PREHOSPITAL TRIAGE
of patients with suspected stroke

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PREHOSPITAL TRIAGE OF PATIENTS WITH SUSPECTED STROKE

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Contents

Chapter 1

General introduction

Stroke

In 2019, over 42,000 patients were admitted to the hospital because of stroke in the Netherlands, and the incidence of stroke is expected to rise because of increasing age and risk factors such as obesity, diabetes mellitus and hypertension.[1, 2] Stroke is one of the leading causes of death and disability.[2] Ischemic strokes cause approximately 85% of the strokes in western Europa and the United States, whereas intracerebral hemorrhages cause the minority of all strokes (approximately 15%).[3] In patients with ischemic stroke, a cerebral artery is occluded by a thrombus leading to disruption in cerebral blood flow. Due to this disruption, part of the brain is deprived of oxygen and glucose, and damage to neurons occurs instantly. This often immediately results in neurological deficits. Symptoms such as impaired speech, facial droop, impaired vision, arm and/or leg paresis or loss of sensation are common in patients with stroke dependent on the location and extent of the occlusion.

Acute reperfusion treatment of ischemic stroke

Time is brain. Every minute after the occlusion of a cerebral artery, on average 1.9 million neurons are lost.[4] If the occluded artery is recanalized in time, this process can be limited. For the best clinical outcome, recanalization should be established as soon as possible. Intravenous treatment with alteplase (IVT) can be used to dissolve the thrombus and thereby open the artery.[5] Nowadays, IVT is standard of care in the treatment of ischemic stroke in patients that can be treated within 4.5 hours after symptom onset, and in selected patients up to 12 hours after symptom onset or in wake-up strokes.[6-8]

Approximately 18 to 25% of the ischemic strokes are caused by an intracranial proximal large vessel occlusion (LVO) in the anterior circulation.[9, 10] In general, LVOs lead to more severe deficit, because a larger part of the brain is affected due to the proximal location in the larger arteries.[11] IVT is less effective in LVO patients.[12] Fortunately, these patients are eligible for mechanical removal of the thrombus, endovascular thrombectomy (EVT).[13] Since the revolutionary publication of The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), followed by the publications of the ESCAPE, REVASCAT, SWIFT PRIME and EXTEND-IA trials, EVT is standard of care in LVO patients within 6 hours after symptom onset.[8, 14-18] Two additional trials showed an effect of EVT in the extended time window up to 24 hours after symptom onset in selected patients.[19, 20] However, the effect of both IVT and EVT declines strongly over time.[21, 22] Therefore, it is essential to initiate reperfusion treatment as soon as possible.

Prehospital delay

Due to the time-sensitive effect of IVT and EVT, shortening the time to treatment after stroke onset is essential to improve functional outcomes of patients with

ischemic stroke. A large part of the onset-to-treatment time is spent in the prehospital setting.[23, 24] Awareness campaigns have been launched to improve onset-to-alert times by direct notification of the emergency medical services.[25, 26] Despite these campaigns, patients with suspected stroke often alert the general practitioner first, whether or not after patient's delay, or do not seek help at all.[27, 28]

After a short assessment by a paramedic, patients with suspected stroke are rapidly transported to the closest hospital with IVT-capabilities. EVT-eligible patients require an additional transfer to an EVT-capable intervention center. These interhospital transfers are time-consuming and are associated with worse functional outcomes.[29-31] Even in the Netherlands, a small country with short interhospital distances, the median delay of EVT by interhospital transfers is almost an hour.[30]

Transportation strategies and prehospital triage

To minimize prehospital delay, several transportation strategies have been proposed for patients with suspected stroke. The most commonly used strategy is the so-called "drip-and-ship" strategy. A patient is presented to the closest hospital so IVT can be initiated promptly. In case of EVT-eligibility, a subsequent interhospital transfer to an intervention center is arranged.[32] Clearly, EVT-eligible patients would benefit from direct transport to an intervention center. Direct transport to an intervention center and thereby bypassing a closer hospital, is known as the "mothership" strategy. However, the mothership strategy may lead to delayed IVT, which is especially harmful in non-LVO ischemic stroke patients. As a side effect this strategy can also lead to crowding of patients with suspected stroke in intervention centers.

Prehospital triage may be the answer to the disadvantages of the drip-and-ship strategy and mothership strategy. Prehospital stroke scales are suggested to select patients with a high likelihood of an LVO for direct transport to an intervention center.[33] Prehospital stroke scales are simple clinical tools derived from the National Institutes of Health Stroke Scale (NIHSS).[33, 34] Numerous prehospital stroke scales have been developed.[33, 34] However, prospective prehospital validation studies are scarce, and the performance of prehospital stroke scales has not been directly compared.[35-42] To reliably determine the performance of prehospital stroke scales, they should be validated prospectively, in the prehospital setting, by paramedics, in a large representative cohort of patients with suspected stroke. The Rapid Arterial oCclusion Evaluation (RACE) scale is the only scale that has been validated extensively in large prospective prehospital studies, but no direct comparison was made with other prehospital stroke scales.[35-37, 41] The clinical presentation of patients with LVO may differ based on the location of the occlusion and the extend of collateral circulation.[43-45]

So far, it is unknown whether prehospital stroke scales are able to identify both proximal and more distal occlusions.

Furthermore, the ideal transportation strategy not only depends on the likelihood of having an LVO, but also on different factors such as driving times, time-since-onset and local treatment times.[46-49] Therefore, a more personalized approach seems reasonable, using a prehospital decision model that takes likelihood of an LVO, driving times, workflow times and the symptom onset time into account.[47] The most important objective of such a transportation strategy should be that improved outcomes through expedited EVT outweigh the harm caused by delayed IVT. Because transportation strategies not only affect treatment times, but also affect patient flows and the occupation time of the ambulance, it is important to consider the impact of transportation strategies before implementation.

In-hospital stroke work-up

After arrival in the hospital, the patient is rapidly assessed by a neurologist, neurology resident or emergency medicine physician. The NIHSS is a widely used standardized scale to quantify neurologic deficits in stroke patients.[50]

After clinical assessment, neuro-imaging is performed. Non-contrast computed tomography (NNCT) is used to assess intracranial hemorrhage and rule out other causes that mimic stroke symptoms. The absence or presence and location of LVO is determined with computed tomography angiography (CTA).[51, 52] In daily clinical practice, CTAs are often not primarily assessed by neuroradiologists or interventionalists, but by radiologists or residents with less experience in vascular neuroradiology. These evaluations might be affected by time-pressure. It is essential that CTAs of patients with suspected stroke are evaluated rapidly and accurately, because missing an occlusion would withhold a patient from effective treatment. However, the accuracy of CTA evaluations in daily clinical practice has never been investigated. In addition, to aid fast CTA evaluation and LVO detection, diagnostic tools with artificial intelligence algorithms have been developed, but their clinical utility has not been evaluated yet.[53-55]

Table 1. Overview of the data sources used in this thesis.

Study	Design	Study population	Time frame of patient inclusion	Number of patients used for the analysis in this thesis
Prehospital triage of patients with suspected stroke (PRESTO)	Prospective multicentre observational cohort study	Patients with suspected stroke who were transported by ambulance	August 2018 - September 2019	436 (Chapter 2) 1039 (Chapter 4.2 & 5) 656 (Chapter 6.1) 646 (Chapter 6.2)
MR Clean Registry	Prospective multicentre observational cohort study	Patients with acute ischemic stroke undergoing EVT	March 2014 – November 2017	3021 (Chapter 3) 1110 (Chapter 6.2)
Leiden Prehospital Stroke Study (LPSS)	Prospective multicentre observational cohort study	Patients with suspected stroke who were transported by ambulance	July 2018 – October 2019	759 (Chapter 5)

Aims and outline of this thesis

All research described in this thesis is the result of the PRESTO, MR CLEAN Registry and LPSS collaborations. The overall aim of my research described in this thesis was to improve the prehospital triage and diagnostic work-up of patients with suspected stroke. More specifically, I investigated the following research questions:

1. Which factors influence the direct notification of emergency medical services by patients with suspected stroke?

2. How sensitive are prehospital stroke scales for the detection of different intracranial large vessel occlusion locations?

3. What is the in-field performance of prehospital stroke scales?

4. What is the impact of prehospital transportation strategies on patient flows and treatment times?

5. What is the diagnostic performance of CTA evaluations in daily clinical practice and of an automated LVO detection algorithm in patients with suspected stroke?

In **Chapter 2**, I explored factors that were associated with calling the emergency medical services instead of the general practitioner and factors that were associated with a delayed onset-to-alert time in the prehospital triage of patients with suspected stroke (PRESTO) data. In **Chapter 3,** I assessed the sensitivity of several prehospital stroke scales for different intracranial large vessel occlusion locations in the MR CLEAN Registry.[56] **Chapter 4.1** is the protocol of the PRESTO study. In **Chapter 4.2**, the main results of the PRESTO study, the validation of eight prehospital stroke scales, were described. In **Chapter 4.3,** the advantages of a multivariable prehospital decision model compared to merely a prehospital stroke scale were explained. Different transportation strategies were modeled in **Chapter 5** to estimate the impact of these strategies in two ambulance regions from the PRESTO study and two ambulance regions from the Leiden Prehospital Stroke Study (LPSS). In **Chapter 6.1**, the accuracy of CTA evaluations in daily clinical practice was investigated using a core laboratory evaluation from the PRESTO study as reference standard. In **Chapter 6.2**, the diagnostic performance of an algorithm for automated LVO detection on CTA was evaluated, for which data of the MR CLEAN Registry and PRESTO study were used.
The main results of my thesis are summarized and discussed in **Chapter 7 and 8.**

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Chapter 2

Medical attention seeking by suspected stroke patients: emergency medical services or general practitioner?

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Abstract

Objective
Awareness campaigns advise the public to call emergency medical services (EMS) directly in case of suspected stroke. We aimed to explore patient and notification characteristics that influence direct EMS notification, the time to alert, and the time to treatment.

Methods
We performed a secondary analysis with data from the PRESTO study, a multicenter prospective observational cohort study that included patients with suspected stroke. We used multivariable binary logistic regression analyses to assess the association with direct EMS notification and multivariable linear regression analyses to assess the association with the onset-to-alert time, onset-to-needle time and onset-to-groin time.

Results
Of 436 included patients, 208 patients (48%) contacted EMS directly. FAST scores (aOR 1.45 for every point increase, 95% CI: 1.14-1.86), alert outside office hours (aOR 1.64 [1.05-2.55]), and onset-to-alert time (aOR for every minute less [≤55 minutes]: 0.96 [0.95-0.97]) were independently associated with direct EMS notification. Direct EMS call was independently associated with shorter onset-to-alert times (27 minutes [54-0.84]) and with shorter onset-to-needle times (-30 minutes [-51- -10]). The association between direct EMS call and the onset-to-groin time was almost similar to the association with onset-to-needle time, though not statistically significant (univariable analysis: 23.7 minutes decrease [-103.7- 56.2]).

Conclusion
More than half of all patients with suspected stroke do not call EMS directly but call their GP instead. Patients with higher FAST scores, alert outside office hours, and a rapid alert, more often call EMS directly. Patients who call EMS directly are treated with IVT 30 minutes faster than patients who call the GP first.

Introduction

The effect of intravenous thrombolytics (IVT) and endovascular thrombectomy in patients with ischemic stroke declines strongly with increasing time to treatment.[1, 2] Direct notification of emergency medical services (EMS) by patient or bystanders after onset of stroke symptoms helps to facilitate rapid arrival at the hospital and subsequent treatment. Over the past years, awareness campaigns have tried to shorten the onset-to-alert times and thereby onset-to-door times of patients with suspected stroke.[3] We aimed to investigate how often patients with suspected stroke call EMS first and to explore factors associated with direct EMS notification. Our secondary aim was to explore the association of direct EMS call with onset-to-alert-times, onset-to-needle times, and onset-to-groin times.

Materials and Methods

We performed a secondary analysis with data from the Prehospital triage of patients with suspected stroke (PRESTO) study, a multicenter prospective observational cohort study that included patients with suspected stroke transported by two different ambulance services (Rotterdam-Rijnmond and Zuid-Holland Zuid).[4, 5] Patients were identified and included by paramedics in the field. Inclusion criteria for the PRESTO study were new neurological deficit, defined as at least one point on the Face-Arm-Speech-Time (FAST) test, age 18 years or older, and serum blood glucose of at least 2.5 mmol/L. For the current analysis, we only included patients who presented at the emergency department within six hours after last-seen-well. This was because in the Netherlands, patients with suspected stroke who present within six hours after last-seen-well are almost always transported by ambulance and the proportion of patients who arrive at the emergency department with their own transport is negligible. Furthermore, we included only patients from the region Zuid-Holland Zuid, because the ambulance service in this region consistently noted the type of ambulance request (patient, GP or other) in the ambulance call report.

Region Zuid-Holland Zuid is populated with 480,000 inhabitants in an area of 720 square kilometers. In The Netherlands, GP guidelines state that an ambulance should be ordered with the highest urgency for patients with suspected stroke, if treatment would be possible within 6 hours.[6] The ambulance should be ordered directly without a prior visit of the GP in these cases. In addition, the Dutch population is instructed to call EMS directly in patients with a positive FAST test by leaflets, banners, relevant websites, social media, and advertising on national television. For this study, paramedics performed a prehospital assessment just before or during transport.[5] Directly after arrival in the hospital, National Institutes of Health Stroke Scale (NIHSS) scores were

assessed by the treating physician. Patient characteristics and data on time metrics were collected from ambulance call reports and through hospital chart review. The time of the EMS notification and the EMS notifier (primarily by patient or bystander, secondarily by GP or GP practice, or unknown) was extracted from ambulance call reports. We defined the onset-to-alert-time as the time from onset or last-seen-well to EMS notification.

Statistical analysis

We used univariable and multivariable binary logistic regression analyses to assess the association of patient characteristics with direct EMS notification. Variables for the univariable analysis were selected based on the clinical assumption of a potential association with direct EMS notification (age, sex, systolic blood pressure, medical history, pre-existent modified Rankin Scale, FAST score, NIHSS score, alert outside office hours and onset-to-alert time). For example, we included blood pressure because patients with extremely low or high blood pressure might be symptomatic and urge to alert EMS directly.

