-4 Hz), theta (4-8 Hz) and alpha (8-13 Hz) band, respectively, by the total spectral power between 1 and 18 Hz. The delta-alpha ratio was defined as:

$$DAR = \frac{P(\partial)-P(\alpha)}{P(\delta)+P(\alpha)}$$

(1)

with $P(\partial)$ the power in the delta frequency band and $P(\alpha)$ the power in the alpha frequency band. The theta-alpha ratio was defined as:

$$TAR = \frac{P(\theta)-P(\alpha)}{P(\theta)+P(\alpha)}$$

(2)

with $P(\partial)$ the power in the delta frequency band and $P(\alpha)$ the power in the alpha frequency band. The delta-alpha and theta-alpha ratio were normalized between -1 (dominance of higher frequencies) and 1 (dominance of lower frequencies). The pairwise derived Brain Symmetry Index evaluates asymmetry in spectral power density along homologous channel pairs and was defined as:

$$pdBSI = \frac{1}{NM} \sum_{j=1}^{M} \sum_{i=1}^{N} \left| \frac{R_{ij}- L_{ij}}{R_{ij}+ L_{ij}} \right|$$

(3)

with $R_{ij}(L_{ij})$ the Fourier coefficient belonging to the frequency i = 1:N of the right (left) hemispheric bipolar derivations j = 1:M. In this study, we used M=1. The pdBSI was calculated in the frequency range of 4-18 Hz and normalized between 0 (perfect symmetry) and 1 (maximal asymmetry). The weighted phase lag index was defined as:

$$WPLI = \frac{|E\{\sin(\Delta\varphi(t))\}|}{E\{|\sin(\Delta\varphi(t))|\}}$$

(4)

with $E\{\sin(\Delta\varphi(t))\}$ the expected value, a weighted average value, of the sine of the relative phase as determined using the Hilbert transform. The WPLI was calculated in the 4-18 Hz frequency range and normalized between 0 (no phase synchronization) and 1 (complete phase synchronization).

Supplemental Table I. Thresholds for the automated artifact detection, chosen based on visual inspection of the EEG data

Artifact	Epoch length(s)	Description
Disconnected electrodes	1	Standard deviation ≤ 5 μV
Movement or poor electrode-skin contact	1	Maximum amplitude > 100 μV
Muscle activity	5	Mean power in higher frequency band (25-40 Hz) ≥ 5 μV^2/Hz, or .5 μV^2/Hz ≤ mean power in higher frequency band (25-40 Hz) < 5 μV^2/Hz, and $\frac{\text{Mean power in higher frequency band (25-40 Hz)}}{\text{Mean power in lower frequency band (4-12 Hz)}} > 1$

Prior to the artifact detection, a band pass (0.5-70 Hz) and notch (50 Hz) filter were applied.

Supplemental Table II. Baseline characteristics of the patients with and without EEG data of sufficient quality for analysis

	All patients (n=100)	Sufficient EEG data quality (n=65)	Insufficient EEG data quality (n=35)	*p*-value[1]
Age – mean ± SD	72 ± 16	73 ± 15	71 ± 19	0.70
Sex – no. of males/total (%)	55/100 (55%)	47/65 (72%)	8/65 (23%)	<0.01
Diagnosis – no./total (%)				
LVO-a stroke	23/100 (23%)	9/65 (14%)	14/35 (40%)	<0.01
Non-LVO-a ischemic stroke	33/100 (33%)	26/65 (40%)	7/35 (20%)	0.05
Transient ischemic attack	12/100 (12%)	8/65 (12%)	4/35 (11%)	1.00
Hemorrhagic stroke	6/100 (6%)	5/65 (8%)	1/35 (3%)	1.00
Seizure	6/100 (6%)	6/65 (9%)	0/35 (0%)	0.09
Other stroke mimic	20/100 (20%)	11/65 (17%)	9/35 (26%)	0.31
NIHSS[2] – median (IQR)	3 (1-12)	2 (0-6)	5 (1-18)	0.04
Transferred from PSC – no./total (%)	21/100 (21%)	11/65 (17%)	10/35 (29%)	0.33
Treatment – no./total (%)				
IVT	26/100 (26%)	18/65 (28%)	8/35 (23%)	0.64
Prior to start EEG[3]	18/100 (18%)	13/65 (20%)	5/35 (14%)	0.59
EVT	14/100 (14%)	6/65 (9%)	8/35 (23%)	0.07
Timeline, minutes – median (IQR)				
Symptom onset to start EEG[4]	270 (122-657)	266 (121-655)	285 (128-610)	0.82
ER arrival to start EEG[5]	47 (34-62)	46 (35-62)	48 (33-62)	0.92
Cap placement to start EEG[6]	2 (2-3)	2 (2-3)	2 (2-3)	0.48
IVT to start EEG[7]	40 (7-75)	25 (7-71)	55 (8-79)	0.78
Hair length				
Short	69/85 (81%)	52/57 (91%)	17/28 (61%)	<0.01
Long	16/85 (19%)	5/57 (9%)	11/28 (39%)	<0.01

EEG = electroencephalography; ER = emergency room; EVT = endovascular thrombectomy; IQR = interquartile range; IVT = intravenous thrombolysis; LVO-a = large vessel occlusion of the anterior circulation; NIHSS = National Institutes of Health Stroke Scale; no. = number; PSC = primary stroke center; SD = standard deviation.

[1]p-value for the comparisons between patients with and without EEG data of sufficient quality for analysis.

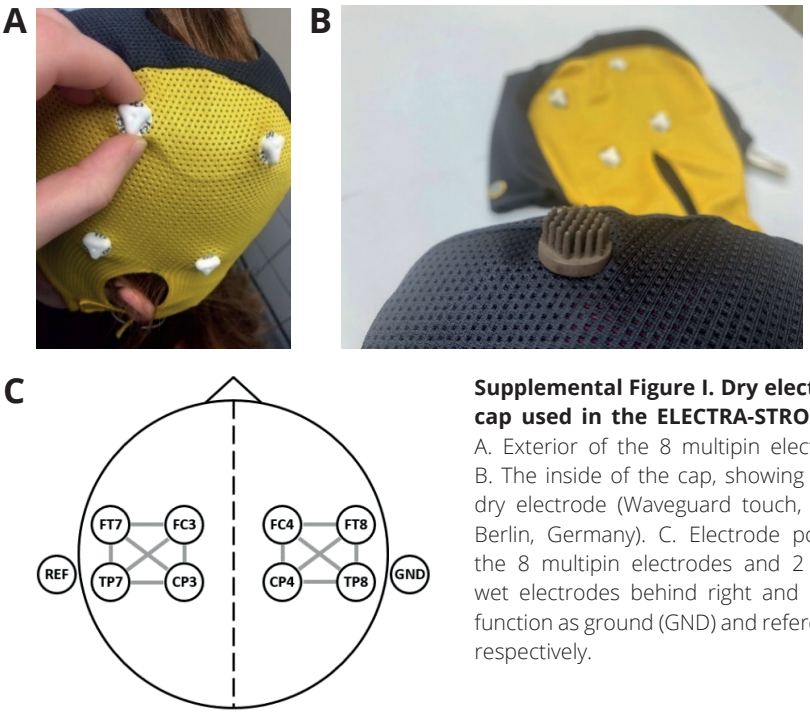
[7]Time from start of initiation of IVT to start of the EEG measurement is reported for the 18 patients in whom IVT was initiated prior to start of the EEG measurement.

Number of missing values: [2]7; [3]3; [4]23; [5]7; [6]7.

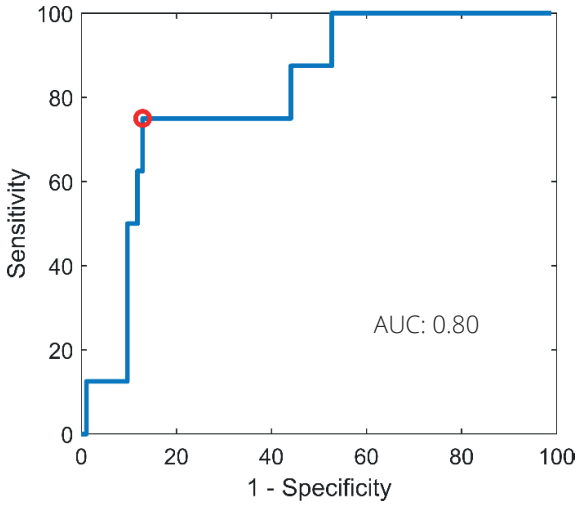
Supplemental Table III. Diagnostic accuracy of combined EEG features for LVO-a stroke diagnosis

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Relative delta + WPLI[1]	50% (22%-78%)	84% (72%-91%)	21% (8%-43%)	95% (88%-98%)
Relative theta + WPLI[2]	100% (68%-100%)	84% (72%-91%)	35% (19%-55%)	100% (95%-100%)
Relative alpha + WPLI[3]	75% (41%-93%)	88% (77%-94%)	35% (17%-58%)	98% (92%-100%)
Delta-alpha ratio + WPLI[4]	63% (31%-87%)	87% (76%-94%)	29% (13%-53%)	96% (89%-99%)
Theta-alpha ratio + WPLI[5]	88% (53%-98%)	81% (69%-89%)	28% (14%-48%)	99% (93%-100%)

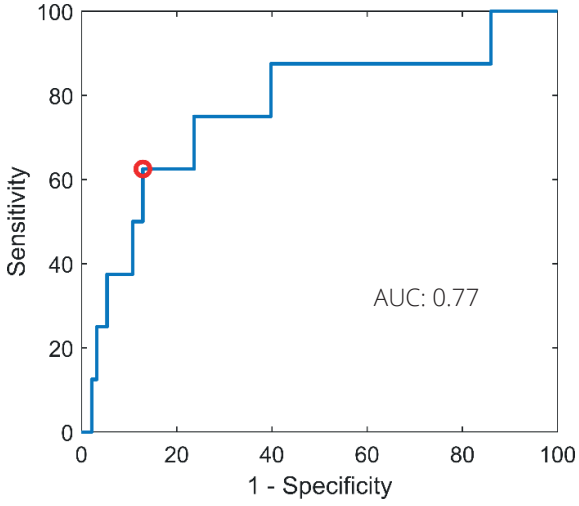
AUC = area under the receiver operating characteristic curve; CI = confidence interval; EEG = electroencephalography; LVO-a = large vessel occlusion of the anterior circulation; NPV = negative predictive value; PPV = positive predictive value; WPLI = weighted phase lag index.
For all combined measure analyses: n=63.
The following cut-off values were used, and were considered to indicate the presence of an LVO-a stroke:
[1]Relative delta power >0.93 and/or WPLI <0.07;
[2]Relative theta power >0.62 and/or WPLI <0.06;
[3]Relative alpha power <0.19 and/or WPLI <0.04;
[4]Delta-alpha ratio >0.92 and/or WPLI <0.06;
[5]Theta-alpha ratio >0.55 and/or WPLI <0.07.