Variables with a P value of ≤0.15 in the univariable analysis were entered into the multivariable analysis. We assessed potential nonlinearity of continuous variables and the outcome with restricted cubic splines.

We used univariable and multivariable linear regression models to assess the association of direct EMS call with the onset-to-alert-time, onset-to-needle-time, and onset-to-groin time. Variables for the univariable analysis were selected based on the clinical assumption of a potential association with these time intervals (direct call to EMS, age, sex, systolic blood pressure, medical history, pre-existent modified Rankin Scale (mRS), FAST score, NIHSS score and alert outside office hours). We assessed and reported completeness of the data. For the regression analyses, missing data of the assessed variables were imputed using multiple imputation using additive regression, bootstrapping and predictive mean matching based on relevant covariates. All analyses were performed with R software (version 3.6.1) and RStudio (version 1.0.153).

Results

Patient characteristics

Between August 13, 2018, and September 2, 2019, 1334 patients were recruited in the PRESTO study, of which 1314 were available for the analysis (supplemental material Figure 1). For this analysis, 878 patients were excluded (last-seen-well over six hours: n=274, age < 18 years: n=1, ambulance service Rotterdam-Rijnmond: n=543, unknown first medical contact: n=60). Of 436 included patients, 208 patients (48%) first notified EMS and 228 patients (52%) called the GP (Table 1). Median age of the included patients was 73 (interquartile range [IQR]: 64-84) for patients who called EMS directly and 74 (IQR: 66-84) for

patients who called the GP first. The majority of patients had a medical history of diabetes mellitus, hypertension, or both: 140/208 (67%) of the patients who called EMS directly, and 156/228 (68%) of the patients who called the GP. Women less often called EMS directly, (84/201 [42%]), compared to men (124/235 [53%]). Patients who called EMS directly more often had an ischemic stroke due to LVO (32/208, 15%), compared to the patients who called the GP (9/228, 4%). Of the 60 patients with unknown first medical contact, patient characteristics were not significantly different from patients with known first medical contact (supplemental material Table 1).

Table 1. Patient characteristics, stratified by first medical contact.

	Emergency number (n=208)	General practitioner (n=228)
Age	73 (64-84)	74 (66-84)
Sex (female)	84 (40%)	117 (51%)
Systolic blood pressure, mean (SD)	159±27	159±26
Medical history		
Atrial fibrillation	49 (24%)	31 (14%)
Hypertension	132 (64%)	150 (66%)
Hypercholesterolemia	150 (72%)	164 (72%)
Diabetes Mellitus	51 (25%)	51 (22%)
Ischemic stroke	67 (32%)	58 (25%)
Myocardial ischemia	25 (12%)	31 (14%)
Intracranial hemorrhage	2 (1%)	7 (3%)
Diabetes Mellitus and/or Hypertension	140 (67%)	156 (68%)
Pre-existent disability (mRS 3-5)	33 (16%)	48 (21%)
FAST test (0-3)	2 (1-2)	1 (0-2)
NIHSS score (0-42)	3 (0-7)	2 (0-5)
Alert outside office hours	97 (47%)	73 (32%)
Onset-to-alert time (minutes)	30 (9-75)	77 (34-170)
Onset-to-needle time (minutes)*	89 (64-141)	119 (95-203)
Onset-to-groin time (minutes)*	145 (105-225)	185 (127-277)

Table 1. *Continued.*

	Emergency number (n=208)	General practitioner (n=228)
Diagnosis		
Ischemic stroke with LVO	32 (15%)	9 (4%)
Ischemic stroke	79 (38%)	102 (45%)
Intracranial hemorrhage	16 (8%)	14 (6%)
Transient ischemic attack	40 (19%)	46 (20%)
Stroke mimic	41 (20%)	57 (25%)

Data are median (interquartile range) or n (%), unless otherwise indicated. mRS: modified Rankin Scale. FAST: Face-Arm-Speech-Time NIHSS: National Institutes of Health Stroke Scale. LVO: large vessel occlusion. *Onset-to-needle-time in patients treated with intravenous thrombolysis (n=139), onset-to-groin time in patients treated with endovascular thrombectomy (n=29). Number of missings: Pre-existent disability: 23, NIHSS: 1, onset-to-alert time: 39

Associations with calling EMS directly

Sex, history of atrial fibrillation, history of ischemic stroke, history of intracranial hemorrhage, score on the FAST test, NIHSS, alert outside office hours, and onset-to-alert-time were at least weakly associated with calling EMS directly ($p \leq 0.15$) and were entered in the multivariable logistic regression model (Table 2). Onset-to-alert time was nonlinearly associated with calling EMS directly ($p < 0.0001$, Figure 1), this remained after adjustment ($p < 0.0001$). None of the other associations with continuous variables were nonlinear. The score on the FAST test (adjusted odds ratio [aOR] for every point 1.45, 95% CI: 1.14 to 1.86), alert outside office hours (aOR 1.64, 95% CI: 1.05 to 2.55), and short onset-to-alert time (aOR for every minute ≤55 minutes: 0.96, 95% CI: 0.95 to 0.97) (Figure 1) were independently associated with calling EMS directly.

Table 2. Factors related to calling the emergency medical services directly, univariable and multivariable logistic regression analysis.

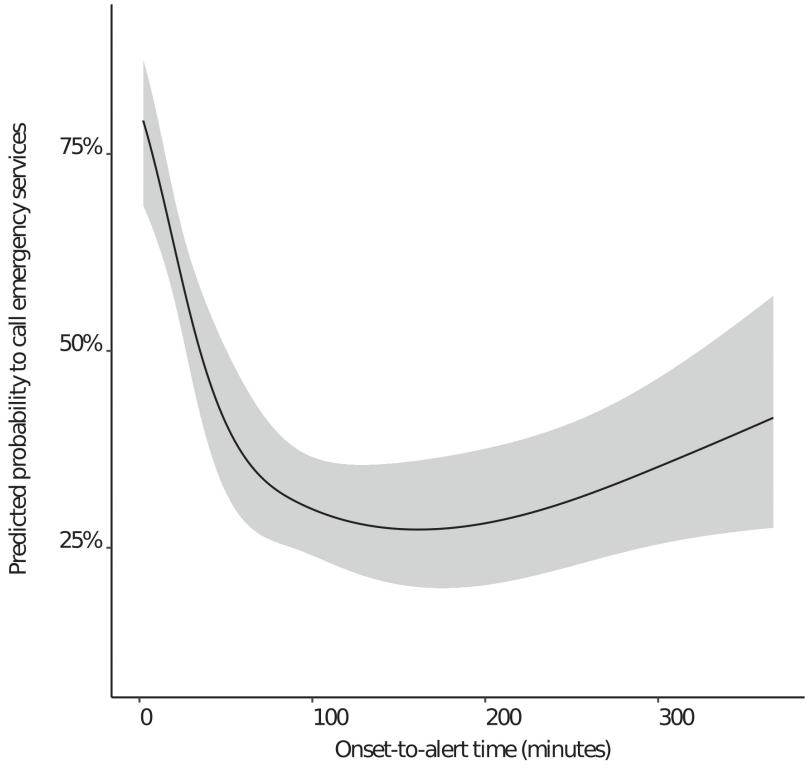
	Univariable analysis - OR (95% CI)	p-value	Multivariable analysis - OR (95% CI)	p-value
Age (years)	0.99 (0.98-1.01)	0.41	-	-
Sex (male)	1.56 (1.06-2.27)	0.02	1.42 (0.93-2.16)	0.10
Systolic blood pressure (mmHg)	1.00 (0.99-1.01)	0.95	-	-

Table 2. *Continued.*

	Univariable analysis - OR (95% CI)	p-value	Multivariable analysis - OR (95% CI)	p-value
History of atrial fibrillation	1.96 (1.19-3.22)	0.008	1.69 (0.97-2.92)	0.06
History of hypertension	0.90 (0.61-1.34)	0.61	-	-
History of hypercholesterolemia	1.01 (0.66-1.53)	0.97	-	-
History of diabetes mellitus	1.13 (0.72-1.76)	0.60	-	-
History of ischemic stroke	1.39 (0.92 – 2.11)	0.12	1.28 (0.04-1.40)	0.30
History of myocardial ischemia	0.87 (0.49-1.53)	0.62	-	-
History of intracranial hemorrhage	0.31 (0.06-1.49)	0.14	0.25 (0.04-1.42)	0.11
Pre-existent modified Rankin Scale (0-5)	0.90 (0.78-1.04)	0.16	-	-
FAST test (0-3)	1.49 (1.23-1.79	<0.0001	1.45 (1.14-1.86)	0.003
NIHSS (0-42)	1.02 (1.00-1.06)	0.10	0.99 (0.75-1.17)	0.57
Alert outside office hours	1.86 (1.26-2.74)	0.002	1.64 (1.05-2.55)	0.03
Onset-to-alert time minutes (<55 minutes)	0.96 (0.95-0.98)	<0.0001	0.96 (0.95-0.97)	<0.0001
Onset-to-alert time minutes (>55 minutes)	0.99 (0.99-1.00)	0.28	1.00 (0.99-1.00)	0.22

OR: odds ratio. CI: Confidence Interval. FAST: Face-Arm-Speech-Time. NIHSS: National Institutes of Health Stroke Scale. Outside office hours was defined as Monday to Friday between 17:00 and 08:00, weekends and public holidays.

Figure 1. Relation of the onset-to-alert time to the probability to call the emergency number. The relation was assessed with restricted cubic splines, p-likelihood ratio test < 0.0001.



Associations with the onset-to-alert time

Direct EMS call, history of diabetes mellitus and pre-existent disability had a p value ≤0.15 and were entered in the multivariable linear regression model (Table 3). Direct EMS call was independently associated with shorter onset-to-alert times (minus 27 minutes, 95% CI: -54 to -0.84). A history of diabetes mellitus was independently associated with a longer onset-to-alert time (plus 36.6 minutes, 95% CI: 2.3 to 70.9).

Table 3. Factors related to the onset-to-alarm time, univariable and multivariable linear regression analysis.

	Univariable analysis - ß (95% CI)	p-value	Multivariable analysis - ß (95% CI)	p-value
Direct call to emergency service	-27.4 (-54.1 – -0.7)	0.04	-27.0 (-54.0 - -0.8)	0.04
Age (years)	0.3 (-0.6 – 1.3)	0.49	-	-
Sex (male)	-4.8 (-32.9 – 23.3)	0.74	-	-
Systolic blood pressure (mmHg)	0.07 (-0.4 – 0.6)	0.77	-	-
History of atrial fibrillation	-5.4 (-44.4 – 33.7)	0.79	-	-
History of hypertension	14.1 (-15.4 – 43.7)	0.35	-	-
History of hypercholesterolemia	17.0 (-16.6 – 50.5)	0.32	-	-
History of diabetes mellitus	39.9 (6.5 – 73.3)	0.02	36.6 (2.3 – 70.9)	0.04
History of ischemic stroke	-15.6 (-44.6 – 13.5)	0.29	-	-
History of myocardial ischemia	0.9 (-45.0 – 46.8)	0.97	-	-
History of intracranial hemorrhage	-20.2 (-111.4 – 70.9)	0.66	-	-
Pre-existent modified Rankin Scale (0-5)	9.0 (-1.1 – 19.1)	0.08	5.2 (-5.2 – 15.6)	0.32
FAST test (0-3)	3.5 (-9.9 – 16.9)	0.61	-	-
NIHSS (0-42)	-0.03 (-2.1 – 2.1)	0.98	-	-
Alert outside office hours	12.4 (-15.6 – 40.5)	0.38	-	-

CI: Confidence Interval. FAST: Face-Arm-Speech-Time. NIHSS: National Institutes of Health Stroke Scale. The reported ß is the coefficient of the analysis and indicates the change in onset-to-alert time in minutes for the presence or point increase of the assessed variable. Outside office hours was defined as Monday to Friday between 17:00 and 08:00, weekends and public holidays.

Associations with the onset-to-needle and onset-to-groin time

Direct EMS call, sex and pre-existent disability had a p value ≤0.15 and were entered in the multivariable linear regression model (supplemental material Table 2). Direct EMS call was independently associated with shorter onset-to-

needle times (minus 30.3 minutes, 95% CI: -51.1 to -9.6, n=139). Onset-to-needle times were 26.4 (95% CI: -47.6 - -5.2) minutes shorter for men than for women. Patients with higher pre-existent mRS had longer onset-to-needle times (12.6 minutes for each point increase, 95% CI: 3.6 - 21.6). The difference in onset-to-alert time of patients within this subgroup was 65 minutes (95% CI: 31-142) for women, versus 37 minutes (95% CI: 17-73) for men.

The association between direct EMS call and the onset-to-groin time was almost similar to the association with onset-to-needle time, but not statistically significant (univariable analysis: 23.7 minutes decrease, 95% CI: -103.7 - 56.2, p= 0.55, n=29).

Discussion

We found that most patients with suspected stroke do not call EMS first after noticing stroke symptoms. Directly calling EMS was observed more frequently in patients with higher scores on the FAST test, notification outside office hours, and when medical help was sought faster. Patients with diabetes mellitus waited longer to alert. Patients who called EMS directly were treated with IVT 30 minutes faster than patients who called the GP first.

In the Netherlands, GPs, also called “family doctors”, are often well known to the patient and easily approachable for patients. This could explain why patients often contact the GP first. Patients with higher FAST scores more often called EMS first, which could be explained by the (Dutch) awareness campaigns that focus on FAST symptoms. Besides, even without knowledge of the FAST test, abnormal FAST symptoms can easily be recognized and urge patients or bystanders to alert the EMS. The NIHSS score was not associated with direct EMS notification or the onset-to-alert time. This may seem contradictory to the finding that the FAST score was associated with direct EMS call, and might be because FAST symptoms are more easily recognized than other items of the NIHSS. Outside office hours, EMS are more often called, most likely because the GP practice is closed, although there is a regional GP on call. The association of shorter onset-to-alert times and alerting EMS directly implies that patients who are aware of the urgency to alert, call EMS directly. Patients with diabetes mellitus wait longer to alert, maybe because they assume they have hypoglycemia or hyperglycemia, focus on their glucose levels first and wait for spontaneous improvement. However, this could also be a coincidental finding based on multiple testing.

Few studies have investigated determinants of calling EMS directly, but these studies confirm that the GP is often contacted first.[7, 8] The remarkable finding that even patients with previous stroke do not always call the EMS, has been described in other studies.[8, 9] Another Dutch study confirmed that outside office hours, patients more often alerted EMS directly.[7] Contrary to the

findings of one other study, we did not find an association between NIHSS score and direct EMS notification.[8] However, that study only included patients with ischemic stroke or transient ischemic attack, which may have strengthened the association. An association with onset-to-alarm time and diabetes has not been described previously. However, none of the studies assessed onset-to-alert time as continuous variable but as dichotomized variable, which might have resulted in the loss of information.[9-11] Furthermore, in the subgroup of patients that were treated with IVT, we demonstrated that directly calling EMS resulted in shorter onset-to-needle times. Even more remarkable was that women treated with IVT had longer onset-to-needle times compared to men. This is largely explained by the difference in onset-to-alert time between women and men in this subgroup. Unfortunately, our study does not provide an explanation why women waited longer to alert.

The strength of our study is that we included patients with suspected stroke who were recruited by paramedics. However, our study has some limitations. Most importantly, we restricted to patients who presented within 6 hours after symptom onset, and all of our patients were transported by the ambulance. Therefore, with this study, we cannot draw any conclusions regarding decision-making of patients who wait over six hours to call for help, or of patients who do not seek help at all. For patients that contacted the GP first, we have no information about the exact time the GP was alerted, but only the time of the GP notification to EMS. Even though GPs are instructed to alert EMS directly, this process will be somewhat delayed and resulted in a minor overestimation of the onset-to-alert time. Due to the nature of the available data, we needed to restrict our study to one region, which is supposed to be less urban compared to the other ambulance region. This might have influenced our results, as patients from rural areas seem to be more hesitant to call EMS.[11] Primary care systems could be differently organized in other countries. However, the conclusions from this research are representative for other countries with a similar primary care system. Finally, we had no knowledge regarding potentially contributing factors to the notification type or time, such as the level of education, living alone, whether the patient or a bystander sought help or the patient's considerations before notification. This could have provided additional insight of determinants to call the EMS directly.

Older studies showed mass media interventions have limited impact on patient decision-making in seeking help.[3] However, these studies should be interpreted with care due to (methodological) weaknesses. For example, these studies did not use a control group or did not perform a before-and-after evaluation.[3, 11] A recent French study investigated the impact of the ReACT campaign on the number of EMS calls and public stroke knowledge in an intervention county and control county.[12] This study showed an increase in EMS calls after the implementation, but no significant increase in symptom

knowledge or decrease in time from onset-to-alert. Other studies have shown that despite knowledge of stroke symptoms, patients often do not recognize the urgency to seek help.[13, 14] However, a time-series study from the United Kingdom showed a significant reduction in delay to seek help in patients with severe stroke after the implementation and regular recurrence of television campaigns on the FAST test.[15] This effect was mostly attributable to an increase in patients directly contacting EMS. Unfortunately, this result was not seen in patients with transient ischemic attack or minor stroke during the same time period.[16] It might be helpful to combine such repetitive media campaigns with more direct or individualized education. In our study, most patients with suspected stroke had a medical history that warrants follow-up by their GP for annual assessment of cardiovascular risk factors. This provides an opportunity for systematic education about how to act on cardiovascular events in general and stroke in particular.

Conclusion

More than half of all patients with suspected stroke do not call EMS directly but call their GP instead. Patients with higher FAST scores, alert outside office hours, and a rapid alert, more often call EMS directly. Patients who call EMS directly are treated with IVT 30 minutes faster than patients who call the GP first.

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Supplemental material

Figure 1. Inclusion flowchart

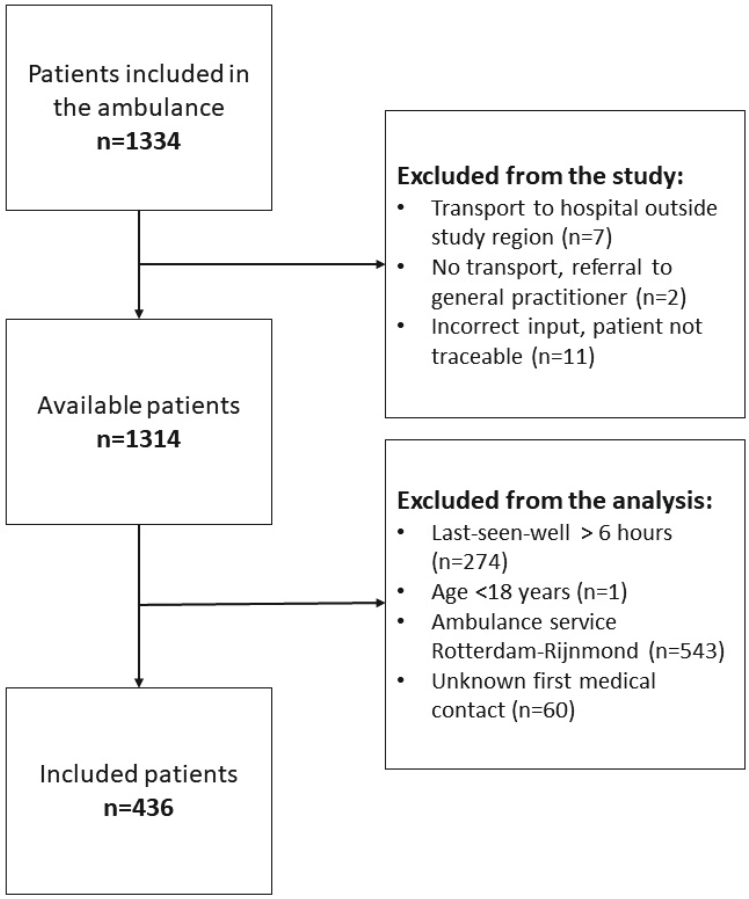

Table 1. Patient characteristics of the patients with known versus unknown first medical contact

	Known (n=436)	Unknown (n=60)	p-value
Age	73 (63-82)	74 (66-84)	0.48
Sex (female)	2-1 (46%)	22 (37%)	0.17
Systolic blood pressure, mean (SD)	159±26	163±29	0.24
Medical history			
Atrial fibrillation	80 (18%)	10 (17%)	0.75
Hypertension	282 (65%)	39 (65%)	0.96
Hypercholesterolemia	314 (72%)	41 (68%)	0.55
Diabetes Mellitus	102 (23%)	9 (15%)	0.14
Ischemic stroke	125 (29%)	15 (25%)	0.55
Myocardial ischemia	56 (13%)	9 (15%)	0.64
Intracranial hemorrhage	9 (2%)	0	0.26
Pre-existent disability (mRS 3-5)	81 (20%)	6 (10%)	0.10
FAST test (0-3)	1 (1-2)	1 (0-2)	0.24
NIHSS score (0-42)	2 (0-6)	2 (0-6)	0.97
Alert outside office hours	170 (39%)	22 (37%)	0.73
Onset-to-alert time (minutes)	55 (18-148)	48 (20-112)	0.96
Onset-to-needle time (minutes)	105 (73-176	93 (75-137)	0.60
Onset-to-groin time (minutes)	155 (113-270)	183 (97-230)	0.99
Diagnosis			0.53
Ischemic stroke with LVO	42 (10%)	10 (17%)	
Ischemic stroke	180 (41%)	23 (38%)	
Intracranial hemorrhage	30 (7%)	5 (8%)	
Transient ischemic attack	96 (20%)	10 (17%)	
Stroke mimic	98 (23%)	12 (20%)	

Table 2. Factors related to the onset-to-needle time, univariable and multivariable linear regression analysis, n=139

	Univariable analysis - ß (95% CI)	p-value	Multivariable analysis - ß (95% CI)	p-value
Direct call to emergency service	-33.0 (-54.6 – -11.3)	0.003	-30.3 (-51.1 - -9.6)	0.005
Sex (male)	-29.6 (-51.9 – -7.4)	0.01	-26.4 (-47.6 – -5.2)	0.02
Pre-existent modified Rankin Scale (0-5)	14.8 (-5.4 – 24.2)	0.002	12.6 (3.6 – 21.6)	0.006

CI: Confidence Interval. The reported ß is the coefficient of the analysis and indicates the change in onset-to-needle time in minutes for the presence or point increase of the assessed variable. Only variables with $p < 0.15$ in the univariable analysis were reported.

Chapter 3

Sensitivity of prehospital stroke scales for different intracranial large vessel occlusion locations

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European Stroke Journal, 2021

Abstract

Introduction
Prehospital stroke scales have been proposed to identify stroke patients with a large vessel occlusion to allow direct transport to an intervention center capable of endovascular treatment (EVT). It is unclear whether these scales are able to detect not only proximal, but also more distal treatable occlusions. Our aim was to assess the sensitivity of prehospital stroke scales for different EVT-eligible occlusion locations in the anterior circulation.

Patients and Methods
The MR CLEAN Registry is a prospective, observational study in all centers that perform EVT in the Netherlands. We included adult patients with an anterior circulation stroke treated between March 2014 and November 2017. We used National Institutes of Health Stroke Scale scores at admission to reconstruct previously published prehospital stroke scales. We compared the sensitivity of each scale for different occlusion locations. Occlusions were assessed with CT angiography by an imaging core laboratory blinded to clinical findings.

Results
We included 3021 patients for the analysis of 14 scales. All scales had the highest sensitivity to detect internal carotid artery terminus occlusions (ranging from 0.21 to 0.97) and lowest for occlusions of the M2 segment (0.08 to 0.84, p-values<0.001).

Discussion and Conclusion
Although prehospital stroke scales are generally sensitive for proximal large vessel occlusions, they are less sensitive to detect more distal occlusions.

Introduction

Because the effect of endovascular treatment (EVT) for ischemic stroke is strongly time-dependent, it is important to optimize prehospital and in-hospital workflows to reduce unnecessary treatment delays.[1-3] Interhospital transfers are an important cause of treatment delay and are associated with worse functional outcome.[4, 5] Prehospital stroke scales may be helpful for the selection of patients with a high likelihood of a large vessel occlusion (LVO), to bypass the primary stroke center for direct transport to an intervention center capable of EVT and thereby avoiding time-consuming interhospital transfers.

Numerous prehospital stroke scales have been published over the past few years.[6-20] These scales have been developed as short and simple clinical tools to identify stroke patients with an LVO. Most scales are derived from the National Institutes of Health Stroke Scale (NIHSS).[21] Patients with a proximal occlusion usually present with high NIHSS scores, but more distal occlusion locations may be associated with lower NIHSS scores.[22, 23] The sensitivity of prehospital stroke scales in detecting different occlusion locations in LVO is unknown. Because all patients treated with EVT in the Netherlands are registered, we had the opportunity to explore this in a large dataset of patients treated with EVT. We aimed to assess and compare the sensitivity of prehospital stroke scales for the detection of occlusions in different locations in the anterior circulation in a representative cohort of EVT-eligible patients.

Methods

Study design

The MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry is a national, prospective, open, multicenter, observational monitoring study for intervention centers that perform EVT in the Netherlands. We collected data from consecutive patients who underwent EVT in 18 hospitals. Details of the MR CLEAN Registry have been reported previously.[24]

Prehospital stroke scales

We selected prehospital stroke scales from the literature and included scales that were developed to detect LVO in the anterior circulation. Scales were only included if a cut point was proposed in the original studies. Scales that could not be reproduced with NIHSS items or scales that contained unavailable variables were excluded.

Study population

All patients with acute ischemic stroke caused by an intracranial LVO, confirmed by CT angiography (CTA), who had at least a groin puncture as start of EVT, were registered in the MR CLEAN Registry. EVT was performed in all patients with an occlusion of the distal part of the ICA, the M1 or M2 segment of the middle cerebral artery, if treatment was possible within six hours after symptom onset, irrespective of the stroke severity. The only contra-indication was intracranial hemorrhage. Ischemic stroke in the affected vascular territory in the six weeks prior to the current event was a relative contra-indication. For the purpose of our analysis, we included patients registered between March 16, 2014 and November 1, 2017. We used the following inclusion criteria: age ≥ 18 years, EVT performed in a center that participated in the MR CLEAN trial, start of EVT within 6.5 hours after stroke onset, and a proximal intracranial occlusion in the anterior circulation (internal carotid artery (ICA), internal carotid artery terminus (ICA-T), middle cerebral artery (M1/M2)).[24] We excluded patients of whom CTA was not available. Standard stroke work-up after arrival in the hospital was rapid assessment of the patient, followed by non-contrast CT and CTA. If indicated, intravenous thrombolysis was initiated just prior or after the CTA. Patients who did not present primarily in an intervention center were transferred for EVT. After transfer and prior to EVT, the NIHSS was assessed by a neurologist or neurology resident in the intervention center.

Imaging assessments

All imaging was adjudicated by an imaging core laboratory, whose members were informed about the side of the affected hemisphere. M1 occlusions located before or during the branching off of lenticulostriate arteries were defined as proximal M1 occlusions. M1 occlusions located after the branching off of lenticulostriate arteries were defined as distal M1 occlusions. The M2 segments were defined as the first post-bifurcation branches of the M1 segment. In case of multiple occlusions, the most proximal occlusion location was used for the analysis.