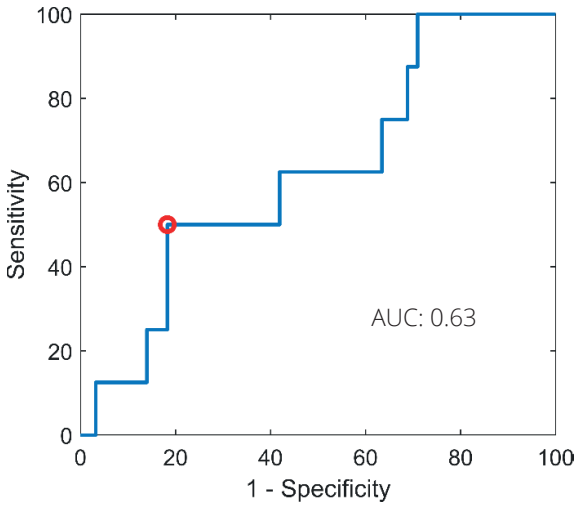
Supplemental Figure I. Dry electrode EEG cap used in the ELECTRA-STROKE study. A. Exterior of the 8 multipin electrode cap. B. The inside of the cap, showing a multipin dry electrode (Waveguard touch, Eemagine, Berlin, Germany). C. Electrode positions of the 8 multipin electrodes and 2 additional wet electrodes behind right and left ear to function as ground (GND) and reference (REF), respectively.



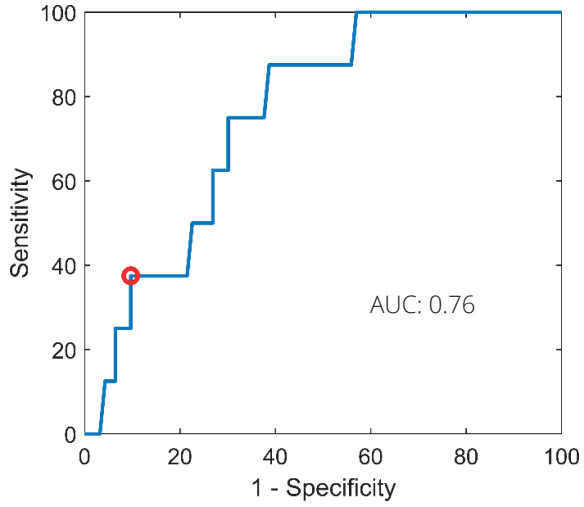
Supplemental Figure II. ROC curve for LVO-a stroke detection by the relative alpha power. Relative alpha power could identify LVO-a stroke with an AUC of 0.80. The red circle is located at a cut-off value of 0.21, with a sensitivity of 75% and a specificity of 87% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.



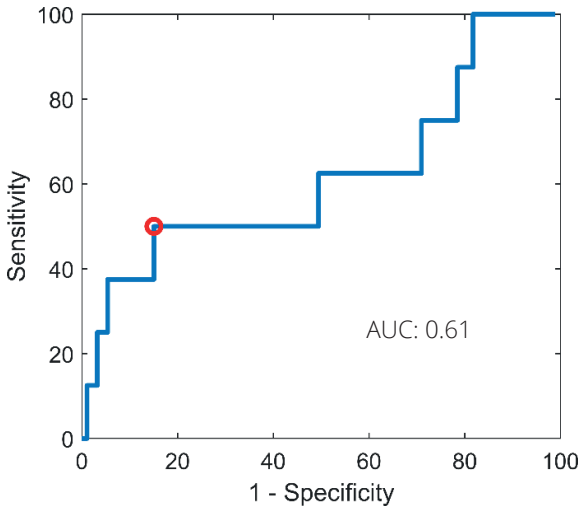
Supplemental Figure III. ROC curve for LVO-a stroke detection by the relative theta power. Relative theta power could identify LVO-a stroke with an AUC of 0.77. The red circle is located at a cut-off value of 0.63, with a sensitivity of 63% and a specificity of 87% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.



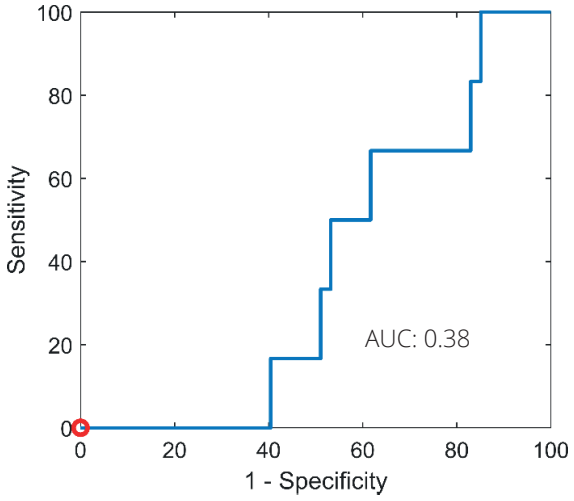
Supplemental Figure IV. ROC curve for LVO-a stroke detection by the relative delta power. Relative delta power could identify LVO-a stroke with an AUC of 0.63. The red circle is located at a cut-off value of 0.88, with a sensitivity of 50% and a specificity of 82% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.



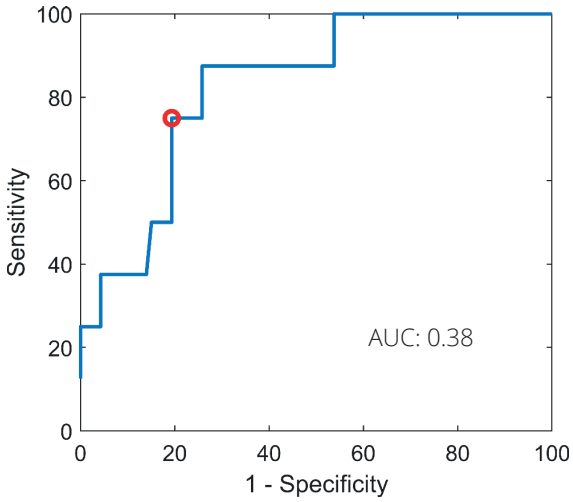
Supplemental Figure V. ROC curve for LVO-a stroke detection by the delta-alpha ratio. Delta-alpha ratio could identify LVO-a stroke with an AUC of 0.76. The red circle is located at a cut-off value of 0.92, with a sensitivity of 38% and a specificity of 90% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.



Supplemental Figure VI. ROC curve for LVO-a stroke detection by the weighted phase lag index. Weighted phase lag index could identify LVO-a stroke with an AUC of 0.61. The red circle is located at a cut-off value of 0.07, with a sensitivity of 50% and a specificity of 85% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.



Supplemental Figure VII. ROC curve for LVO-a stroke detection by the pairwise derived Brain Symmetry Index. Brain Symmetry Index could identify LVO-a stroke with an AUC of 0.38. The red circle is located at a cut-off value of 0.67, with a sensitivity of 0% and a specificity of 100% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.



Supplemental Figure VIII. ROC curve for LVO-a stroke detection by the theta-alpha ratio. Theta-alpha ratio could identify LVO-a stroke with an AUC of 0.83. The red circle is located at a cut-off value of 0.43, with a sensitivity of 75% and a specificity of 81% for LVO-a stroke. AUC = area under the receiver operating characteristic curve; LVO-a = large vessel occlusion of the anterior circulation; ROC = receiver operating characteristic curve.

CHAPTER 8

GENERAL DISCUSSION

The aim of the research projects described in this thesis was to improve the prehospital and interhospital workflow for patients with a large vessel occlusion (LVO) stroke who are treated with endovascular thrombectomy (EVT), in order to shorten time to treatment and thereby improve clinical outcome. Ideally, this could be achieved by developing and implementing a method for prehospital LVO detection that would enable paramedics to transport patients with an LVO stroke directly to a comprehensive stroke center (CSC), while all other patients are brought to the nearest primary stroke center (PSC). However, as long as the current 'drip-and-ship model' is still in place, in which patients are often first presented to a PSC and subsequently transferred to a CSC, we must also continue to improve the workflow within this model. In the first part of this thesis, we focused on improving the current workflow. We provided an overview of the pre- and interhospital time metrics for patients with an LVO stroke in the Netherlands and discussed several potential measures to shorten time to treatment within this workflow. In the second part of this thesis, we shifted our focus to the pre- and interhospital stroke workflow that we envision for the future. We outlined the necessary characteristics of an efficient prehospital LVO detection method, discussed previously studied methods, and proposed electroencephalography (EEG) as a potentially suitable instrument for this purpose.

PART I: CURRENT WORKFLOW

Although several studies have shown that primary presentation of patients with an LVO stroke to a PSC is associated with substantial treatment delay,[1, 2] the drip-and-ship model is the most feasible model for transportation of patients with an LVO stroke at this point in time. A reliable prehospital LVO detection method is currently not available, and transporting all suspected stroke patients directly to a CSC would overburden these hospitals. Furthermore, direct presentation of all suspected stroke patients could lead to longer initial ambulance travel times, thereby delaying initiation of IVT for the majority of patients with an acute ischemic stroke, most of whom do not have an LVO. In the absence of a feasible alternative, many have set out to find ways to shorten time to treatment within the drip-and-ship model. Most previous studies have focused on shortening EVT-related time intervals inside the CSC (e.g. door-to-groin time),[3-6] and several measures that do so have been successfully implemented in clinical practice.[4-8] Now that EVT-related logistics inside the CSC have become fairly streamlined, to further shorten time to treatment, there is much more to gain by focusing on improving the workflow prior to arrival at the CSC.

Public awareness

Although it was not the main focus of this thesis, it is important to recognize that public awareness of the symptoms of stroke and the immediate call for help when these

symptoms occur play a crucial part in shortening time to treatment. In Chapter 2, we described the considerable treatment delay of 36 minutes associated with referral of LVO stroke patients by a general practitioner instead of an ambulance dispatch center. Although this only applied to 5% of patients in our study, the percentage of patients with ST-elevation myocardial infarction who are referred by a general practitioner in the Netherlands is even lower: 2.5%.[9] This implies that the general public better recognizes (the significance of) symptoms of acute myocardial infarction than symptoms of acute stroke. The importance of the latter should be reiterated to the public, at least in the Netherlands.