Statistical analysis

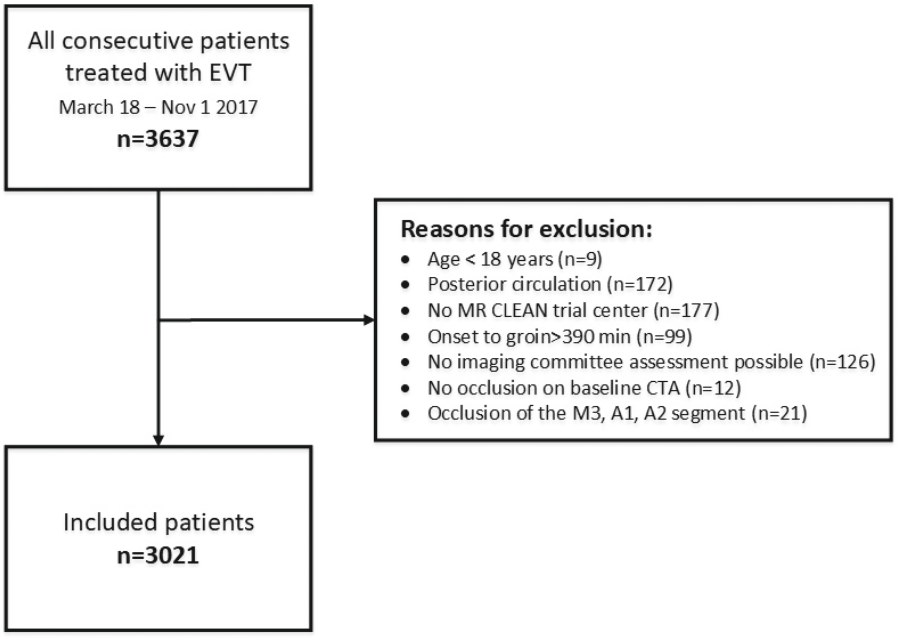
Prehospital stroke scales were reconstructed with the NIHSS items assessed at baseline in the intervention center. The scales were assessed as positive or negative, using the cut point proposed in the original publication. We calculated the sensitivity for the detection of LVO for each prehospital stroke scale, both stratified by occlusion location and for all occlusion locations combined. For each prehospital stroke scale, the sensitivities for different occlusion locations were compared using Chi-square tests. Additionally, we plotted the sensitivity for all possible cut points of the prehospital stroke scales, stratified by occlusion location. Potential differences in sensitivity across prehospital stroke scales may

be caused by variation in the included NIHSS items. Therefore, we calculated the percentage of patients in our cohort who had an abnormal score on each NIHSS item. All analyses were performed using R software version 3.6.1 and Rstudio version 1.0.153.

Results

Fourteen prehospital stroke scales were available for our analysis.[6-20] In total, 3637 patients were registered in the MR CLEAN Registry between March 16, 2014 and November 1, 2017. We excluded 616 patients who did not meet our inclusion criteria (Figure 1).

Figure 1. Selection of study population.



Of the 3021 included patients, the median age was 72 years and 52% of the patients were men (Table 1). Most patients, 1333 of 3021 (44%) had a baseline NIHSS of 17 or higher, but 190 patients (6%) had a low baseline NIHSS, ranging from 0 to 4. The most common occlusion location was the distal M1 segment (n=1026, 34%). The least common occlusion locations were the M2 segment (n=462, 15%) and the intracranial ICA (n=155, 5%).

Table 1. Baseline characteristics of the 3021 included patients.

Characteristics	N = 3021	Missings
Age, median (IQR)	72 (61 - 81)	0
Male sex	1564 (52%)	0
Occlusion side: left hemisphere	1601 (53%)	0
Baseline NIHSS		0
0-4	190 (6%)	
5-8	323 (11%)	
9-12	466 (15%)	
13-16	709 (24%)	
≥ 17	1333 (44%)	
Systolic blood pressure, mean ±SD	150±25	83 (2.7%)
Treatment with IVT	2309 (76%)	7 (0.2%)
Medical history		
Previous stroke	501 (17%)	27 (0.9%)
Atrial fibrillation	727 (24%)	40 (1.3%)
Diabetes mellitus	475 (16%)	23 (0.08%)
Myocardial infarction	416 (14%)	59 (2.0%)
Hypertension	1545 (51%)	66 (2.2%)
Pre-stroke mRS		65 (2.2%)
0-2	2612 (86%)	-
≥3	344 (11%)	-
Transferred to intervention center	1650 (55%)	1 (0.03%)
Onset-to-door time in minutes, median (IQR)	132 (62 - 188)	146 (4.8%)
Door-to-CTA-time in minutes*, median (IQR)	15 (-64–27)	732 (24.2%)
Door-to-needle-time in minutes, median (IQR)	24 (18 - 33)	495 (16.4%)
Door-to-groin-time in minutes*, median (IQR)	60 (35 - 90)	267 (8.8%)
ASPECTS at baseline, median (IQR)	9 (8 - 10)	61 (2.2%)
Collateral score at baseline		86 (2.8%)
Grade 0	185 (6%)	-
Grade 1	1063 (35%)	-
Grade 2	1143 (38%)	-
Grade 3	544 (18%)	-

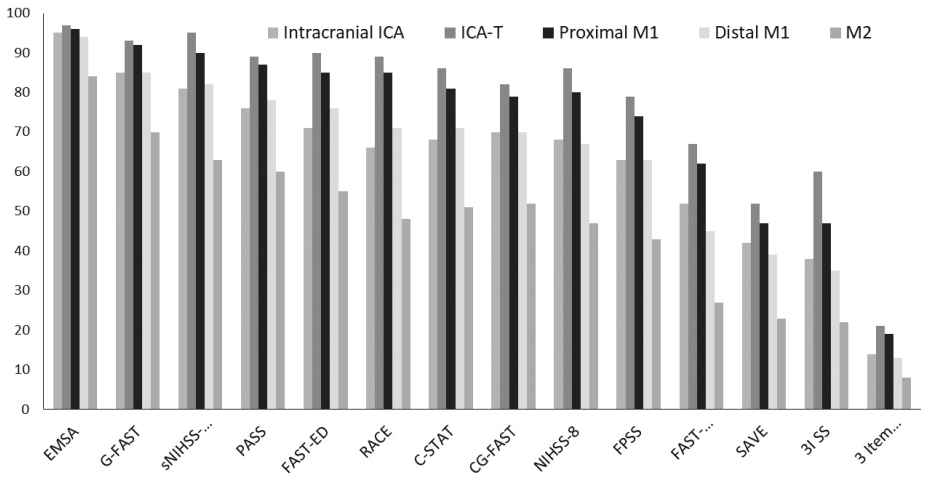
Table 1. *Continued.*

Characteristics	N = 3021	Missings
Level of occlusion on CTA†		0
Intracranial ICA	155 (5%)	-
ICA-T	640 (21%)	-
Proximal M1	738 (24%)	-
Distal M1	1026 (34%)	-
M2	462 (15%)	-

Values are expressed in numbers (%) unless otherwise indicated.
IQR: interquartile range, SD: standard deviation, NIHSS: National Institutes of Health Stroke Scale, IVT: intravenous thrombolysis, mRS: modified Rankin Scale, ASPECTS: Alberta Stroke Program Early CT Score, ICA: internal carotid artery.
* Door-to-CTA-time and door-to-groin-time were calculated using the door-time of the intervention center.
† Percentages do not add up to 100% due to rounding.

For all scales, sensitivity was highest for ICA-T occlusions, with sensitivities ranging from 0.21 to 0.97 (Table 2). Sensitivities decreased for the more distal occlusion segments as well as for the intracranial ICA compared to ICA-T occlusions. M2 occlusions were least likely to be detected, with sensitivities ranging from 0.08 to 0.84 (Figure 2). The difference in sensitivity between occlusion locations was significant for all scales ($p<0.001$). The Emergency Medical Stroke Assessment (EMSA) and Gaze-Face-Arm-Speech-Time (G-FAST) had the highest sensitivity for all different occlusion locations. The Speech Arm Vision Eyes Scale (SAVE), 3-Item Stroke Scale (3I SS), and three-item NIHSS had the lowest sensitivity, for all different occlusion locations. The sensitivity of prehospital stroke scales to detect LVO for all occlusion locations together also varied widely, from 0.15 to 0.94.

Figure 2. Bar plots of the sensitivity per stroke scale, stratified by occlusion location.



The NIHSS items motor arm, aphasia and dysarthria (combined in one item), and facial paresis were the most frequently affected items in our cohort (Table 3). The scales with the highest sensitivity mainly consisted of commonly affected items, whereas the scales with the lowest sensitivity consisted largely of the least affected items.

Table 2. Sensitivity (with 95% confidence interval) for the detection of LVO by fourteen prehospital stroke scales in the full study cohort and stratified by occlusion location.

Prehospital stroke scale	Full cohort	Intracranial ICA	ICA-T	Proximal M1	Distal M1	M2	p-value
EMSA ≥ 3	0.94 (0.93-0.94)	0.95 (0.91-0.98)	0.97 (0.96-0.99)	0.96 (0.95-0.97)	0.94 (0.92-0.95)	0.84 (0.80-0.87)	<0.001
G-FAST ≥ 3	0.86 (0.85-0.87)	0.85 (0.79-0.90)	0.93 (0.92-0.95)	0.92 (0.89-0.94)	0.85 (0.82-0.87)	0.70 (0.65-0.73)	<0.001
sNIHSS-EMS ≥ 6	0.84 (0.68-0.72)	0.81 (0.75-0.87)	0.95 (0.93-0.97)	0.90 (0.88-0.93)	0.82 (0.80-0.85)	0.63 (0.59-0.68)	<0.001
PASS ≥ 2	0.79 (0.78–0.81)	0.76 (0.69-0.82)	0.89 (0.87-0.91)	0.87 (0.84-0.89)	0.78 (0.75-0.80)	0.60 (0.55-0.64)	<0.001
FAST-ED ≥ 4	0.78 (0.76-0.79)	0.71 (0.64-0.78)	0.90 (0.88-0.92)	0.85 (0.82-0.87)	0.76 (0.73-0.78)	0.55 (0.50-0.60)	<0.001
RACE ≥5	0.75 (0.73-0.76)	0.66 (0.58-0.73)	0.89 (0.87-0.92)	0.85 (0.83-0.88)	0.71 (0.68-0.74)	0.48 (0.43-0.52)	<0.001
C-STAT ≥ 2	0.73 (0.72-0.75)	0.68 (0.60-0.75)	0.86 (0.83-0.89)	0.81 (0.78-0.84)	0.71 (0.68-0.73)	0.51 (0.46-0.55)	<0.001
CG-FAST ≥ 4	0.72 (0.71-0.74)	0.70 (0.62-0.77)	0.82 (0.79-0.85)	0.79 (0.76-0.82)	0.70 (0.68-0.73)	0.52 (0.47-0.57)	<0.001
NIHSS-8 ≥ 8	0.71 (0.69-0.73)	0.68 (0.61-0.76)	0.86 (0.86-0.89)	0.80 (0.77-0.83)	0.67 (0.64-0.70)	0.47 (0.42-0.51)	<0.001
FPSS ≥ 5	0.66 (0.64-0.68)	0.63 (0.55-0.70)	0.79 (0.75-0.82)	0.74 (0.71-0.77)	0.63 (0.60-0.66)	0.43 (0.38-0.47)	<0.001
FAST-PLUS positive*	0.52 (0.50-0.53)	0.52 (0.44-0.60)	0.67 (0.64-0.71)	0.62 (0.58-0.65)	0.45 (0.42-0.48)	0.27 (0.23-0.31)	<0.001

Table 2. *Continued.*

Prehospital stroke scale	Full cohort	Intracranial ICA	ICA-T	Proximal M1	Distal M1	M2	p-value
SAVE ≥ 4	0.42 (0.40-0.43)	0.42 (0.34-0.50)	0.52 (0.48-0.56)	0.47 (0.44-0.51)	0.39 (0.36-0.42)	0.23 (0.18-0.26)	<0.001
3I SS ≥ 4	0.42 (0.39-0.43)	0.38 (0.30-0.46)	0.60 (0.58-0.63)	0.47 (0.43-0.50)	0.35 (0.32-0.38)	0.22 (0.19-0.26)	<0.001
3 Item NIHSS ≥ 5	0.15 (0.14-0.17)	0.14 (0.08-0.19)	0.21 (0.18-0.24)	0.19 (0.17-0.22)	0.13 (0.11-0.15)	0.08 (0.05-0.10)	<0.001

* FAST-PLUS is an algorithm and does not have a cut point

Table 3. Overview of prehospital stroke scales.

Prehospital stroke scales	Cut point / total score	Motor arm	Language and dysarthria*	Facial paresis	Motor leg	Dysarthria	Gaze	LOC questions	Aphasia	Visual fields	Sensation	Extinction	LOC commands	LOC responsiveness
Abnormal score per item	-	91%	90%	87%	84%	68%	66%	59%	57%	55%	49%	49%	42%	21%
EMSA	3/6	•	•	•	•		•							
G-FAST	3/4	•	•	•			•							
sNIHSS-EMS	6/29	•		•	•	•			•		•			•
PASS	2/3	•					•	•						
FAST-ED	4/9	•	•	•			•					•		
RACE	5/9	•		•	•		•					•	•	
C-STAT	2/4	•					•	•					•	
CG-FAST	4/5	•	•	•			•	•						
NIHSS-8	8/24	•		•		•	•	•				•	•	•
FPSS	5/8	•	•	•	•		•			•				
FAST-PLUS	‡	•	•	•	•									
SAVE	4/4	•	•				•			•				

Table 3. *Continued.*

Prehospital stroke scales	Cut point / total score	Motor arm	Language and dysarthria*	Facial paresis	Motor leg	Dysarthria	Gaze	LOC questions	Aphasia	Visual fields	Sensation	Extinction	LOC commands	LOC responsiveness
3I SS	4/6	•			•		•							•
3 Item NIHSS	5/8	•									•	•		

Prehospital stroke scales are ordered based on their sensitivity in the full cohort, from high to low. Percentage of the abnormal score per item is the percentage of patients with a score > 0 for the corresponding NIHSS item. NIHSS items are ordered based on this percentage, from high to low. EMSA: Emergency Medical Stroke Assessment, G-FAST: Gaze-Face-Arm-Speech-Time, sNIHSS-EMS: shortened NIH Stroke Scale for emergency medical services, PASS: Prehospital Acute Stroke Severity scale, FAST-ED: Field Assessment Stroke Triage for Emergency Destination, RACE: Rapid Arterial oCclusion Evaluation, C-STAT: Cincinnati Stroke Triage Assessment Tool, CG-FAST: Conveniently-Grasped Field Assessment Stroke Triage, NIHSS-8: National Institutes of Health Stroke Scale-8, FPSS: Finnish Prehospital Stroke Scale, SAVE: Speech Arm Vision Eyes Scale, 3I SS: 3-Item Stroke Scale.