Prehospital workflow

Emergency medical services (EMS) play a pivotal role in acute stroke management, and thereby in the avoidance of treatment delay. In the Netherlands, EMS are well-organized and relatively short ambulance response times are achieved for patients with a suspected stroke compared to other countries (Chapter 2). For example, in a recent cohort study of patients transferred for EVT in the USA, average time between first call to the dispatch center and arrival of EMS at the patient's location was 16 minutes,[10] compared to 7 minutes in our study. There is, however, potential for further improvement of EMS logistics when it comes to stroke workflow. It may be useful to transport suspected stroke patients with a contraindication for IVT directly to a CSC, while maintaining the drip-and-ship model for patients who are potentially eligible for IVT. In the latter population, bypassing the nearest PSC for direct presentation to a CSC may delay initiation of IVT. This disadvantage does not apply to patients with a contraindication for IVT and, as described in Chapter 3, direct presentation of these patients to a CSC can decrease time to EVT by 18 minutes on average. However, it is unknown whether determining contraindications for IVT by ambulance paramedics would negatively affect prehospital time metrics. Therefore, further research on this matter is required prior to potential implementation in clinical practice.

Interhospital workflow

When it comes to interhospital transfer of patients with an LVO stroke, we need to look at the time spent inside the PSC (door-in-door-out-time), the time it takes to transport the patient from the PSC to the CSC (transfer time), and the time spent inside the CSC (door-to-groin time). These time intervals may be influenced by EMS, PSC and CSC logistics, and by the way these partners work together.

The average door-in-door-out time for LVO stroke patients in the Netherlands is approximately 85 minutes (Chapter 2), which is similar to that in other countries,[11, 12] but may be further improved. A previous study found that PSC time metrics could be shortened by enforcing a quality improvement program, including a task force dedicated to improving door-in-door out time and a streamlined protocol for

imaging transfer to the nearest CSC.[12] In Chapter 4, we hypothesized that more exposure to LVO stroke patients may also positively affect PSC workflow (i.e. lower door-in-door out times), as it may result in more streamlined care pathways and more experienced staff within the PSC. If there were such an effect, this could be an argument for centralization of primary stroke care. However, in our cohort study, we found no association between PSC volume and EVT-related treatment times. Based on these findings, at least in the Netherlands, centralization of primary stroke care would probably not lead to shorter EVT-related treatment times in patients with an LVO stroke.

When it comes to transportation of patients from the PSC to the CSC, urgent dispatch of the transferring ambulance is essential. As discussed in Chapter 2, the transferring ambulance is too often not dispatched with the highest level of urgency – this was the case for 14% of patients in our study. Ambulance dispatch with a lower urgency level was associated with a 28-minute treatment delay. Several national and international stroke care protocols currently do not provide a recommendation regarding the urgency with which ambulances transferring patients from a PSC for EVT should be dispatched.[13-15] Standard ambulance dispatch at the highest level of urgency for EVT transfers should be implemented, and its importance needs to be conveyed to dispatch and EMS organizations, as well as PSCs.

After arrival of a transferred patient at the CSC, EVT needs to be initiated as soon as possible. Therefore, unnecessary repetition of neuroimaging should be avoided. In Chapter 5, we showed that repeating imaging at the CSC is associated with a treatment delay of 20 minutes. While repeating imaging was useful in patients who showed clinical improvement, as the LVO had resolved in 58% of these patients, it rarely yielded relevant findings in patients with clinical deterioration. Therefore, in the latter population, refraining from repeating imaging is warranted in most cases. To be able to avoid unnecessary repetition of imaging at the CSC, a fast and reliable system for transferring imaging data from PSC to CSC needs to be in place. Recently, a randomized trial has shown that patients with an LVO stroke benefit from direct presentation to the angiography suite, as this reduces door-to-groin time by 24 minutes and improves clinical outcome.[16] Therefore, in transferred patients who do not need to undergo repeated neuroimaging at the CSC, direct presentation to the angiography suite should be recommended.

Further improvements

In order to further improve the pre- and interhospital workflow leading up to EVT, we may be able to benefit from decades of research in the field of interventional cardiology, which deals with similar logistical challenges. As with LVO stroke, patients with myocardial infarction require urgent transportation to a hospital capable of

endovascular treatment – in this case, percutaneous coronary intervention (PCI). Despite having electrocardiography as a prehospital triage method, which enables accurate selection of the majority of eligible patients for direct transportation to a PCI-capable hospital, 15-50% of patients are first transported to a hospital where PCI cannot be performed.[17, 18] Several studies have examined the pre- and interhospital workflow for patients who undergo interhospital transfer for PCI, and as it turns out, time metrics are generally much shorter in PCI transfers than in LVO stroke patients transferred for EVT. For example, time between first alarm and start of the intervention is 143-160 minutes on average in patients transferred for PCI,[17, 19, 20] including time spent within the intervention center, which is approximately 36-43 minutes.[20, 21] Thus, time between first alarm and arrival at the intervention center is considerably shorter than the 162 minutes in LVO stroke patients that we found in Chapter 2. Time between arrival at and departure from the primary hospital (door-in-door-out time) is also shorter in the PCI population than in patients transferred for EVT: 52 minutes versus 85 minutes.[17] Although the characteristics of these two populations differ, it may be worth exploring whether measures that have been effective in shortening PCI-related time metrics could also improve the EVT workflow. For example, the European Society of Cardiology recommends that ambulance paramedics presenting a patient with suspected myocardial infarction to a non-PCI-capable hospital await the diagnosis inside the hospital, in order to continue transportation to an intervention center if indicated.[22] Furthermore, having an attending interventional cardiologist on site 24/7 shortens time to treatment by 15 minutes on average.[23] Implementation of similar measures in the EVT workflow could put a strain on EMS services and neurointerventionalists, but this may be outweighed by the potential for improvement of patient outcome if a substantial decrease in treatment times can be achieved.

PART II: FUTURE WORKFLOW

To achieve a logistical system in which patients with an LVO stroke are directly transported to a CSC while all other suspected stroke patients are brought to the nearest PSC, a prehospital LVO detection method is necessary. Such a method would not only drastically improve time metrics prior to arrival at the CSC, but could also shorten door-to-groin time by enabling direct presentation to the angiography suite in case of high likelihood of an LVO stroke. Overall, for the acute management of patients with a suspected stroke, an effective prehospital triage method would be a major game-changer.

Potential solutions

Various methods for prehospital LVO detection have been previously proposed, some of which seem more promising than others. In Chapter 6, we described our views on the requirements of an effective prehospital LVO detection method, which

include high diagnostic accuracy, fast application and interpretation, user-friendliness, compactness, and low costs. Currently, none of the previously studied methods seem to fulfill these requirements.

For some methods, improvement to a point where they would be suitable for prehospital implementation seems unlikely. Such a method is the use of clinical scales, which contain items for scoring the severity of neurological deficits and thereby predict the likelihood of an LVO stroke, as a stand-alone triage instrument. Although there are some clinical scales that can reach relatively high sensitivity and specificity,[24] this requires extensive and repetitive training of ambulance paramedics. More importantly, there is little room for improvement of the diagnostic accuracy of these scales. A substantial proportion of patients with an LVO stroke initally have relatively mild neurological deficits and will therefore probably be classified incorrectly by clinical scales.[25, 26] Furthermore, the relatively low exposure of ambulance paramedics to suspected stroke patients combined with the complexity of a standard neurological examination make reliable application of clinical scales in the prehospital setting difficult.

Another example of a prehospital LVO detection method with many downsides is the Mobile Stroke Unit (MSU). MSUs are ambulances with built-in CT equipment, which enable direct, 'on-scene' diagnosis and even treatment with IVT. Athough this seems promising at first glance, MSUs require specifically trained personnel, often including a CT technician and a vascular neurologist,[23] and are very expensive.[27] These requirements and the lack of cost-effectiveness of this method make broad implementation practically impossible.

Fortunately, other methods for prehospital LVO detection seem more promising. One of these methods is Transcranial Doppler (TCD), a technique that uses ultrasound for the measurement of cerebral blood flow. Preliminary studies have shown that TCD can detect LVO stroke with high diagnostic accuracy in patients with a suspected stroke in an in-hospital setting.[34-36] However, prehospital use of TCD is currently not feasible because measurement times are long and existing systems are not user-friendly in their application and interpretation. New TCD devices that are portable and use automated algorithms for LVO detection are currently being developed.[27, 28] If measurement times can be decreased and user-friendliness is improved, TCD may be suitable for prehospital LVO detection.

In Chapter 6, we proposed EEG as a potential method for prehospital LVO detection. Because EEG is sensitive to cerebral hypoxia, it can detect changes in brain activity in patients with an acute ischemic stroke.[29, 30] Traditional EEG measurements require long preparation times, which makes application of EEG in the prehospital setting challenging. However, solutions for faster and easier application are available.

Dry electrodes, for example, require no skin preparation and can shorten EEG preparation time to less than 5 minutes.[31] In Chapter 7, we presented the first results of ELECTRA-STROKE (NCT03699397), an ongoing study with the primary aim to determine the diagnostic accuracy of dry electrode EEG for LVO detection in the prehospital setting. To gain insight into which EEG features best discriminate between patients with and without an LVO stroke, dry electrode EEGs are also performed in suspected stroke patients in the emergency room within ELECTRA-STROKE. In the first 100 patients enrolled in the emergency room, using a model with two combined EEG features, EEG was able to identify LVO stroke with a sensitivity of 100% and a specificity of 84% (Chapter 6). However, this model may have been over-fitted and requires external validation. Furthermore, 35% of included patients had EEG data that were of insufficient quality for analysis. This may have been due to very short EEG preparation times, as well as the relatively low signal quality that is inherent to the use of dry electrodes. EEG quality did improve over the course of the study as personnel performing the measurements became more experienced and other storing file formats were used (32-bit instead of 16-bit files). Nonetheless, additional measures to improve signal quality are necessary. Possibilities to further improve EEG data quality may include increasing the electrode surface area and the number of electrodes, enforcing better electrode-skin contact by adding a conductive substance and increasing the pressure of the electrodes on the skin, and providing live feedback of the signal quality prior to starting the EEG recording.

Finally, instead of using a single LVO detection instrument, combining multiple instruments may be the future of prehospital stroke triage. In this scenario, instruments could be used either simultaneously or consecutively to boost diagnostic accuracy. An example of two instruments being used simultaneously is the combination of EEG and a clinical scale. A previous study of suspected stroke patients in the emergency room found that EEG alone could predict LVO stroke with an area under the curve of 69, but when combined with clinical data, the area under the curve increased to 86.[31] Consecutive use of two instruments could entail using a simple instrument with high sensitivity first, to 'exclude' patients with a low probability of LVO stroke, followed by a more complex or invasive test in the remaining population. A clinical scale or perhaps a point of care biomarker test (CINTICS project, Netherlands Trial Register number: NL8961) may be used as the first 'screening' instrument, followed by EEG or TCD, for example. Such a method could improve positive predicitive value by increasing the a priori probability of LVO stroke for the second diagnostic test.

Future directions

When ELECTRA-STROKE is completed, we will have a first indication of whether EEG may be suitable for prehospital LVO detection. With the data collected in the prehospital phase of the study, we will expand our knowledge of which EEG features

best discriminate between patients with and without an LVO stroke. However, because we have already learned that EEG data quality and diagnostic accuracy will need to be further improved, this will be the focus of a second study that is currently being prepared: AI-STROKE (NL75429.018.20). This study will commence after completion of ELECTRA-STROKE and has the primary objective to increase data quality and diagnostic accuracy of prehospital dry electrode EEG. Ambulance paramedics will perform dry electrode EEG measurements in a maximum of 1000 patients, whose data will be used to develop artificial intelligence-based algorithms for artefact rejection and LVO detection. Furthermore, several hardware adjustments to improve EEG signal quality will be applied and tested in cooperation with a manufacturer of dry electrode EEG caps. If AI-STROKE is successful, the effect of prehospital LVO detection with dry electrode EEG on treatment times and clinical outcome will need to be investigated in a large (randomized) clinical trial.

CONCLUSIONS

The current drip-and-ship model for the transportation of patients with an LVO stroke for EVT is far from ideal. Although it is currently the most feasible model, there is certainly room for improvement. Measures that could be implemented relatively easily are standard ambulance dispatch with the highest level of urgency for EVT transfers and refraining from repetition of neuroimaging at the CSC in patients with neurological deterioration. These two measures can decrease time to treatment by 28 and 20 minutes, respectively.

Even more importantly, a method for prehospital LVO detection is necessary to enable paramedics to transport patients directly to the right hospital and abandon the drip-and-ship model once and for all. Dry electrode EEG may be suitable for this purpose, as preliminary results of our diagnostic accuracy study indicated that this method can detect LVO stroke with fairly high accuracy. However, signal quality needs to be improved and validation in the prehospital setting is necessary.

REFERENCES

1. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311-2321
2. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V, et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923-930
3. Goyal M, Almekhlafi MA, Fan L, Menon BK, Demchuk AM, Yeatts SD, et al. Evaluation of interval times from onset to reperfusion in patients undergoing endovascular therapy in the interventional management of stroke iii trial. *Circulation*. 2014;130:265-272
4. Mehta BP, Leslie-Mazwi TM, Chandra RV, Bell DL, Sun CH, Hirsch JA, et al. Reducing door-to-puncture times for intra-arterial stroke therapy: A pilot quality improvement project. *J Am Heart Assoc*. 2014;3:e000963
5. Aghaebrahim A, Streib C, Rangaraju S, Kenmuir CL, Giurgiutiu DV, Horev A, et al. Streamlining door to recanalization processes in endovascular stroke therapy. *J Neurointerv Surg*. 2017;9:340-345
6. Kamal N, Smith EE, Menon BK, Eesa M, Ryckborst KJ, Poppe AY, et al. Improving reperfusion time within the escape endovascular clinical trial. *Eur Stroke J*. 2017;2:64-69
7. Psychogios MN, Behme D, Schregel K, Tsogkas I, Maier IL, Leyhe JR, et al. One-stop management of acute stroke patients: Minimizing door-to-reperfusion times. *Stroke*. 2017;48:3152-3155
8. Goldstein ED, Schnusenberg L, Mooney L, Raper CC, McDaniel S, Thorpe DA, et al. Reducing door-to-reperfusion time for mechanical thrombectomy with a multitiered notification system for acute ischemic stroke. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:119-128
9. Tra J, van der Wulp I, de Bruijne MC, Wagner C. Exploring the treatment delay in the care of patients with st-elevation myocardial infarction undergoing acute percutaneous coronary intervention: A cross-sectional study. *BMC Health Serv Res*. 2015;15:340
10. Kunte SA, Anderson D, Brown-Espaillat K, Froehler MT. Total transfer time for ground vs. Air transport for interhospital and scene transfers of acute stroke patients. *J Stroke Cerebrovasc Dis*. 2021;30:105704
11. McTaggart RA, Moldovan K, Oliver LA, Dibiasio EL, Baird GL, Hemendinger ML, et al. Door-in-door-out time at primary stroke centers may predict outcome for emergent large vessel occlusion patients. *Stroke*. 2018;49:2969-2974
12. Choi PMC, Tsoi AH, Pope AL, Leung S, Frost T, Loh PS, et al. Door-in-door-out time of 60 minutes for stroke with emergent large vessel occlusion at a primary stroke center. *Stroke*. 2019;50:2829-2834
13. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2018;49:e46-e110
14. Adeoye O, Nystrom KV, Yavagal DR, Luciano J, Nogueira RG, Zorowitz RD, et al. Recommendations for the establishment of stroke systems of care: A 2019 update. *Stroke*. 2019;50:e187-e210
15. Nederland A. Nationwide protocol ambulance care (in dutch: Landelijk protocol ambulancezorg), version 8.1. June 2016.
16. Requena M, Olive-Gadea M, Muchada M, Hernandez D, Rubiera M, Boned S, et al. Direct to angiography suite without stopping for computed tomography

imaging for patients with acute stroke: A randomized clinical trial. *JAMA Neurol*. 2021

17. Mahmoud KD, Gu YL, Nijsten MW, de Vos R, Nieuwland W, Zijlstra F, et al. Interhospital transfer due to failed prehospital diagnosis for primary percutaneous coronary intervention: An observational study on incidence, predictors, and clinical impact. *Eur Heart J Acute Cardiovasc Care*. 2013;2:166-175
18. Manari A, Ortolani P, Guastaroba P, Casella G, Vignali L, Varani E, et al. Clinical impact of an inter-hospital transfer strategy in patients with st-elevation myocardial infarction undergoing primary angioplasty: The emilia-romagna st-segment elevation acute myocardial infarction network. *Eur Heart J*. 2008;29:1834-1842
19. Dorsch MF, Greenwood JP, Priestley C, Somers K, Hague C, Blaxill JM, et al. Direct ambulance admission to the cardiac catheterization laboratory significantly reduces door-to-balloon times in primary percutaneous coronary intervention. *Am Heart J*. 2008;155:1054-1058
20. Rathod KS, Jain AK, Firoozi S, Lim P, Boyle R, Nevett J, et al. Outcome of inter-hospital transfer versus direct admission for primary percutaneous coronary intervention: An observational study of 25,315 patients with st-elevation myocardial infarction from the london heart attack group. *Eur Heart J Acute Cardiovasc Care*. 2020;9:948-957
21. Wang TY, Peterson ED, Ou FS, Nallamothu BK, Rumsfeld JS, Roe MT. Door-to-balloon times for patients with st-segment elevation myocardial infarction requiring interhospital transfer for primary percutaneous coronary intervention: A report from the national cardiovascular data registry. *Am Heart J*. 2011;161:76-83 e71
22. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 esc guidelines for the management of acute myocardial infarction in patients presenting with st-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with st-segment elevation of the european society of cardiology (esc). *Eur Heart J*. 2018;39:119-177
23. Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. 2006;355:2308-2320
24. Duvekot MHC, Venema E, Rozeman AD, Moudrous W, Vermeij FH, Biekart M, et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (presto): A prospective observational study. *Lancet Neurol*. 2021;20:213-221.
25. Lee VH, Thakur G, Nimjee SM, Youssef PP, Lakhani S, Heaton S, et al. Early neurologic decline in acute ischemic stroke patients receiving thrombolysis with large vessel occlusion and mild deficits. *J Neurointerv Surg*. 2020;12:1085-1087
26. Maas WJ, Lahr MMH, Buskens E, van der Zee DJ, Uyttenboogaart M, Investigators C. Pathway design for acute stroke care in the era of endovascular thrombectomy: A critical overview of optimization efforts. *Stroke*. 2020;51:3452-3460
27. Inc. BC. Sonas: Diagnosis and monitoring.
28. Expedite study evaluates neural analytics' portable transcranial doppler technology to measure early strokes. 2017
29. Finnigan S, van Putten MJ. Eeg in ischaemic stroke: Quantitative eeg can uniquely inform (sub-)acute prognoses and clinical management. *Clin Neurophysiol*. 2013;124:10-19
30. van Putten MJ, Tavy DL. Continuous quantitative eeg monitoring in hemispheric stroke patients using the brain symmetry index. *Stroke*. 2004;35:2489-2492
31. Erani F, Zolotova N, Vanderschelden B, Khoshab N, Sarian H, Nazarzai L, et al. Electroencephalography might improve diagnosis of acute stroke and large vessel occlusion. *Stroke*. 2020:Strokeaha120030150

SUMMARY

Chapter 1: General introduction and thesis outline

Patients with a large vessel occlusion (LVO) stroke often have severe neurological deficits and a high risk of permanent disability and death. There are two types of acute treatment for LVO stroke: intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). Both treatments need to be initiated as soon as possible, because this improves the prognosis of patients. While IVT can be given in all hospitals that provide acute stroke care, EVT can only be performed in specialized hospitals, so-called comprehensive stroke centers (CSCs). Patients with a suspected stroke are often first transported to a primary stroke center (PSC) for a diagnostic work-up and possible initiation of IVT. If they turn out to be eligible for EVT, they are subsequently transported to the nearest CSC. This 'drip-and-ship model' delays initiation of EVT by approximately 40 to 106 minutes and decreases the chance of functional independence by about 8%. Nonetheless, it is currently the most feasible model, as transporting all suspected stroke patients directly to a CSC would overburden these hospitals and would delay treatment with IVT for all patients with an acute ischemic stroke, including those without an LVO.

To be able to abandon the drip-and-ship model, a method for prehospital LVO detection is necessary. Such a method would enable paramedics to transport patients with an LVO stroke directly to a CSC, while all other patients would be transported to the nearest PSC. However, as long as the drip-and-ship model is still in place, we must also aim to improve the workflow within this model. In the first part of this thesis, we focus on improving the current workflow. We provide an overview of the current pre- and interhospital time metrics for LVO stroke patients in the Netherlands and discuss several measures to shorten time to EVT within the drip-and-ship model. In the second part of this thesis, we outline the necessity of and possibilities for a prehospital LVO detection method, and propose electroencephalography (EEG) as a potentially suitable instrument for this purpose.