* In most prehospital stroke scales, NIHSS item 9 (language) and 10 (speech) were merged.

‡ FAST-PLUS is an algorithm and does not have a cut point.

Discussion

In this study, we demonstrated large differences in sensitivity of the prehospital stroke scales between different occlusion locations. In general, prehospital stroke scales are most sensitive to detect ICA-T occlusions and least sensitive to detect M2 occlusions.

The decrease in sensitivity of prehospital stroke scales for more distal occlusion locations can be explained by the cerebrovascular anatomy. Proximal occlusions affect a larger brain territory than distal occlusions, which generally results in more severe clinical symptoms. This general rule does not apply to the intracranial ICA, probably due to the collateral function of the circle of Willis.

The variation in sensitivity between different scales can be largely explained by the cut point that is used and the likelihood of its scale-items being affected. For example, the most sensitive scale, EMSA, has a low cut point of three out of six, containing the four most frequently affected items. The least sensitive scales, 3I SS and the Three Item NIHSS were both constructed out of less frequently affected items, and they have relatively high cut points, which resulted in low sensitivity. In addition, some scales (e.g. 3I SS, Rapid Arterial oCclusion Evaluation (RACE), G-FAST, Cincinnati Stroke Triage Assessment Tool (C-STAT), and NIHSS-8) were not primarily designed to detect isolated M2 occlusions.

So far, no studies have focused on the sensitivity of prehospital stroke scales for different occlusion locations. Only one study briefly addressed the sensitivity of the FPSS per occlusion location and was in accordance with our findings.[16] One other study showed that in patients with a Field Assessment Stroke Triage for Emergency Destination (FAST-ED) < 4, a higher prevalence of M2 occlusions was found than in patients with FAST-ED ≥ 4.[13] A validation study of the RACE scale demonstrated M1 and M2 occlusions will be missed more often than ICA-T occlusions.[25] Furthermore, in two separate studies, subgroup analyses excluding M2 occlusions showed a higher sensitivity for the RACE scale, 3I SS and C-STAT.[26, 27]

The MR CLEAN Registry is a large nationwide registry including all patients treated with EVT. All baseline CTAs were assessed by an experienced imaging core laboratory, providing accurate information about the occlusion location. Previously reported sensitivities of prehospital stroke scales could have been influenced by the distribution of the different occlusion locations within the validated cohort. Since our cohort is an unselected representation of patients treated with EVT, it reflects daily clinical practice. Nevertheless, we did not include undiagnosed LVO patients (because CTA was omitted) or untreated LVO patients. However, we expect that this bias will be limited because the Dutch national guideline recommends CTA in all ischemic stroke patients.[28] Furthermore, due to the broad EVT treatment criteria in this guideline, almost

all LVO patients are treated. Only sporadically, patients with low NIHSS, mostly in combination with distal occlusions such as the M2 segment, will not be treated. Therefore, the sensitivity to detect occlusions in the M2 segment might be slightly overestimated. However, even if we would have been able to include the small number of untreated LVO patients, we expect the effect on our results to be limited. We cannot fully exclude between-center differences in EVT indications. We did not account for this in the statistical analysis because potential center differences might also be explained by differences in case-mix and this falls out of the scope of this study. In our opinion, the multicenter nature of the study is a strength, which allowed us to stratify for occlusion location in a large representative cohort of the Dutch EVT population.

Our study has some limitations. We reconstructed prehospital stroke scale scores based on the NIHSS performed by experienced physicians at the emergency department. Prehospital stroke scales should be validated in a prehospital setting by paramedics, as this is the setting in which the scales will be used. However, a prehospital study that acquires substantial numbers for every occlusion location is practically impossible to carry out. It would require a very large sample size.[29] Even though scale assessment by paramedics might differ from the assessment of experienced physicians, we expect the overall decay in sensitivity towards more distal occlusion locations will also apply in the prehospital assessments by paramedics. Additionally, there is some evidence that prehospital assessments are comparable with assessments by physicians, as demonstrated for the RACE and FAST-ED.[30, 31] Because we did not include patients with an LVO in the anterior cerebral artery (A1/A2), we were not able to calculate the sensitivity for A1/A2 occlusions. However, isolated A1/A2 occlusions are uncommon and our cohort counted only 12 (0.3%) of those occlusions. Unfortunately, we could not include all published prehospital stroke scales, as some scales could not be derived from NIHSS items. For example, the commonly used Los Angeles Motor Scale (LAMS) contains the item “grip strength”, which is not incorporated in the NIHSS, and the ambulance clinical triage for acute stroke treatment (ACT-FAST) algorithm also contains several items that were unavailable.[7, 32]

The design of the MR CLEAN Registry allowed us to assess the sensitivity of prehospital stroke scales for different occlusion locations. However, our study does not provide sufficient information to decide on the most accurate scale, because our cohort only consists of patients with LVO. This does not allow us to calculate other diagnostic test parameters of the prehospital stroke scales, such as specificity. The ideal prehospital stroke scale is based on a trade-off between sensitivity and specificity. Prospective, prehospital validation studies such as the recently published PRESTO study and a similar study provide a better insight in the prehospital stroke scale performance.[33, 34] However, in these studies it was not possible to assess the sensitivity of different occlusion

locations because of the relatively small numbers of LVO patients. Finally, since endovascular treatment possibilities are developing further, the added value of prehospital stroke scales to detect LVO patients in the delayed time window or to detect more distal occlusion locations needs to be investigated.

Conclusions

The sensitivity of prehospital stroke scales varies widely between different occlusion locations. Our study demonstrates that prehospital stroke scales are most sensitive in detecting ICA-T occlusions and least sensitive in detecting M2 occlusions. Since the treatment of isolated M2 occlusions is considered effective and safe,[22, 23] it is important to realize that a considerable proportion of treatable LVO patients will be missed.

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Chapter 4.1

Prehospital triage of patients with suspected stroke symptoms (PRESTO): protocol of a prospective observational study

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BMJ Open, 2019

Abstract

Introduction

The efficacy of both intravenous treatment (IVT) and endovascular treatment (EVT) for patients with acute ischemic stroke strongly declines over time. Only a subset of patients with ischemic stroke caused by an intracranial large vessel occlusion (LVO) in the anterior circulation can benefit from EVT. Several prehospital stroke scales were developed to identify patients that are likely to have an LVO, which could allow for direct transportation of EVT eligible patients to an endovascular-capable centre without delaying IVT for the other patients. We aim to prospectively validate these prehospital stroke scales simultaneously to assess their accuracy in predicting LVO in the prehospital setting.

Methods and analysis

PRESTO is a prospective multicentre observational cohort study in the southwest of the Netherlands including adult patients with suspected stroke in the ambulance. The paramedic will assess a combination of items from five prehospital stroke scales, without changing the normal workflow. Primary outcome is the clinical diagnosis of an acute ischemic stroke with an intracranial LVO in the anterior circulation. Additional hospital data concerning the diagnosis and provided treatment will be collected by chart review. Logistic regression analysis will be performed, and performance of the prehospital stroke scales will be expressed as sensitivity, specificity and area under the receiver operator curve.

Ethics and dissemination

The Institutional Review Board of the Erasmus MC University Medical Centre has reviewed the study protocol and confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) is not applicable. The findings of this study will be disseminated widely through peer-reviewed publications and conference presentations. The best performing scale, or the simplest scale in case of clinical equipoise, will be integrated in a decision model with other clinical characteristics and real-life driving times to improve prehospital triage of suspected stroke patients.

Strengths and limitations of this study

- Prospective simultaneous validation of several prehospital stroke scales allows for direct comparison of their accuracy.
- In contrast to previous studies based on in-hospital assessment by experienced physicians, assessment of the prehospital stroke scales will be performed by paramedics in daily clinical practice.
- The results of this study will provide unique insight in the characteristics of an unselected group of patients with suspected stroke in the prehospital setting.
- The best performing scale will be integrated in a prehospital decision tool with other clinical characteristics and real-life driving times to select those patients that benefit from direct transportation to an endovascular-capable centre.
- Performance will be measured with the area under the receiver operator curve, which does not always relate directly to the clinical usefulness of these scales.

Introduction

Rapid treatment with intravenous thrombolytics (IVT) is effective for patients with an ischemic stroke of less than 4.5 hours after onset.[1, 2] However, the effect of IVT is limited for ischemic stroke caused by an intracranial large vessel occlusion (LVO) in the anterior circulation, which accounts for approximately 30% of the patients.[3] These patients can benefit from endovascular treatment (EVT), preferably started within 6 hours after symptom onset, but this treatment can only be performed in specialized intervention centres.[4] The effect of both treatments strongly declines over time.[5-7] In current clinical practice, most suspected stroke patients are transported by ambulance to the nearest hospital for immediate treatment with IVT. Patients can subsequently be transferred to an endovascular capable centre, if eligible for EVT. This is one of the main causes of treatment delay and is associated with worse functional outcomes after EVT.[8, 9]

Several prehospital stroke scales were developed to identify patients that are likely to have an LVO, which could allow for direct transportation of EVT eligible patients to an endovascular capable centre without delaying IVT for the other patients.[10, 11] Most of these scales were derived from the National Institute of Health Stroke Scale (NIHSS) score, and external validation was often attempted by retrospective assessment of the items based on the NIHSS score completed by the treating physician at the emergency department.[12-14] The results of existing prehospital validation studies are limited due to small sample sizes, selected populations or the exclusion of stroke mimics.[15-18] Further prospective validation is therefore required to assess and compare the accuracy of these scales when used by emergency medical services (EMS) personnel in a broad population of suspected stroke patients under circumstances that reflect usual care.

Objective

The primary objective of this study is to prospectively validate several prehospital stroke scales simultaneously to assess their accuracy in predicting the likelihood of ischemic stroke caused by an intracranial LVO in the prehospital setting.

Methods and analysis

Study design

PRESTO is a prospective multicentre observational cohort study. Patients will be recruited in the ambulance and a combination of items from different prehospital stroke scales will be assessed by the paramedic. The normal workflow will not be affected and there is no intervention. Additional hospital

data will be collected by chart review. Routinely performed neuroimaging will be collected and centrally assessed. Follow-up will only be performed in patients with a final diagnosis of ischemic stroke.

Study population

We will include patients in the southwest of the Netherlands, a region with approximately 2 million inhabitants. Participating paramedics have ample experience with the initial management of patients with acute neurological deficits, and they received additional training before the start of the study with regards to the study procedures and the use of the prehospital stroke scales. Additional to the prior training, an instruction video is available for all paramedics. Also, during the duration of the study, regular visits are paid to all ambulance stations to provide feedback and address uncertainty or questions of the paramedics. All adult patients with acute neurological deficit, defined as at least one point on the Face-Arm-Speech-Test (FAST), and a suspected diagnosis of stroke by the paramedic, will be included. Patients with a blood glucose level below 2.5 mmol/L will be excluded.

Prehospital stroke scales

We choose five well known prehospital stroke scales to validate: the Los Angeles Motor Scale (LAMS)[19, 20], the Rapid Arterial oCclusion Evaluation (RACE)[18], the Cincinnati Stroke Triage Assessment Tool (C-STAT)[21], the Prehospital Acute Stroke Severity scale (PASS)[22] and the Gaze-Face-Arm-Speech-Test (G-FAST)[23]. These scales have many similarities in the items that are being used, but there are differences in the scoring systems and the degree of complexity of these scores. In the PRESTO study, we will assess a combination of the items used in these five scales (Table 1).

Table 1. Overview of the items and corresponding scores used in the prehospital stroke scales.

	LAMS	RACE	C-STAT	PASS	G-FAST	Items collected in this study
Answering questions (age and current month)						
A. Correctly answers both questions			0	0		0
B. Correctly answers one question			1*	1		1
C. Does not correctly answer either question						
Following commands ('close your eyes, 'make a fist')						
A. Correctly performs both tasks		0†	0			0
B. Correctly performs one task		1†	1*			1
C. Does not correctly perform either task		2†				2
Head and gaze deviation						
A. Normal; able to follow pen or finger to both sides		0	0	0	0	0
B. Gaze palsy or deviation (total or partial)		1	2	1	1	1
Facial palsy						
A. Normal and symmetrical movement	0	0			0	0
B. Mild palsy (flattened nasolabial fold or minor asymmetry in smile)		1			1	1
C. Moderate to severe palsy	1	2				2

Table 1. *Continued.*

	LAMS	RACE	C-STAT	PASS	G-FAST	Items collected in this study
Grip strength						
A. Normal grip strength	0					0
B. Weak grip strength	1					1
C. No grip possible	2					2
Motor function arm						
A. Normal	0	0	0	0	0	0
B. Drift (minimal drift with closed eyes)	1					
C. Mild palsy (arm drifts down within 10 seconds)		1	1	1	1	1
D. Severe palsy (not able to lift arm)	2	2				2
Motor function leg						
A. Normal		0				0
B. Drift (minimal drift with closed eyes)						
C. Mild palsy (leg drifts down within 5 seconds)		1				1
D. Severe palsy (not able to lift leg)		2				2

Table 1. *Continued.*

	LAMS	RACE	C-STAT	PASS	G-FAST	Items collected in this study
Language						
A. Normal speech					0	0
B. Speech problems (dysarthria, language abnormality, or unable to speak)					1	1
Agnosia						
A. Patient recognises his/her arm and the impairment		0‡				0‡
B. Does not recognises his/her arm or the impairment		1‡				1‡
C. Does not recognises his/her arm nor the impairment		2‡				2‡

*1 point if the patient answers at least one question incorrect and does not follow at least one command
†Only scored if right hemiparesis ‡Only scored if left hemiparesis

Data collection

Eligible patients presenting with suspected stroke symptoms will be recruited in the ambulance. The items from the prehospital stroke scales will be assessed by the paramedic and entered in a web-based database. The paramedic will also enter the transportation number (to link with EMS data and hospital data), the time of symptom onset or last known well (according to patient or bystander), the side of the hemiparesis (if applicable), and the presence of a known neurological deficit on the symptomatic side. Data concerning demographics, vital functions, general neurological examination and transportation times will be collected from the EMS databases.