PART I: CURRENT WORKFLOW

Chapter 2: Pre- and interhospital workflow times for patients with large vessel occlusion stroke in the Netherlands

In this cohort study, we used data from the regional emergency medical service and our own EVT registry to provide an overview of the pre- and interhospital time metrics in patients transferred from a PSC for EVT in the Netherlands. Furthermore, we analyzed associations between various clinical and workflow-related factors and time to EVT. We included 198 patients with an LVO stroke. Median time between first call to the ambulance dispatch center and arrival at the PSC was 37 minutes, time between

arrival at the PSC and departure from the PSC was 85 minutes, and travel time from PSC to CSC by ambulance was 28 minutes. Altogether, median time between first call and arrival at the CSC (call-to-CSC time) was 162 minutes. We found that dispatching the transferring ambulance with the highest level of urgency, which was done in 86% of cases, was associated with a 28-minute decrease (95% CI: 4 to 51 minutes) in time to arrival at the CSC. If the first call to the dispatch center was made by a general practitioner, this was associated with a delay of 34 minutes (95% CI: 7 to 61 minutes), although this was the case for only 5% of patients. No clinical characteristics were associated with call-to-CSC time. We concluded by recommending that the general population should be instructed to contact the local emergency phone number directly when symptoms of stroke are recognized, and that incorporating standard ambulance dispatch with the highest level of urgency for EVT transfers into stroke care protocols should be considered.

Chapter 3: Interhospital transfer vs. direct presentation of patients with a large vessel occlusion not eligible for i.v. thrombolysis

Using data from a large, nationwide EVT registry, we assessed whether interhospital transfer prior to EVT of patients who are not eligible for IVT is associated with treatment delay and worse clinical outcome. We included patients who were treated with EVT, but not with IVT. This was the case for 680/3637 (19%) patients in the registry. The most common contraindications for IVT were anticoagulation use (49%) and presentation >4.5 hours after onset (26%). Of the 680 included patients, 389 (57%) were directly presented to a CSC and 291 (43%) were transferred from a PSC. Time between arrival at the first hospital and initiation of EVT (first-door-to-groin time) was shorter for the directly presented group (adjusted time difference = 51 minutes [95% CI: 38 to 64 minutes]). Even when we additionally adjusted for increased ambulance travel time, first-door-to-groin time was substantially shorter, with an adjusted time difference of 28 minutes (95% CI: 15 to 41 minutes). Clinical outcome was also slightly better in directly presented patients, although this was not statistically significant. We suggested that, since there is no obvious disadvantage in bypassing the PSC in this patient population, directly presenting patients with a suspected stroke and a contraindication for IVT to a CSC may be considered if logistically feasible.

Chapter 4: Relationship between primary stroke center volume and time to endovascular thrombectomy in acute ischemic stroke

In this study, we hypothesized that the volume of patients with an LVO stroke presented to a PSC may affect EVT-related treatment times, as more exposure to these patients may be associated with more streamlined care pathways within the PSC, more experienced staff when it comes to acute stroke treatment, and better

facilities for acute stroke imaging. We investigated whether the annual number of patients referred from a PSC for EVT is associated with treatment times and functional outcome, using multivariable regression modelling. We included 1541 patients who were referred from 65 PSCs for EVT. EVT referral volume was not associated with time between arrival at the PSC and initiation of EVT (adjusted coefficient: -0.49 minutes/annual referral, 95% CI: -1.27 to 0.29 minutes) or other treatment times. We also found no association between EVT referral volume and clinical outcome. Based on our data, in acute stroke care systems like that in the Netherlands, increasing PSC volumes would not appear to translate into better EVT-related time metrics or patient outcome.

Chapter 5: Value of repeated imaging in patients with a stroke who are transferred for endovascular treatment

Stroke patients who are transferred to a CSC for EVT often undergo repeated neuroimaging prior to EVT. In this chapter, we evaluated the diagnostic yield of repeating imaging in these patients and its effect on treatment times. We included patients who were referred to our hospital for EVT, and excluded those who underwent repeated imaging because primary imaging was unavailable, incomplete or of insufficient quality. Of the 551 included patients, 165 (30%) underwent repeated imaging, mostly because of clinical improvement (86/165 [52%]) or deterioration (40/165 [24%]). Repeated imaging patients had longer door-to-groin times than patients without repeated imaging (adjusted time difference: 20 minutes, 95% CI: 15 to 25 minutes). Among patients who underwent repeated imaging because of clinical improvement, the LVO had resolved in 50/86 (58%). In patients with clinical deterioration, repeated imaging led to refrainment from EVT in 3/40 (8%). No symptomatic intracranial hemorrhages were identified. We concluded that repeating neuroimaging does not seem beneficial in patients with clinical deterioration, but is very useful in patients with clinical improvement, since it helps avoid futile diagnostic angiographies in more than half of this population.

PART II: FUTURE WORKFLOW

Chapter 6: Detection of large vessel occlusion stroke in the prehospital setting: electroencephalography as a potential triage instrument

In this chapter, we outlined our view on the requirements of an effective prehospital LVO detection method, namely: high diagnostic accuracy, fast application and interpretation, user-friendliness, compactness, and low costs. We argued that existing methods for prehospital LVO detection, including clinical scales, Mobile Stroke Units and transcranial Doppler, do not fulfill all criteria, hindering broad implementation of these methods. Instead, electroencephalography (EEG) may be

suitable for prehospital LVO detection, since in-hospital studies have shown that several measures that quantify hypoxia-induced changes in the EEG signal have good diagnostic accuracy for LVO stroke. Although performing EEG measurements in the prehospital setting comes with challenges, solutions for fast and simple application of this method are available. Currently, the feasibility and diagnostic accuracy of EEG in the prehospital setting are being investigated in clinical trials.

Chapter 7: Detection of large vessel occlusion stroke with electroencephalography in the emergency room: first results of the ELECTRA-STROKE study

ELECTRA-STROKE (NCT03699397) investigates the diagnostic accuracy of dry electrode EEG for LVO stroke detection in the prehospital setting. To determine which EEG features are most useful for this purpose and to assess data quality, EEGs are also performed in the emergency room (ER). In this chapter, we reported data of the first 100 patients included in the ER. Patients presented to the ER with a suspected stroke or known LVO stroke underwent a single EEG prior to EVT. Diagnostic accuracy of frequency band power, brain symmetry and phase synchronization measures were evaluated. EEG data were of sufficient quality for analysis in 65/100 included patients. Of these, 35/65 (54%) had an acute ischemic stroke, of whom 9 (14% of the 65 analyzed patients) had an LVO stroke. Median time between symptom onset and EEG acquisition was 266 minutes (IQR: 121 to 655 minutes) and median EEG recording time was 3 minutes (IQR 3 to 5 minutes). The EEG feature with the highest diagnostic accuracy for LVO stroke was theta-alpha ratio (AUC 0.83; sensitivity 75%; specificity 81%). Combined, weighted phase lag index and relative theta-power best identified LVO stroke (sensitivity 100%; specificity 84%). We concluded that dry electrode EEG is a promising tool for LVO detection, but data quality needs to be improved and validation in the prehospital setting is necessary.

CONCLUSION

The current model for transportation of patients with an LVO stroke for EVT can be substantially improved by implementing some relatively simple measures, such as standard ambulance dispatch with the highest level of urgency for EVT transfers and refraining from repetition of neuroimaging at the CSC in patients with neurological deterioration. These two measures can decrease time to treatment by 28 and 20 minutes, respectively.

Even more importantly, a method for prehospital LVO detection is necessary to enable paramedics to transport patients directly to the right hospital and abandon the current model once and for all. Preliminary results of our diagnostic accuracy study indicate that dry electrode EEG may be suitable for this purpose. However, signal quality needs to be improved and validation in the prehospital setting is necessary.

DUTCH SUMMARY (NEDERLANDSTALIGE SAMENVATTING)

Hoofdstuk 1: Introductie en inhoud van de thesis

Patiënten met een herseninfarct op basis van een occlusie van een groot bloedvat, een zogeheten *large vessel occlusion* (LVO), hebben vaak ernstige neurologische uitval en een hoog risico op permanente invaliditeit en overlijden. Er zijn twee soorten acute behandeling van LVO's: intraveneuze trombolyse (IVT) en intra-arteriële trombectomie (IAT). Beide behandelingen moeten zo snel mogelijk worden gestart, omdat dit de prognose van patiënten verbetert. IVT kan gegeven worden in alle ziekenhuizen die acute behandeling van herseninfarcten bieden, maar IAT wordt alleen gedaan in gespecialiseerde ziekenhuizen ('IAT-ziekenhuizen'). Patiënten met verdenking op een herseninfarct worden vaak eerst naar een regulier ziekenhuis gebracht, waar diagnostiek gedaan wordt en IVT kan worden gestart, maar geen IAT kan worden gedaan. Als blijkt dat zij in aanmerking komen voor IAT, dan worden ze vervolgens naar een IAT-ziekenhuis overgebracht. Dit *drip-and-ship* model vertraagt het starten van IAT met 40 tot 106 minuten en verkleint de kans op functionele onafhankelijkheid met ongeveer 8%. Desalniettemin is het momenteel het meest uitvoerbare model, gezien het direct naar een IAT-ziekenhuis transporteren van alle patiënten met verdenking op een herseninfarct deze ziekenhuizen enorm zou belasten. Daarnaast zou dit behandeling met IVT vertragen voor alle patiënten met een herseninfarct, hetgeen met name nadelig zou zijn voor degenen die geen LVO hebben.

Om van het *drip-and-ship* model af te kunnen stappen, is een methode voor prehospitale detectie van LVO's nodig. Zo'n methode zou ambulanceverpleegkundigen ertoe in staat stellen om patiënten met een LVO direct naar een IAT-ziekenhuis te brengen, terwijl alle andere patiënten naar het dichtstbijzijnde reguliere ziekenhuis worden gebracht. Echter, zo lang het *drip-and-ship* model nog in gebruik is, moeten we proberen de *workflow* binnen dit model zoveel mogelijk te verbeteren. In het eerste deel van deze thesis focussen we ons op het verbeteren van de huidige *workflow*. We geven een overzicht van de huidige pre- en interhospitale tijdsintervallen bij patiënten die in Nederland worden overgeplaatst voor IAT. Tevens beschrijven we een aantal methoden waarmee de tijd tot het starten van IAT kan worden verkort binnen het *drip-and-ship* model. In het tweede deel van deze thesis bespreken we de noodzaak tot en de mogelijkheden voor het vinden van een methode voor prehospitale LVO detectie. Tenslotte dragen we electroencefalografie (EEG) aan als een potentieel geschikt instrument voor dit doel.

DEEL I: HUIDIGE WORKFLOW

Hoofdstuk 2: Pre- en interhospitale workflow bij patiënten met een LVO in Nederland

Voor deze cohort-studie hebben we data gebruikt van de regionale ambulancedienst en onze eigen IAT-registratie om een overzicht te geven van pre- en interhospitale tijdsintervallen bij patiënten die voor IAT worden overgeplaatst in Nederland. Daarnaast hebben we associaties tussen verschillende klinische en logistieke factoren en behandeltijden geanalyseerd. We hebben 198 patiënten met een LVO geïncludeerd. Mediane tijd tussen het eerste telefonisch contact met de ambulance-meldkamer en aankomst bij het eerste ziekenhuis was 37 minuten, tijd tussen aankomst bij het eerste ziekenhuis en vertrek uit dat ziekenhuis was 85 minuten, en reistijd per ambulance tussen het eerste ziekenhuis en het IAT-ziekenhuis was 28 minuten. In totaal was de mediane tijd tussen het eerste contact met de meldkamer en aankomst in het IAT-ziekenhuis 162 minuten. We zagen dat als de ambulance voor de overplaatsing met het hoogste niveau van urgentie was uitgestuurd, hetgeen in 86% van de gevallen gedaan was, dit geassocieerd was met een 28 minuten (95% CI: 4 tot 51 minuten) kortere tijd tot behandeling. Als het eerste contact met de meldkamer via de huisarts verliep, was dat geassocieerd met een vertraging van 34 minuten (95% CI: 7 tot 61 minuten). Dit laatste was echter slechts bij 5% van de patiënten het geval. Klinische karakteristieken waren niet geassocieerd met tijd tot behandeling. We concludeerden dat de algemene bevolking geïnstrueerd moeten worden om het lokale noodnummer te bellen als zich symptomen van een herseninfarct voordoen en dat het standaard uitsturen van ambulances voor IAT-overplaatsingen met het hoogste niveau van urgentie moet worden geïmplementeerd.

Hoofdstuk 3: Overplaatsing versus directe presentatie van patiënten met een LVO die niet voor intraveneuze trombolyse in aanmerking komen

Met behulp van data uit een grote, nationale IAT-registratie hebben we onderzocht of overplaatsing voor IAT van patiënten die niet voor IVT in aanmerking komen, geassocieerd is met vertraging van de behandeling en slechtere klinische uitkomst. We hebben patiënten geïncludeerd die wel met IAT, maar niet met IVT behandeld waren, hetgeen het geval was bij 680/3637 (19%) patiënten in de registratie. De meest voorkomende contra-indicaties voor IVT waren gebruik van antistolling (49%) en presentatie meer dan 4,5 uur na ontstaan van de symptomen (26%). Van de 680 geïncludeerde patiënten waren er 389 (57%) direct in een IAT-ziekenhuis gepresenteerd en 291 (43%) overgeplaatst vanuit een regulier ziekenhuis. Tijd tussen aankomst in het eerste ziekenhuis en starten van IAT (eerste-deur-tot-lies-tijd) was korter voor patiënten die direct gepresenteerd waren (gecorrigeerd tijdsverschil: 51 minuten [95% CI: 38 tot 64 minuten]). Zelfs wanneer we aanvullend corrigeerden

voor ambulance-reistijd bleef de eerste-deur-tot-lies-tijd substantieel korter voor direct gepresenteerde patiënten, met een gecorrigeerd tijdsverschil van 28 minuten (95% CI: 15 tot 41 minuten). Klinische uitkomst was ook iets beter, hoewel dit verschil niet statistisch significant was. We hebben gesuggereerd dat, gezien er geen evident nadeel is van directe presentatie in een IAT-ziekenhuis voor deze populatie, directe presentatie van patiënten met verdenking op een herseninfarct en een contra-indicatie voor IVT kan worden overwogen indien dit logistiek haalbaar is.

Hoofdstuk 4: De relatie tussen het volume van het verwijzende ziekenhuis en tijd tot behandeling met intra-arteriële trombectomie

De hypothese van deze studie was dat het volume van patiënten met een LVO die jaarlijks worden doorverwezen vanuit reguliere ziekenhuizen de tijd tot behandeling met IAT zou kunnen beïnvloeden, gezien dit volume geassocieerd zou kunnen zijn met een meer gestroomlijnde *workflow*, meer ervaren werknemers en/of betere faciliteiten voor acute beeldvorming in het verwijzende ziekenhuis. We hebben onderzocht of het verwijs-volume van ziekenhuizen voor IAT geassocieerd is met tijd tot behandeling en klinische uitkomst. Hiervoor gebruikten we multilevel regressieanalyse. We includeerden 1541 patiënten, die vanuit 65 verschillende ziekenhuizen waren verwezen voor IAT. Verwijs-volume bleek niet geassocieerd met tijd tussen aankomt in het verwijzende ziekenhuis en het starten van IAT (gecorrigeerde coëfficiënt: -0,49 minuten/jaarlijkse verwijzing, 95% CI: -1,27 tot 0,29 minuten) of andere behandeltijden. We vonden ook geen associatie tussen verwijs-volume en klinische uitkomst. Op basis van onze data lijkt het erop dat, in een zorgsysteem als dat in Nederland, het vergroten van het volume van ziekenhuizen die patiënten voor IAT verwijzen zich niet zou vertalen in snellere IAT-gerelateerde behandeltijden of betere klinische uitkomsten.

Hoofdstuk 5: De waarde van herhaalde beeldvorming bij patiënten die overgeplaatst worden voor intra-arteriële trombectomie

Patiënten met een herseninfarct die voor IAT worden overgeplaatst, ondergaan vaak voorafgaand aan IAT herhaalde beeldvorming van de hersenen bij aankomst in het IAT-ziekenhuis. In dit hoofdstuk hebben we de diagnostische waarde van deze herhaalde beeldvorming onderzocht, evenals het effect van herhaalde beeldvorming op de tijd tot behandeling. We hebben patiënten geïncludeerd die naar ons ziekenhuis waren verwezen voor IAT en patiënten geëxcludeerd die herhaalde beeldvorming ondergingen omdat de beeldvorming uit het verwijzende ziekenhuis niet beschikbaar, incompleet of van onvoldoende kwaliteit was. Van de 551 geïncludeerde patiënten ondergingen er 165 (30%) herhaalde beeldvorming, meestal omdat er sprake was van klinische verbetering (86/165 [52%]) of klinische achteruitgang (40/165 [24%]).

Bij patiënten met herhaalde beeldvorming was de tijd tussen aankomst in het IAT-ziekenhuis en starten van IAT langer dan bij patiënten zonder herhaalde beeldvorming (gecorrigeerd tijdsverschil: 20 minuten, 95% CI: 15 tot 25 minuten). Patiënten die herhaalde beeldvorming ondergingen vanwege klinische verbetering hadden in 50/86 (58%) gevallen geen LVO meer. Bij patiënten die herhaalde beeldvorming ondergingen in verband met klinische achteruitgang leidde herhaalde beeldvorming in 3/40 (8%) gevallen tot het besluit geen IAT te verrichten. Er werden geen symptomatische hersenbloedingen gezien op de herhaalde beeldvorming. We concludeerden dat het herhalen van beeldvorming van de hersenen niet zinvol lijkt bij patiënten met klinische achteruitgang, maar wel erg nuttig is bij patiënten met klinische verbetering, gezien het in die populatie in meer dan de helft van de gevallen een zinloze diagnostische angiografie voorkomt.

DEEL II: TOEKOMSTIGE WORKFLOW

Hoofdstuk 6: LVO detectie in de prehospitale setting: electroencefalografie als potentieel triage-instrument

In dit hoofdstuk hebben we onze visie op de criteria voor een effectieve methode voor prehospitale LVO detectie beschreven. Deze criteria zijn hoge diagnostische accuratesse, snelle toepassing en interpretatie, gebruiksvriendelijkheid, compactheid en lage kosten. We bepleitten dat bestaande methoden voor prehospitale LVO detectie, waaronder klinische schalen, 'Mobile Stroke Units' en transcraniële Doppler, niet voldoen aan de genoemde criteria. In plaats van deze methoden droegen we het EEG aan als een potentieel geschikt instrument voor dit doel. Eerdere studies hebben laten zien dat EEG de door zuurstoftekort veroorzaakte veranderingen in de elektrische activiteit van de hersenen kan detecteren bij patiënten met een LVO, met vrij goede diagnostische accuratesse. Hoewel het verrichten van EEG-metingen in de prehospitale setting uitdagingen met zich meebrengt, zijn er methoden voor snelle en simpele toepassing voorhanden. Momenteel worden de haalbaarheid en diagnostische accuratesse van het EEG voor LVO detectie in de prehospitale setting onderzocht in klinische studies.

Hoofdstuk 7: LVO detectie met electroencefalografie op de spoedeisende hulp: eerste resultaten van de ELECTRA-STROKE studie

ELECTRA-STROKE (NCT03699397) onderzoekt de diagnostische accuratesse van EEG met droge electroden voor LVO detectie in de prehospitale setting. Om te kunnen bepalen welke EEG-karakteristieken het meest bruikbaar zijn voor dit doel en om datakwaliteit van de EEG's te analyseren, worden binnen ELECTRA-STROKE ook EEG's op de spoedeisende hulp (SEH) verricht. In dit hoofdstuk beschreven we de resultaten van de eerste 100 patiënten die op de SEH zijn geïncludeerd. Patiënten die op de

SEH werden gepresenteerd met een verdenking op een herseninfarct of een reeds elders vastgestelde LVO ondergingen een EEG voorafgaand aan IAT. We evalueerden de diagnostische accuratesse van verschillende EEG-karakteristieken. EEG-data waren van voldoende kwaliteit voor analyse in 65/100 geïncludeerde patiënten. Van deze patiënten hadden 35/65 (54%) een herseninfarct, van wie er 9 (14% van de 65 geanalyseerde patiënten) een LVO hadden. Mediane tijd tussen ontstaan van de symptomen en verrichten van het EEG was 266 minuten (IQR: 121 tot 655 minuten) en mediane EEG-duur was 3 minuten (IQR 3-5 minuten). Het EEG-karakteristiek met de hoogste diagnostische accuratesse voor LVO detectie was de theta-alfa ratio (AUC 0,83; sensitiviteit 75%; specificiteit 81%). Gecombineerd presteerden de *weighted phase lag index* en de relatieve theta het beste, met een sensitiviteit van 100% bij een specificiteit van 84%. We concludeerden dat EEG met droge electroden een veelbelovend instrument voor prehospitale LVO detectie is, maar dat de kwaliteit van de EEG-data moet worden verbeterd en dat validatie in de prehospitale setting nodig is.