After arrival in the hospital, patients will receive the usual care. A non-contrast CT scan and additional imaging (e.g. CT angiography (CTA), digital subtraction angiography (DSA) and/or CT perfusion) can be performed as part of the regular workup of a suspected stroke. No additional imaging will be performed in the context of this study. Clinical data concerning the medical history, medication use, laboratory results, physical examination, and diagnosis will be collected by chart review. All diagnostic neuroimaging data and radiology reports will be collected. If applicable, we will also collect information on the given treatment and corresponding treatment times (e.g. the door-to-needle time, the door-to-groin time, the imaging-to-treatment time, and the door-in-door-out time of transferred patients).

Follow-up will only be collected for patients with a final diagnosis of acute ischemic stroke. We will use the outcome registration of the hospitals to collect length of hospital stay, discharge destination, and the modified Rankin Scale (mRS) score after 90 days.

Outcome measures

Primary outcome will be the clinical diagnosis of an acute ischemic stroke with an intracranial LVO in the anterior circulation, defined as an occlusion of the internal carotid artery, the middle cerebral artery segment M1 or M2, or the anterior cerebral artery segment A1 or A2 (assessed on CTA or DSA). Secondary outcome measures include the presence of an LVO in the posterior circulation (vertebral artery or basilar artery), the final diagnosis at hospital discharge, the given treatment (IVT, EVT, or both) and corresponding treatment times and the functional outcome, measured with the 90-day mRS.

Sample size calculation

At least 100 events (i.e. intracranial LVOs) are required for the external validation of predictive models.[24, 25] The annual incidence of suspected ischemic stroke within 6 hours after onset of symptoms is estimated to be 50 per 100.000 people, based on an earlier cohort study.[14] In the catchment area of the participating EMS (approximately 2 million inhabitants), this would imply 1000

patients every year presenting with stroke symptoms within the 6-hour time window. Of these 1000 patients, approximately 15% are assumed to have an ischemic stroke due to an LVO; 31% an ischemic stroke without the presence of an LVO; 9% a transient ischemic attack (TIA); 10% an intracerebral hemorrhage; and 35% a stroke mimic.[14] To reach the required number of 100 stroke patients with an LVO, we will have to include at least (number of cases / prevalence = 100 / 0.15) 667 patients with stroke symptoms of less than 6 hours. To allow for a 5% loss of follow up, we will aim for a sample size of 700 patients.

After inclusion of the first 500 patients, we will perform an interim analysis to calculate the percentage of LVO in our study population. If necessary, the required sample size will be adjusted based on this information. Although patients presenting after 6 hours will be included in the study, they will not count for the required sample size.

Data analysis plan

After completion of the last inclusion, the data will be checked, and the database will be locked for statistical analyses. We will report the absolute numbers and percentages of patients based on the final diagnosis (e.g. ischemic stroke, hemorrhagic stroke, TIA or stroke mimic) and, if applicable, the location of the intracranial LVO. For ischemic stroke patients, we will report the given treatment (IVT, EVT, or both) and corresponding treatment times, the number of inter-hospital transfers and the functional outcome after 90 days. Missing values will be imputed with simple imputation based on the mean or mode (if less than 5% missing) or multiple imputation based on relevant covariates and outcome (if more than 5% missing).

The different prehospital stroke scales will be reconstructed based on the items assessed in the ambulance (Table 1). We will validate the prehospital stroke scales for patients presented within 6 hours after symptom onset using a logistic regression model with the presence of an LVO in the anterior circulation as outcome measure. We will analyse the scores both continuously and dichotomized, based on the previously reported cut points in the original studies. Sensitivity and specificity of all cut points will be reported separately. The global performance of the prehospital stroke scales will be expressed as the area under the receiver operator curve.

Prespecified sensitivity analyses will be performed for patients that presented more than 6 hours after symptom onset, for the separate occlusion locations and for the presence of an LVO in the posterior circulation. We will also assess the original outcome definitions as defined in each prehospital stroke scale instead of our own primary outcome and we will analyse the correlation between the prehospital stroke scales and the NIHSS assessed at the emergency department. Additional analyses will be performed to predict the probability of

treatment with EVT based on the prehospital stroke scales and relevant factors in the medical history, medication use or vital signs.

Patient and public involvement

Patients and public were not involved in the development of the research questions or the design of this study. All study participants and every interested person in the public will have the possibility to read regular project updates on the project website (www.presto-studie.nl).

Duration and current status of the study

The study was registered in The Netherlands Trial Register on November 11, 2018 under number NTR7595 (www.trialregister.nl). The study started on August 13, 2018 in the region Zuid-Holland Zuid and on September 1, 2018 in the region Rotterdam-Rijnmond. Recruitment of patients is ongoing and at the time of submission, April, 2019, 665 patients have been included in the study within 6 hours of symptom onset. In anticipation of a formal interim analysis, first raw data analysis shows a prevalence of 8% LVO in our study population. Based on this information, we increased our sample size to 1250 patients. With the current inclusion rate, we expect to reach the required sample size of 1250 patients by September 2019.

Ethics and dissemination

Ethical aspects and informed consent

This study will be conducted in accordance with the principles of Good Clinical Practice, the Dutch Agreement on Medical Treatment Act (WGBO) and the European General Data Protection Regulation The Institutional Review Board of the Erasmus MC University Medical Centre has reviewed the study protocol and confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) is not applicable.

Acquiring informed consent can be very challenging in the prehospital inclusion of suspected stroke patients. Many patients suffer from a language deficit, anosognosia, or other cognitive symptoms that impede an informed consent procedure, and often there is no (legal) representative of the patient present in the prehospital setting. Furthermore, an adequate informed consent procedure takes time, which is not available in the prehospital setting. Sometimes a deferred consent procedure can be used, but in the context of the WGBO this should be done by the treating physician. Since our unselected population of patients, including many stroke mimics, will spread towards different directions after presentation in the hospital, a disproportionate number of health care providers from a variety of specialisms (e.g. neurologists, emergency physicians,

internists, cardiologists) should be involved in the research to enable a deferred consent procedure.

The extent of the effort by a large number of health care providers needed to obtain permission from the participating patients is disproportionate to the relatively limited sensitivity of the collected and linked personal data and the related limited intrusion to the personal privacy. We will therefore use an opt-out procedure in this study. The including paramedic will provide a leaflet with information about the study to the patient or their relatives. In this leaflet, we will explain that some routinely collected data can be collected from the EMS databases and the hospital charts for further analysis. Patients or their relatives are offered the opportunity to object to the use of these data in this study. When a patient or relative objects to study participation, all data will be destroyed, and the patient will be excluded from the study.

Dissemination plan

The main study results will be disseminated via publication in an international peer-reviewed journal and presentation at international conferences for stroke and emergency medicine experts. Representatives of the EMS providers and participating hospitals will be given the opportunity to comment on the manuscript and to participate as co-author, following the recommendations of the International Committee of Journal Editors. We plan to disseminate the results of the planned secondary analyses in one or more separate papers.

The best performing scale or the simplest scale in case of clinical equipoise, will be integrated in a decision model with other clinical characteristics and real-life driving times.[26] This model can be implemented in an online tool to improve prehospital triage of patients with suspected stroke symptoms without harming those patients that benefit from rapid IVT in the nearest hospital. Patients eligible for EVT will be directly transported to an endovascular capable centre, which will lead to an increased number of treated patients, reduced treatment times and improved patient outcomes. Moreover, avoiding unnecessary inter-hospital transfers will lead to more efficient use of EMS resources.

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Chapter 4.2

Comparison of eight prehospital stroke scales to detect intracranial large vessel occlusion in prehospital triage of patients with suspected stroke (PRESTO): a prospective observational cohort, validation study

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Abstract

Background

Due to the time-sensitive effect of endovascular treatment, rapid prehospital identification of large-vessel occlusion (LVO) in suspected stroke patients is essential to optimize outcome. Inter-hospital transfers are an important cause of delay of EVT. Prehospital stroke scales have been proposed to select patients with LVO for direct transport to an endovascular-capable intervention center. We aimed to prospectively validate eight prehospital stroke scales in the field.

Methods

We did a multicenter prospective, observational cohort study of adults with suspected stroke (aged≥18 years) who were transported by ambulance to one of eight hospitals in southwest Netherlands. Suspected stroke was defined by a positive Face-Arm-Speech-Time (FAST) test. We included patients with a blood glucose of at least 2.5 mmol/L. Patients who presented more than six hours after symptom onset were excluded from the analysis. After structured training, paramedics used a mobile app to assess items from eight prehospital stroke scales: Rapid Arterial oCclusion Evaluation (RACE), Los Angeles Motor Scale (LAMS), Cincinnati Stroke Triage Assessment Tool (C-STAT), Gaze-Face-Arm-Speech-Time (G-FAST), Prehospital Acute Stroke Severity (PASS), Cincinnati Prehospital Stroke Scale (CPSS), Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST), and the FAST PLUS (Face-Arm-Speech-Time plus severe arm or leg motor deficit) test. The primary outcome was the clinical diagnosis of ischemic stroke with a proximal intracranial LVO in the anterior circulation (aLVO) on CT angiography. Baseline neuroimaging was centrally assessed by neuroradiologists to validate the true occlusion status. Prehospital stroke scale performance was expressed as the area under the receiver operating characteristic curve (AUC) and was compared with National Institutes of Health Stroke Scale (NIHSS) scores assessed by clinicians at the emergency department.

Findings

Between August 13, 2018 and September 2, 2019, 1039 patients (median age 72 years [IQR: 61-81]) with suspected stroke were identified by paramedics, of whom 120 (12%) were diagnosed with aLVO. Of all prehospital stroke scales, the AUC for RACE was highest (0.83, 95% CI: 0.79-0.86), followed by the AUC for G-FAST (0.80, 0.76-0.84), CG-FAST (0.80, 0.76-0.84), LAMS (0.79, 0.75-0.83), CPSS (0.79, 0.75-0.83), PASS (0.76, 0.72-0.80), C-STAT (0.75, 0.71-0.80), and for FAST PLUS (0.72, 0.67-0.76). The NIHSS did somewhat better than the prehospital stroke scales with an AUC of 0.86 (95% CI 0.83-0.89).

Interpretation

Prehospital stroke scales detect aLVO with acceptable-to-good accuracy. RACE, G-FAST and CG-FAST are the best performing prehospital stroke scales out of the eight scales tested and approach the performance of the clinician-assessed NIHSS. Further studies are needed to investigate whether the use of these scales in regional transport strategies can optimize outcomes of patient with ischemic stroke.

Research in context

Evidence before this study

We searched PubMed with no language restrictions for papers published from database inception up to July 6, 2020, to include prehospital prospective validation studies of prehospital stroke scales. We used the search terms “prehospital triage”, “prehospital stroke scale”, “large vessel occlusion”, and “mechanical thrombectomy” or “endovascular therapy”, and we cross-checked references of eligible papers. Many prehospital stroke scales have been developed, but prospective prehospital validation studies are scarce. We identified nine studies validating prehospital stroke scales in the field. None of these studies validated multiple scales simultaneously and most were done in small or selected populations, limiting the generalizability of their results.

Added value of this study

To the best of our knowledge, our study is the first to validate eight prehospital stroke scales simultaneously in a large unselected population of suspected stroke patients by paramedics in the field using a mobile app. Our study provided reliable estimates of the in-field performance of eight prehospital stroke scales. CT angiographies were done in-hospital and reassessed by an Imaging Core Laboratory to validate the true occlusion status.

Implications of all the available evidence

Prehospital stroke scales are helpful to guide prehospital selection of suspected stroke patients. In general, prehospital stroke scales detect large-vessel occlusions well and the different scales perform similarly. The best in our study were Rapid Arterial oCclusion Evaluation (RACE), Gaze-Face-Arm-Speech-Time (G-FAST) and Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST), which approached the performance of the clinician-assessed National Institutes of Health Stroke Scale (NIHSS). However, due to its complexity, NIHSS is not the ideal scale for assessment by paramedics in the field. Our finding that the field-assessed RACE score of 5 or higher corresponds to a 40% or higher risk of aLVO (positive predictive value 0.40), supports implementation of RACE (another prehospital stroke scales with a similar threshold) in clinical practice in most urban and suburban regions. However, in rural areas with longer driving times to the intervention center, higher positive predictive value thresholds should be considered. With our study evidence, health-care professionals and policy makers might be able to better decide on the most suitable prehospital stroke scale and threshold to customize prehospital triage to regional characteristics, such as distribution of hospitals and their stroke treatment capabilities, population density, and regional workflow times.

Background

Worldwide, stroke is one of the leading causes of death or disability, particularly in patients with ischemic stroke caused by a proximal intracranial large vessel occlusion (LVO).[1] Both intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) have been proven effective in ischemic stroke patients, but their effect is highly time-dependent.[2, 3] In patients with ischemic stroke due to LVO, IVT is less effective and EVT is generally indicated.[4] In current clinical practice, suspected stroke patients are usually transported to the nearest hospital for rapid IVT. EVT-eligible patients are subsequently transferred to a specialized intervention center. Despite optimization of the prehospital and in-hospital workflow, interhospital transfers remain an important cause of delay in EVT and are associated with worse outcomes for patients, compared with those who have EVT who do not require transfer.[5-7] Prehospital triage to identify EVT-eligible patients at an early stage could prevent unnecessary interhospital transfers and optimize clinical outcomes of ischemic stroke patients due to LVO. Prehospital stroke scales can be used to detect patients with a high likelihood of having an LVO and could guide who should be transported directly to an intervention center.[8]

Prehospital stroke scales are designed as short and simple clinical methods for assessment of patients by paramedics in the field. Most scales are derived from the National Institutes of Health Stroke Scale (NIHSS).[8] Many scales have been published, and some have already been implemented as triage tools.[9] However, prospective prehospital studies validating these scales are scarce, and performance of prehospital stroke scales has not been directly compared.[9-16] In the prehospital triage of patients with suspected stroke (PRESTO) study, we aimed to prospectively validate and compare eight prehospital stroke scales to assess their accuracy in estimating the likelihood of an intracranial LVO in suspected stroke patients in the prehospital setting.