CONCLUSIE

Het huidige *drip-and-ship* model voor transport van patiënten die voor IAT in aanmerking komen, zou substantieel kunnen worden verbeterd door het implementeren van een aantal relatief simpele maatregelen. Het standaard uitsturen van ambulances voor IAT-overplaatsingen met het hoogste niveau van urgentie en het afzien van herhalen van beeldvorming bij aankomst in het IAT-ziekenhuis bij patiënten met neurologische achteruitgang kunnen tijd tot behandeling verkorten met 28 en 20 minuten, respectievelijk.

Misschien wel nog belangrijker is het vinden van een methode voor prehospitale LVO detectie. Zo'n methode zou het mogelijk maken om patiënten direct naar het juiste ziekenhuis te vervoeren en af te stappen van het huidige *drip-and-ship* model. De eerste resultaten van onze diagnostische studie wijzen erop dat het EEG mogelijk een geschikt instrument is voor dit doel. Echter, kwaliteit van de EEG-data moet eerst verbeterd worden en validatie in de prehospitale setting is nodig.

LIST OF ABBREVIATIONS

A1	first segment of the anterior cerebral atery
ACA	anterior cerebral artery
ACM	middle cerebral artery
AI-STROKE	Algorithm development through artificial intelligence for the triage of stroke patients in the ambulance with electroencephalography
AIS	acute ischemic stroke
ALS	advanced life support
AMC	Amsterdam UMC, location AMC
ANOVA	analysis of variance
aOR	justed odds ratio
ASPECTS	Alberta Stroke Program Early CT Score
AUC	area under the receiver operating curve
BSI	Brain Symmetry Index
CI	confidence interval
CINTICS	Circulating Nanotraces to Identify the Cause of Stroke
CSC	comprehensive stroke center
CSC DTGT	time from arrival at the comprehensive stroke center to groin puncture
CT	computed tomography
CTA	computed tomopgraphy angiography
DOAC	direct oral anticoagulant
DTGT	time from arrival at the hospital to groin puncture (door-to-groin time)
DTNT	door to needle time
ECG	electrocardiography
EEG	electroencephalography
ELECTRA-STROKE	EEG controlled triage in the ambulance for acute ischemic stroke
ER	emergency room
eTICI	extended thrombolysis in cerebral infarction
EVT	endovascular thrombectomy

FAST	Face-Arm-Speech-Time scale
FDGT	first-door-to-groin time
G-FAST	Gaze-Face-Arm-Speech-Time scale
ICA	internal carotid artery
ICH	intracranial hemorrhage
Inc.	incorporation
INR	International Normalized Ratio
IQR	interquartile range
IVT	intravenous thrombolysis
LVO	large vessel occlusion
LVO-a	large vessel occlusion of the anterior circulation
M1	first segment of the middle cerebral artery
M2	second segment of the middle cerebral artery
MR CLEAN	Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands
mRS	modified Rankin Scale
MSU	Mobile Stroke Unit
NA	not applicable
NCCT	non-contrast computed tomography
NCT	National Clinical Trial number
NIHSS	National Institutes of Health Stroke Scale
NPV	negative predictive value
PCI	percutaneous coronary intervention
pdBSI	pairwise derived Brain Symmetry Index
PPV	positive predictive value
PSC	primary stroke center
PSC DTGT	time from arrival at the primary stroke center to groin puncture
OGT	time from stroke onset to groin puncture (onset-to-groin time)
OR	odds ratio
qEEG	quantative electroencephalography
RACE	Rapid Arterial Occlusion Evaluation scale
RACECAT	A Trial Comparing Transfer to the Closest Local Stroke Center vs. Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory

ROC	receiver operating curve
SD	standard deviation
sICH	symptomatic intracranial hemorrhage
SPIDER	Stroke Prehospital Informed Decision-making using EEG Recordings
SPSS	Statistical Product and Service Solutions
STRATIS	Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke
TCD	transcranial Doppler
VIPS	volumetric impedance phase shift spectroscopy
WPLI	weighted phase lag index

CONTRIBUTING AUTHORS AND AFFILIATIONS

Arrarte Terreros N.	Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam
	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam
Beenen, L.F.M.	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam
Coutinho, J.M.	Neurology, Amsterdam UMC, University of Amsterdam
Dippel, D.W.	Neurology, Erasmus MC University Medical Center, Rotterdam
Emmer, B.J.	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam
van Es, A.C.G.M.	Radiology and Nuclear Medicine, Leiden University Medical Center
Geuzebroek, G.	Emergency Medical Services, Ambulance Amsterdam
van Grondelle, J.A.F.	Emergency Medical Services, Ambulance Amsterdam
Groot, A.E.	Neurology, Amsterdam UMC, University of Amsterdam
Halkes, P.H.A.	Neurology, Noordwest Ziekenhuisgroep, Alkmaar
den Hartog, S.J.	Neurology, Erasmus MC University Medical Center, Rotterdam
	Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam
	Public Health, Erasmus MC University Medical Center, Rotterdam
Kappelhof, M.	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam
Koelman, J.H.T.M.	Clinical Neurophysiology, Amsterdam UMC, University of Amsterdam
	Neurology, Amsterdam UMC, University of Amsterdam
Kommer, G.J.	National Institute of Public Health and the Environment, Center for Nutrition, Prevention and Health services, Bilthoven
Lingsma, H.F.	Public Health, Erasmus MC University Medical Center, Rotterdam
Majoie, C.B.L.M.	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam

Marquering, H.A.	Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam
	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam
Potters, W.V.	Clinical Neurophysiology, Amsterdam UMC, University of Amsterdam
	Neurology, Amsterdam UMC, University of Amsterdam
van der Ree, T.C.	Neurology, Dijklander Ziekenhuis, Hoorn
Riedijk, F.	Emergency Medical Services North-Holland North, Alkmaar
Roos, Y.B.W.E.M.	Neurology, Amsterdam UMC, University of Amsterdam
Roozenbeek, B.	Neurology, Erasmus MC University Medical Center, Rotterdam
Schonewille, W.J.	Neurology, St. Antonius Ziekenhuis, Nieuwegein
Siegers, A.	Emergency Medical Services, Ambulance Amsterdam
Smeekes, M.D.	Emergency Medical Services North-Holland North, Alkmaar
van Stigt, M.N.	Clinical Neurophysiology, Amsterdam UMC, University of Amsterdam
Stolp, J.	Neurology, Amsterdam UMC, University of Amsterdam
van der Veen, B.	Neurology, Noordwest Ziekenhuisgroep, Alkmaar
Venema, E.	Neurology, Erasmus MC University Medical Center, Rotterdam
	Public Health, Erasmus MC University Medical Center, Rotterdam
van der Worp, H.B.	Neurology and Neurosurgery, Brain Center, University Medical Center Utrecht

MR CLEAN REGISTRY GROUP AUTHORS

Executive committee

Diederik W.J. Dippel[1];Aad van der Lugt[2];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Jelis Boiten[14];Jan Albert Vos[8]

Study coordinators

Josje Brouwer[4];Sanne J. den Hartog[1,2,40];Wouter H. Hinsenveld[5,6];Manon Kappelhof[3];Kars C.J. Compagne[2];Robert- Jan B. Goldhoorn[5,6]; Maxim J.H.L. Mulder[1,2]; Ivo G.H. Jansen[3]

Local principal investigators

Diederik W.J. Dippel[1];Bob Roozenbeek[1];Aad van der Lugt[2];Adriaan C.G.M. van Es[2];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Bart J. Emmer[3];Jonathan M. Coutinho[4];Wouter J. Schonewille[7];Jan Albert Vos[8]; Marieke J.H. Wermer[9];Marianne A.A. van Walderveen[10];Julie Staals[5];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Jeannette Hofmeijer[11];Jasper M. Martens[12];Geert J. Lycklama à Nijeholt[13];Jelis Boiten[14];Sebastiaan F. de Bruijn[15];Lukas C. van Dijk[16];H. Bart van der Worp[17];Rob H. Lo[18];Ewoud J. van Dijk[19];Hieronymus D. Boogaarts[20];J. de Vries[22];Paul L.M. de Kort[21]; Julia van Tuijl[21] ;Jo Jo P. Peluso[26];Puck Fransen[22];Jan S.P. van den Berg[22];Boudewijn A.A.M. van Hasselt[23];Leo A.M. Aerden[24];René J. Dallinga[25];Maarten Uyttenboogaart[28];Omid Eschgi[29];Reinoud P.H. Bokkers[29];Tobien H.C.M.L. Schreuder[30];Roel J.J. Heijboer[31];Koos Keizer[32];Lonneke S.F. Yo[33];Heleen M. den Hertog[22];Emiel J.C. Sturm[35]; Paul Brouwers[34]

Imaging assessment committee

Charles B.L.M. Majoie[3](chair);Wim H. van Zwam[6];Aad van der Lugt[2];Geert J. Lycklama à Nijeholt[13];Marianne A.A. van Walderveen[10];Marieke E.S. Sprengers[3];Sjoerd F.M. Jenniskens[27];René van den Berg[3];Albert J. Yoo[38];Ludo F.M. Beenen[3];Alida A. Postma[6];Stefan D. Roosendaal[3];Bas F.W. van der Kallen[13];Ido R. van den Wijngaard[13];Adriaan C.G.M. van Es[2];Bart J. Emmer[3];Jasper M. Martens[12]; Lonneke S.F. Yo[33];Jan Albert Vos[8]; Joost Bot[36], Pieter-Jan van Doormaal[2]; Anton Meijer[27];Elyas Ghariq[13]; Reinoud P.H. Bokkers[29];Marc P. van Proosdij[37];G. Menno Krietemeijer[33];Jo P. Peluso[26];Hieronymus D. Boogaarts[20];Rob Lo[18];Dick Gerrits[35];Wouter Dinkelaar[2]Auke P.A. Appelman[29];Bas Hammer[16];Sjoert Pegge[27];Anouk van der Hoorn[29];Saman Vinke[20].

Writing committee

Diederik W.J. Dippel[1](chair);Aad van der Lugt[2];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Geert J. Lycklama à Nijeholt[13];Jelis Boiten[14];Jan Albert Vos[8];Wouter J. Schonewille[7];Jeannette Hofmeijer[11];Jasper M. Martens[12];H. Bart van der Worp[17];Rob H. Lo[18]

Adverse event committee

Robert J. van Oostenbrugge[5](chair);Jeannette Hofmeijer[11];H. Zwenneke Flach[23]

Trial methodologist

Hester F. Lingsma[40]

Research nurses / local trial coordinators

Naziha el Ghannouti[1];Martin Sterrenberg[1];Corina Puppels[7];Wilma Pellikaan[7];Rita Sprengers[4];Marjan Elfrink[11];Michelle Simons[11];Marjolein Vossers[12];Joke de Meris[14];Tamara Vermeulen[14];Annet Geerlings[19];Gina van Vemde[22];Tiny

Simons[30];Cathelijn van Rijswijk[21];Gert Messchendorp[28];Nynke Nicolaij[28];Hester Bongenaar[32];Karin Bodde[24];Sandra Kleijn[34];Jasmijn Lodico[34];Hanneke Droste[34];Maureen Wollaert[5];Sabrina Verheesen[5];D. Jeurrissen[5];Erna Bos[9];Yvonne Drabbe[15];Michelle Sandiman[15];Marjan Elfrink[11];Nicoline Aaldering[11];Berber Zweedijk[17];Mostafa Khalilzada[15];Jocova Vervoort[21];Hanneke Droste[34];Nynke Nicolaij[2];Michelle Simons[11];Eva Ponjee[22];Sharon Romviel[19];Karin Kanselaar[19];Erna Bos[9];Denn Barning[10].

PhD / Medical students

Esmee Venema[40]; Vicky Chalos[1,40];Ralph R. Geuskens[3]; Tim van Straaten[19];Saliha Ergezen[1]; Roger R.M. Harmsma[1]; Daan Muijres[1]; Anouk de Jong[1];Olvert A. Berkhemer[1,3,6];Anna M.M. Boers[3,39]; J. Huguet[3];P.F.C. Groot[3];Marieke A. Mens[3];Katinka R. van Kranendonk[3];Kilian M. Treurniet[3];Ivo G.H. Jansen[3];Manon L. Tolhuisen[3,39];Heitor Alves[3];Annick J. Weterings[3],Eleonora L.F. Kirkels[3],Eva J.H.F. Voogd[11];Lieve M. Schupp[3];Sabine Collette[28,29];Adrien E.D. Groot[4];Natalie E. LeCouffe[4];Praneeta R. Konduri[39];Haryadi Prasetya[39];Nerea Arrarte-Terreros[39];Lucas A. Ramos[39].

List of affiliations

Department of Neurology[1], Radiology[2], Public Health[40], Erasmus MC University Medical Center;
Department of Radiology and Nuclear Medicine[3], Neurology[4], Biomedical Engineering & Physics[39], Amsterdam UMC, University of Amsterdam, Amsterdam;
Department of Neurology[5], Radiology[6], Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM);
Department of Neurology[7], Radiology[8], Sint Antonius Hospital, Nieuwegein;
Department of Neurology[9], Radiology[10], Leiden University Medical Center;
Department of Neurology[11], Radiology[12], Rijnstate Hospital, Arnhem;
Department of Radiology[13], Neurology[14], Haaglanden MC, the Hague;
Department of Neurology[15], Radiology[16], HAGA Hospital, the Hague;
Department of Neurology[17], Radiology[18], University Medical Center Utrecht;
Department of Neurology[19], Neurosurgery[20], Radiology[27], Radboud University Medical Center, Nijmegen;
Department of Neurology[21], Radiology[26], Elisabeth-TweeSteden ziekenhuis, Tilburg;
Department of Neurology[22], Radiology[23], Isala Klinieken, Zwolle;
Department of Neurology[24], Radiology[25], Reinier de Graaf Gasthuis, Delft;
Department of Neurology[28], Radiology[29], University Medical Center Groningen;
Department of Neurology[30], Radiology[31], Atrium Medical Center, Heerlen;
Department of Neurology[32], Radiology[33], Catharina Hospital, Eindhoven;
Department of Neurology[34], Radiology[35], Medisch Spectrum Twente, Enschede;
Department of Radiology[36], Amsterdam UMC, Vrije Universiteit van Amsterdam, Amsterdam; Department of Radiology[37], Noordwest Ziekenhuisgroep, Alkmaar;
Department of Radiology[38], Texas Stroke Institute, Texas, United States.

LIST OF PUBLICATIONS

THIS THESIS

Van Meenen LCC, den Hartog SJ, Groot AE, Emmer BJ, Smeekes MD, Siegers A et al. Relationship between primary stroke center volume and time to endovascular thrombectomy in acute ischemic stroke. *Eur J Neurol.* 2021; doi: 10.1111/ene.15107 (online ahead of print).

Van Meenen LCC*, van Stigt MN*, Marquering HA, Majoie CBLM, Roos YBWEM, Koelman JHTM et al. Detection of large vessel occlusion stroke with electroencephalography in the emergency room: first results of the ELECTRA-STROKE study. *J Neurol.* 2021;9:1-9. *Shared first authorship

Van Meenen LCC, Riedijk F, Stolp J, van der Veen B, Halkes PHA, van der Ree TC et al. Pre- and interhospital workflow times for patients with large vessel occlusion stroke transferred for endovascular thrombectomy. *Front Neurol.* 2021;12:730250.

Van Meenen LCC*, van Stigt MN*, Siegers A, Smeekes MD, van Grondelle JAF, Geuzebroek G et al. Detection of large vessel occlusion stroke in the prehospital setting: electroencephalography as a potential triage instrument. *Stroke.* 2021;52:e347-e355. *Shared first authorship

Van Meenen LCC, Arrarte Terreros N, Groot AE, Kappelhof M, Beenen LFM, Marquering HA et al. Value of repeated imaging in patients with a stroke who are transferred for endovascular treatment. *J Neurointerv Surg.* 2021; doi: 10.1136/neurintsug-2020-017050 (online ahead of print).

Van Meenen LCC, Groot AE, Venema E, Emmer BJ, Smeekes MD, Kommer GJ et al. Interhospital transfer vs. direct presentation of patients with a large vessel occlusion not eligible for i.v. thrombolysis. *J Neurol.* 2020;267:2142-2150.

OTHER PUBLICATIONS

Arrarte Terreros N, Bruggeman AAE, Swijnenburg ISJ, **van Meenen LCC**, Groot AE, Coutinho JM et al. Early recanalization in large-vessel occlusion stroke patients transferred for endovascular treatment. *J Neurointerv Surg.* 2021; doi: 10.1136/neurintsurg-2021-017441 (online ahead of print).

Van Meenen LCC, Koopman MS, Roos YBWEM, Emmer BJ, Majoie CBLM, Coutinho JM. Late intra-arteriële behandeling van herseninfarcten. *Ned Tijdschr Geneeskd*. 2019;163:D3373.

Van Meenen LCC, van Meenen DMP, de Rooij SE, ter Riet G. Risk prediction models for postoperative delirium: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2014;62:2383-2390.

PHD PORTFOLIO

	Year	ECTS
Courses		
BROK	2018	1.0
Practical Biostatistics	2019	1.0
Clinical Epidemiology: Evaluation of Medical Tests	2021	1.0
Clinical Epidemiology: Observational Epidemiology	2021	1.0
Talents in PhD	2021	0.2
Conferences		
Amsterdam Neuroscience	2019-2021	0.75
European Stroke Organisation Conference	2019-2021	2.25
Acute Zorg Congres	2021	0.25
World Stroke Conference	2021	0.75
Seminars and meetings		
European Society of Neuroradiology annual meeting	2018	0.25
Research meeting Cerebrovascular Diseases, Amsterdam UMC (bi-weekly)	2018-2021	3.0
Research seminar Department of Neurology, Amsterdam UMC (bi-weekly)	2018-2021	1.5
Presentations		
Oral presentations		
Amsterdamsche Neurologenvereeniging	2018	0.5
Late intra-arteriële behandeling van herseninfarcten		
European Stroke Organisation Conference	2020	0.5
Value of repeated imaging in patients with a stroke who are transferred for endovascular treatment		
Amsterdamsche Neurologenvereeniging	2020	0.5

	Year	ECTS
Detection of large vessel occlusion stroke with electroencephalography in the emergency room: first results of the ELECTRA-STROKE study		
European Stroke Organisation Conference	2021	0.5
Relationship between primary stroke center volume and time to endovascular thrombectomy in acute ischemic stroke		
Acute Zorg Congres	2021	0.5
Detection of large vessel occlusion stroke with electroencephalography in the emergency room: first results of the ELECTRA-STROKE study		
World Stroke Conference	2021	0.5
Pre- and interhospital workflow times for patients with large vessel occlusion stroke transferred for endovascular thrombectomy		
E-presentations		
European Stroke Organisation Conference	2020	0.5
Interhospital transfer vs. direct presentation of patients with a large vessel occlusion not eligible for i.v. thrombolysis		
European Stroke Organisation Conference	2021	0.5
Detection of large vessel occlusion stroke with electroencephalography in the emergency room: first results of the ELECTRA-STROKE study		
Poster presentations		
Amsterdam Neuroscience	2019	0.5
EEG controlled triage in the ambulance for acute ischemic stroke (ELECTRA-STROKE)		
European Stroke Organisation Conference	2019	0.5
EEG controlled triage in the ambulance for acute ischemic stroke (ELECTRA-STROKE)		

	Year	ECTS
Teaching		
Neurology course for Master Physician Assistant (InHolland)	2018-2019	0.5
Neurology course for nurses (AmstelAcademie)	2018-2019	0.5
Neurological examination training of medical students (UvA)	2018-2019	0.2
Elective course 'Hoofd-Hals' for medical students (UvA)	2019	1.0
Neurology course 'Waarnemen, denken, doen' for medical students (UvA)	2021	0.2
Professional conduct course for medical students (UvA)	2021	0.5
Student mentoring		
Pinar Ozkaynar (Bachelor thesis)	2018	1.0
Maritta van Stigt (Master thesis)	2019-2020	2.0
Anita van de Munckhof (Master thesis)	2021	1.0
Other		
Peer reviewer *Stroke*	2019-2021	1.0

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ABOUT THE AUTHOR

Laura van Meenen was born on November 21, 1991 in Leiderdorp, the Netherlands. She grew up in Leiden and graduated from Stedelijk Gymnasium Leiden with honors in 2009. After a gap year in Spain with friends, she started her medical training at the University of Amsterdam in 2010. During her Bachelor studies, she worked as an assistant teacher of fellow medical students in pulmonary and cardiac physiology and as a research assistant at the department of Pulmonology of Amsterdam UMC, location AMC. After obtaining her Bachelor's degree in 2013, she started her clinical internships at the AMC. In 2014, her daughter Naomi was born. Following her clinical internships, Laura did a scientific internship with the Movement Disorders group at the department of Neurology of the AMC. With that, she completed her medical training and subsequently went on to work as a resident not in training at the department of Neurology of the AMC in 2017. In 2018, she started working as a PhD student with the Cerebrovascular Diseases group of the same department. Meanwhile, she continued to do clinical work and was involved in several teaching activities. In 2022, Laura started her Neurology residency at the AMC.

Laura lives in Leiden with her partner Sander and daughter Naomi, and is expecting her second child in June 2022.