Methods

Study design and patients

PRESTO was a multicenter, prospective, observational cohort study in southwest Netherlands, an area with approximately two million inhabitants. Eight different hospitals are located in the study region, and two centers are capable of EVT. Suspected stroke patients were recruited in the ambulance by paramedics from two ambulance services operating in the study region: Rotterdam-Rijnmond and Zuid-Holland Zuid. All participating hospitals and ambulance services were part of a regional collaboration for acute neurological care. Inclusion criteria were new neurological deficit defined as at least one point on the Face-Arm-Speech-Time (FAST) test, age 18 years or older, and blood glucose of at least 2.5 mmol/L.

Patients who presented more than six hours after symptom onset (or more than six hours after they were last known well), which was assessed by paramedics in the field, were included in the study but were excluded from the current analysis. We applied this restriction because, during the recruitment period, CT angiography was not done routinely outside the six hour time window.

This study was done in accordance with the Dutch Agreement on Medical Treatment Act and the European General Data Protection Regulation. The Institutional Review Board of the Erasmus MC University Medical Centre has reviewed the study protocol and confirmed that the Dutch Medical Research Involving Human Subjects Act is not applicable. Because our study met the exceptions of informed consent regulations, the need for informed consent was waived. Patients or their relatives were informed about the study and could withdraw from the study through an opt-out system. This information was provided in an leaflet handed to the patients or their relative in the ambulance. Detailed information regarding the methods are described elsewhere.[17]

Procedures

Patients with suspected stroke symptoms were recruited in the ambulance by paramedics from two ambulance services operating in the study region (Rotterdam-Rijnmond and Zuid-Holland Zuid). Eight different hospitals were located in this region, two of these centers were capable of EVT. All participating hospitals and ambulance services were part of a regional collaboration for acute neurologic care. Inclusion criteria were new neurological deficit, defined as at least one point on the Face-Arm-Speech-Time (FAST) test, age 18 years or over, and a blood glucose level of at least 2.5 mmol/L. Patients who presented more than six hours after last-known-well (LKW), assessed by the paramedics in the field, were included in the study, but were excluded from the current analysis. We applied this restriction because CTA imaging was not yet routinely performed outside the six-hour time window during the recruitment period.

In the Netherlands, paramedics are registered nurses that received specialized education (as an emergency department nurse, intensive care unit nurse or an anaesthetic technician) with an additional training of seven months at the Academy for Ambulance Care. The assessment of the Face-Arm-Speech-Time (FAST) test was already part of the routine in the assessment of suspected stroke patients. Before the start of the study, paramedics received training with regard to the study procedures and the assessment of the prehospital stroke scales. Items from the prehospital stroke scales were entered in a web-based database accessible through a mobile application. This application was designed to guide the paramedic through the assessment. Pocket cards and an instruction video were available for all paramedics and MHCD, EV, DD and BR paid regular visits to ambulance stations to refresh and evaluate the study procedures.

Paramedics assessed a combination of nine items from eight prehospital stroke scales, on scene or during transport (supplemental material, Table 1). During the study conception and design, these scales were selected based on previous literature and expert opinion of two vascular neurologists (DD, BR). PRESTO was originally designed to validate five prehospital stroke scales: RACE scale, Los Angeles Motor Scale (LAMS), Cincinnati Stroke Triage Assessment Tool (C-STAT), Gaze-Face-Arm-Speech-Time (G-FAST), and Prehospital Acute Stroke Severity (PASS) scale.[15, 18-21] During the start-up phase of the study, two additional prehospital stroke scales consisting of similar items were published; therefore the Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST) and the FAST PLUS Test were added.[13, 22] The Cincinnati Prehospital Stroke Scale (CPSS) was originally designed to identify stroke in general but was later suggested as a prehospital tool to detect LVO, therefore CPSS was also added.[23, 24]

Prehospital stroke scales were reconstructed based on the prehospital items (supplemental material, Table 1). The first category of the item "Motor function arm" actually spans two categories in LAMS, PASS, G-FAST, CPSS, and FAST PLUS. During the design of the study, we decided to merge these categories for practical reasons. After arrival in the hospital, usual care was continued. This included assessment of the NIHSS at the emergency department (ED) by the neurologist, neurology resident, or ED physician, prior to any treatment. Missing NIHSS was retrospectively scored using a standardized score chart based on the reported neurologic examination. As part of the regular work-up, non-contrast CT (NCCT), CT angiography (CTA), CT perfusion, magnetic resonance imaging or digital subtraction angiography could be performed, based on the assessment of the treating physician. All neuro-imaging was stored in an imaging database (XNAT; Neuroinformatics Research Group, St Louis, MO). Additional clinical data were collected through hospital chart review and ambulance call reports.

Four neuroradiologists (AvdL, JB, ASP, JHH) and three interventional neuroradiologists (ACGMvE, PJvD, GJL) formed the imaging core-laboratory that assessed CTA at baseline. Baseline NCCT was provided along with the CTA. Imaging was primarily assessed by one of six core-laboratory members (JB, ASP, JHH, ACGMvE, PJvD, GJL). In case of discordant CTA assessments between the local radiologist and the core-laboratory, the seventh core-laboratory member (AvdL) reassessed imaging, blinded for the prior assessments. If the two core-laboratory assessments did not match, disagreements were resolved in consensus by the co-chairs of the core-laboratory (ACGMvE, AvdL).

Before assessment, the core-laboratory was provided with guidelines including relevant definitions. We distinguished between proximal and distal M1 occlusions based on the proximal versus the distal half of the M1 segment. The M2 segments were defined as the post-bifurcation branches distal to the M1 segment. In case of multiple occlusions, the most proximal occlusion was used for the analysis. The core-laboratory was blinded for the final diagnosis

of the local physicians and the scores on the prehospital stroke scales, but was informed about the prehospital clinical symptoms. Clinical symptoms were defined as either side of the hemiparesis, presence of aphasia, or non-localizing symptoms for the patients without hemiparesis or aphasia.

Table 1. Patient characteristics stratified by diagnosis.

	Total cohort	Ischemic stroke with aLVO	Ischemic stroke without aLVO	Intracranial hemorrhage	TIA	Stroke mimic	Total missings
N	1039	120 (12%)	402 (39%)	72 (7%)	191 (18%)	254 (25%)	0
Age (years)	72 (61-81)	73 (62-81)	74 (63-82)	74 (60-82)	73 (64-82)	68 (56-79)	0
Sex (women)	479 (46%)	58 (48%)	170 (42%)	32 (44%)	80 (42%)	139 (55%)	0
Medical history							
Atrial fibrillation	185 (18%)	26 (22%)	65 (16%)	15 (21%)	43 (23%)	36 (14%)	0
Hypertension	676 (65%)	83 (69%)	273 (68%)	44 (61%)	136 (71%)	140 (55%)	0
Hypercholesterolaemia	740 (71%)	82 (68%)	304 (76%)	45 (63%)	150 (79%)	159 (63%)	0
Diabetes Mellitus	200 (19%)	25 (21%)	85 (21%)	4 (6%)	45 (24%)	41 (16%)	0
Ischemic stroke	256 (25%)	16 (13%)	115 (29%)	8 (11%)	44 (23%)	73 (29%)	0
Myocardial infarction	116 (11%)	14 (12%)	47 (12%)	5 (7%)	24 (13%)	26 (10%)	0
Intracranial hemorrhage	16 (2%)	0	2 (1%)	2 (3%)	4 (2%)	8 (3%)	0
Pre-stroke mRS							67 (6%)
0-2	808 (78%)	93 (78%)	316 (79%)	54 (75%)	152 (80%)	193 (76%)	
3-5	164 (16%)	19 (16%)	64 (16%)	9 (13%)	27 (14%)	45 (18%)	
Prehospital assessment							
RACE	2 (0-4)	6 (3-7)	2 (1-3)	5 (2-7)	0 (0-1)	1 (0-2)	0
G-FAST	1 (1-2)	3 (2-4)	1 (1-2)	2 (1-3)	1 (0-1)	1 (0-2)	0
CG-FAST	2 (1-3)	3 (2-4)	2 (1-3)	3 (2-4)	1 (0-2)	1 (0-2)	0
LAMS	1 (0-3)	4 (3-5)	1 (0-3)	4 (3-5)	0 (0-1)	0 (0-3)	0

Table 1. *Continued.*

	Total cohort	Ischemic stroke with aLVO	Ischemic stroke without aLVO	Intracranial hemorrhage	TIA	Stroke mimic	Total missings
CPSS	1 (1-2)	3 (2-3)	1 (1-2)	2 (1-3)	1 (0-1)	1 (0-2)	0
PASS	1 (0-1)	2 (1-2)	1 (0-1)	1 (1-2)	0 (0-1)	0 (0-1)	0
C-STAT	0 (0-1)	1 (1-3)	1 (0-1)	1 (1-3)	0 (0-0)	0 (0-1)	0
FAST-PLUS positive	224 (22%)	72 (60%)	67 (17%)	43 (60%)	8 (4%)	34 (13%)	0
In-hospital assessment							
SBP mean±SD	160 ± 28	155 ±24	162±26	181±31	162±27	152±30	11 (1%)
NIHSS score	2 (0-6)	13 (7-18)	3 (2-6)	11 (5-18)	0 (0-1)	1 (0-3)	6 (1%)
GCS score							3 (1%)
3-8	17 (2%)	1 (1%)	3 (1%)	6 (8%)	0	7 (3%)	
9-13	127 (12%)	39 (33%)	39 (10%)	25 (35%)	0	24 (9%)	
14-15	892 (86%)	80 (67%)	359 (89%)	40 (56%)	191 (100%)	222 (87%)	
Workflow times (minutes)							
Onset-to-alert*	51 (16-130)	44 (10-118)	62 (20-161)	25 (10-81)	42 (16-85)	57 (20-131)	112 (11%)
Onset-to-door*	86 (53-161)	74 (47-157)	91 (55-197)	63 (47-109)	80 (51-119)	96 (61-164)	32 (3%)

Table 1. *Continued.*

	Total cohort	Ischemic stroke with aLVO	Ischemic stroke without aLVO	Intracranial hemorrhage	TIA	Stroke mimic	Total missings
Door-to-CT*	9 (6-13)	8 (5-10)	9 (6-12)	9 (6-13)	10 (7-21)	10 (6-15)	27 (3%)

Data are median (IQR) or n (%), unless otherwise indicated. aLVO= anterior circulation large vessel occlusion, defined as an occlusion of the internal carotid artery, the middle cerebral artery segment M1 or M2 or the anterior cerebral artery segment A1 or A2. TIA= transient ischemic attack. mRS= modified Rankin Scale. RACE= Rapid Arterial oCclusion Evaluation. G-FAST= Gaze-Face-Arm-Speech-Time. CG-FAST= Conveniently-Grasped Field Assessment Stroke Triage. LAMS= Los Angeles Motor Scale. CPSS= Cincinnati Prehospital Stroke Scale. PASS= Prehospital Acute Stroke Severity. C-STAT= Cincinnati Stroke Triage Assessment Tool. SBP= Systolic Blood Pressure. SD= Standard Deviation. NIHSS = National Institutes of Health Stroke Scale. GCS=Glasgow Coma Scale. * “onset” is either the time of symptom onset or the time the patient was last known well. “Door” is defined as the time the patient enters the (first) hospital.

Outcomes

Primary outcome was a clinical diagnosis of ischemic stroke with a core-laboratory- confirmed intracranial LVO in the anterior circulation (aLVO), defined as an occlusion of the intracranial part of the internal carotid artery (ICA), the middle cerebral artery segment M1 or M2 or the anterior cerebral artery segment A1 or A2, assessed on CTA. We included M2 occlusions in the primary outcome, because the Dutch national guideline advises EVT in all patients with an occlusion of the distal part of the ICA and M1/M2 segment, if treatment is possible within six hours after symptom onset, irrespective of the stroke severity. We did not include occlusions in the posterior circulation in the primary outcome. Even though posterior circulation occlusions could cause severely disabling stroke, the efficacy of EVT for posterior circulation occlusions is uncertain.[25] Also, several scales were not designed to detect LVO in the posterior circulation and to triage patients with lowered level of consciousness.

Secondary outcomes included the presence of an LVO in the posterior circulation (vertebral artery, basilar artery, and (in addition to the secondary outcomes in our protocol) the posterior cerebral artery segment P1 or P2), the final diagnosis at hospital discharge (ischemic stroke with or without aLVO, intracranial hemorrhage, transient ischemic attack (TIA), stroke mimic), the provided treatment (IVT, EVT or both), corresponding treatment times (door-to-needle time and door-to-groin-time) and functional outcome. EVT was defined as arterial groin puncture in the interventional suite. Door-to-groin-time was defined as the time in minutes from entry in the intervention center to groin puncture. Functional outcome, measured with the 90-day modified Rankin Scale (mRS), was obtained in patients with a clinical diagnosis of ischemic stroke. This was a pragmatic decision, as the 90-day mRS was only standardly registered for ischemic stroke patients during the course of the study. If mRS was not available at 90 days, the last known mRS was reported. However, any mRS score of 0 to 5 assessed during the hospital stay was assumed to be a suboptimal reflection of the true outcome at 90 days and therefore treated as missing value for the analysis.

Sample size

At least 100 events are required for the external validation of predictive models.[26] Prior to the study, we estimated that the prevalence of aLVO patients in suspected stroke patients was 15%.[27] Based on this percentage, the initial required sample size was calculated at 700. Based on an interim analysis, the prevalence of aLVO appeared to be approximately 10%. Therefore, we repeated the sample size calculation and aimed at including at least 1,000 suspected stroke patients. Patients presenting beyond six hours last-known-well were included in the study, but did not count for the required sample size.

Statistical analysis

We reported completeness of data, medians and interquartile range (IQR) or means and standard deviation (SD) for continuous variables, when appropriate. We reported numbers and percentages for categorical variables. Between-group comparisons were made with the Mann Whitney U test for continuous variables and Chi Square Test or Fisher's exact test for categorical variables.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of aLVO, at each possible cut point were calculated. For the calculation of these test characteristics, we assumed ischemic stroke patients without CTA were aLVO negative. Global performance of the prehospital stroke scales was expressed as the area under the receiver operating characteristic curve (AUC). In a post-hoc analysis, AUCs were compared with the DeLong test, a method to compare AUCs of paired ROC curves.[28]

We performed several sensitivity analyses. First, we added basilar artery occlusions to the outcome definition. Second, we used the local-assessed aLVO status instead of core-laboratory assessed outcome. Since EVT of the A1, A2 or M2 occlusions is not recommended by all international guidelines[29], we performed a third sensitivity analysis with only intracranial ICA and M1 occlusions as outcome definition. In the fourth sensitivity analysis , intracranial hemorrhage was included in the outcome definition.

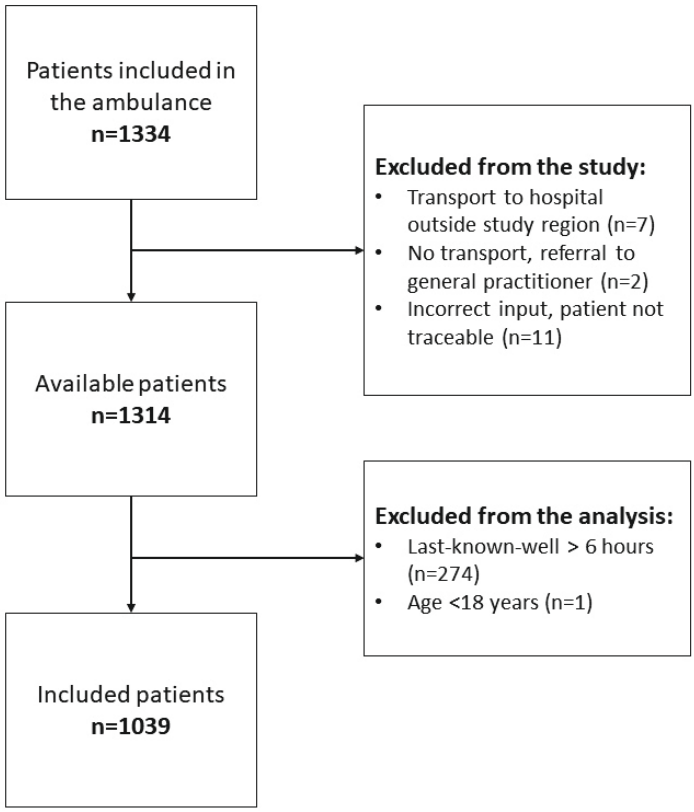
Additionally, we performed a post-hoc exploratory analysis to estimate the potential impact of the merged categories in the item "Motor function arm". For this analysis, drift was assessed positive if paramedics scored "0" in the motor arm item and physicians scored the NIHSS motor arm item (left or right) as "1: drift" for the LAMS, PASS, G-FAST, CPSS and FAST PLUS. Then, we recalculated ROC curves and test characteristics at the original cut points.

All analyses were performed using R software (version 3.6.1) and RStudio (version 1.0.153).

Results

In total, 1334 patients were enrolled between August 13, 2018, and September 2, 2019. Twenty patients were excluded from the study because of an incorrect input or because the patient was transferred to a hospital outside the study region. We excluded 274 patients from the analysis because they presented beyond six hours from symptom onset and one patient because of an age below 18 (Figure 1). Paramedics entered all items in the mobile application in 2.6 minutes, median (IQR: 1.9-3.8).

Figure 1. Flowchart of study inclusion.



Of the 1039 included patients, the median age was 72 years (IQR 61-81), and 479/1039 (46%) were women (Table 1). Five hundred twenty-two of 1039 patients (50%) were diagnosed with ischemic stroke, of which 120 patients were diagnosed with an aLVO (12% of the total cohort). Of all 1039 patients, 254 (25%) were diagnosed with a stroke mimic, 191/1039 patients (18%) with TIA and 72/1039 patients (7%) with intracranial hemorrhage. Baseline NIHSS was highest in patients with aLVO, with a median of 13 (IQR 7-18), compared to patients with non aLVO ischemic stroke, intracranial hemorrhage, TIA or stroke mimic.

Of the patients with aLVO, M2 occlusions were most common (52/120, 43%, Table 2). In 66/402 (16%) of the non aLVO ischemic stroke patients, CTA was not performed. In these patients, median NIHSS was 2 (IQR 1-4). Of all 193 ischemic stroke patients with an NIHSS of 2 or lower, 11 (6%) were diagnosed with aLVO. EVT was performed in 89/121 (74%) of the aLVO patients, with a median door-to-groin-time of 48 (IQR: 25-67) minutes. The remaining secondary outcomes can be found in Table 2. The main reason aLVO patients were not treated

with EVT was because the occlusion was not detected by the local radiologist (supplemental material, Table 2).

Table 2. Treatment-related characteristics and functional outcome of ischemic stroke patients.

	Ischemic stroke with aLVO	Ischemic stroke without aLVO	p-value*	Total missings
N	120 (23%)	402 (77%)		
CTA performed	120 (100%)	336 (84%)	<0·0001	0
Occlusion location			<0·0001	0
Infraclinoid ICA	5 (4%)	-	-	-
Supraclinoid ICA	3 (3%)	-	-	-
ICA-T	7 (6%)	-	-	-
M1 (proximal)	24 (20%)	-	-	-
M1 (distal)	26 (22%)	-	-	-
M2	52 (43%)	-	-	-
A1	0	-	-	-
A2	3 (3%)	-	-	-
M3	0	2 (1%)	-	-
BA/VA	0	7 (2%)	-	-
P2	0	5 (1%)	-	-
Reperfusion treatment and treatment times (minutes)				
Treated with IVT	79 (66%)	246 (61%)	0·36	0
Door-to-needle-time	18 (15-24)	20 (15-25)	0·32	1 (0·001%)
Treated with EVT	89 (74%)	2 (0·5%)	<0·0001	0
Door-to-groin-time	48 (25-67)	67 (60-74)	0·24	1 (0·001%)
Transferred patients†	45 (38%)	2 (0·5%)	<0·0001	0
Door-in-door-out time	62 (47-81)	72 (69-74)	0·49	1 (0·001%)
Driving time between hospitals	12 (9-15)	23 (22-24)	0·06	1 (0·001%)
mRS at 90 days			0·03	93 (18%)
0-2	57 (48%)	264 (66%)	-	-
3-6	30 (25%)	78 (19%)	-	-

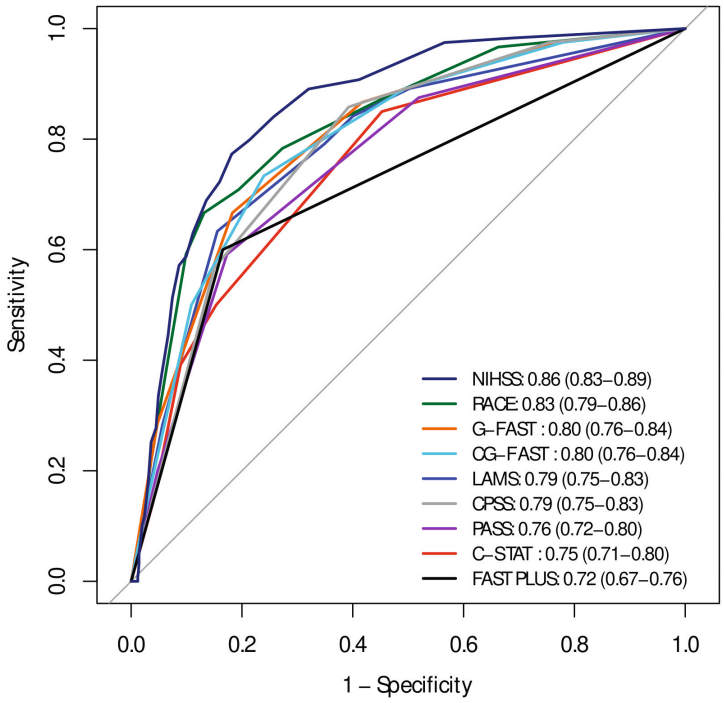
Table 2. *Continued.*

	Ischemic stroke with aLVO	Ischemic stroke without aLVO	p-value*	Total missings
Follow-up time (days)	92 (58-98)	85 (57-97)	0·08	93 (18%)

Data are median (IQR) or n (%), unless otherwise indicated. *p-values were derived from the Mann-Whitney U test for continuous characteristics and χ^2 statistics or Fisher's exact test for categorical characteristics. aLVO = anterior circulation large vessel occlusion, defined as an occlusion of the internal carotid artery, the middle cerebral artery segment M1 or M2 or the anterior cerebral artery segment A1 or A2. † Patients with an LVO that were transferred to an intervention center. CTA = CT angiography. ICA = Internal Carotid Artery. ICA-T = Internal Carotid Artery Terminus. BA = Basilar Artery. VA = Vertebral Artery. IVT = intravenous thrombolysis. EVT = Endovascular thrombectomy. mRS = modified Rankin Scale.

AUCs of the prehospital stroke scales ranged from 0.72 (95% confidence interval (CI): 0.67-0.76) for FAST PLUS to 0.83 (95% CI: 0.79-0.86) for RACE (Figure 2 and supplemental material, Table 3). AUCs for G-FAST (AUC=0.80, 95% CI: 0.76-0.84, p=0.13) and CG-FAST (AUC=0.80 , 95% CI: 0.76-0.84, p=0.09) were not significantly different from the AUC for RACE, but AUCs for LAMS (0.79, 95% CI: 0.75-0.83, p=0.01), CPSS (0.79, 95% CI: 0.75-0.83, p=0.03), PASS (0.76, 95% CI: 0.72-0.80, p<0.0001), C-STAT (0.75, 95% CI: 0.71-0.80, p<0.0001), and FAST PLUS (p<0.0001) were significantly different from the AUC for RACE, based on the DeLong test. Physician-assessed NIHSS performed better than the prehospital stroke scales, with an AUC for the NIHSS of 0.86 (95% CI: 0.83-0.89, supplemental material, Table 3). The other comparisons between prehospital stroke scales can be found in the supplemental material, Table 3. When using the original cut points for the distinction between negativity and positivity of the scores, RACE had the highest sensitivity (0.67, 95% CI: 0.58-0.75) with a high specificity (0.87, 95% CI: 0.85-0.89, supplemental material, Table 4). CG-FAST had the highest specificity (0.89. 95% CI: 0.87-0.91) with the lowest sensitivity (0.50, 95% CI: 0.41-0.59). PPV ranged from 0.30 (95% CI: 0.25-0.35, C-STAT) to 0.40 (95% CI: 0.35-0.45, RACE) and NPV ranged from 0.93 (95% CI: 0.92-0.94, CG-FAST, C-STAT) to 0.95 (95% CI: 0.93-0.96, LAMS).

Figure 2. Receiver under the Operating Characteristics Curves for prehospital stroke scales and the physician-assessed NIHSS.



Sensitivity analyses demonstrated no clinically relevant changes when basilar occlusions were added to the aLVO group. The sensitivity analysis based on the local-assessed aLVO status showed a higher sensitivity (0.02 - 0.08 increase) with a marginal change in specificity. The sensitivity analysis in which A1, A2 and M2 occlusions were excluded from the outcome definition showed an overall better performance with a higher sensitivity (0.11 - 0.20 increase) without a relevant change in specificity. The sensitivity analysis with hemorrhage patients added to the outcome definition showed a lower sensitivity (0.01 - 0.08 decrease) with a small increase in specificity (0.02 - 0.04 increase).

The exploratory analysis regarding arm drift demonstrated that the AUCs for FAST PLUS and CPSS remained unchanged. AUCs for LAMS, PASS and G-FAST increased minimally with 0.01. When using the original cut points, PASS demonstrated an increase of 0.02 in sensitivity with a decrease of 0.02 in specificity. G-FAST and CPSS showed an increase in sensitivity of 0.06, with a small decrease in specificity (0.02 decrease for G-FAST and 0.01 decrease for CPSS).

Discussion

We performed an in-field validation study of eight prehospital stroke scales to detect aLVO in a relatively unselected population of suspected stroke patients. Baseline neuroimaging was centrally assessed by experienced neuroradiologists, resulting in a validation against the true occlusion status. In general, the performance of prehospital stroke scales in the field is acceptable to good. RACE, G-FAST and CG-FAST have the highest AUCs and approach the physician-assessed NIHSS in the emergency department.

RACE, G-FAST and CG-FAST may have performed slightly better because these scores combine both cortical symptoms (gaze palsy, neglect, not obeying commands) which are quite specific for aLVO patients, and items of the FAST test, which are highly sensitive to detect aLVO. PASS and C-STAT include gaze palsy as well, but these scales have a shorter range with fewer items. Thereby, a change of one point in PASS and C-STAT results in a larger change in sensitivity or specificity, and a smaller AUC compared to scales with a wider range and more items.

In clinical practice, prehospital stroke scales will be used as positive or negative, defined by a certain threshold. We found that sensitivity at the suggested cut points is lower for most scales, compared to other studies.[9-15, 20-22, 30] An explanation of the overall lower sensitivity is that we aimed to detect A1, A2 and M2 occlusions next to intracranial ICA and M1 occlusions, while some studies aimed to detect only basilar, ICA and M1 occlusions.[10, 15] Several aLVOs found in our cohort were initially not reported by the local radiologist, this concerned mostly M2 occlusions. M2 occlusions may be missed easily, so the proportion of M2 occlusions might be systematically underestimated in other suspected stroke cohorts. Consequently, since M2 occlusions are less likely to be detected by prehospital stroke scales, the large proportion of M2 occlusions in our cohort resulted in the lower sensitivity. This was confirmed by the sensitivity analysis using the local-assessed aLVO status, which showed higher sensitivity for all scores.

Specificity of the scales is high in our study, compared to other studies.[9-15, 20-22, 30] This might be explained by the relatively low proportion of intracranial hemorrhage patients in our cohort. Other cohorts with higher proportions of intracranial hemorrhage reported lower specificity[9, 11], probably because patients with intracranial hemorrhage have the highest chance to be assessed as false-positive. The hemorrhagic/ischemic stroke ratio in the Netherlands' national stroke registry is comparable with our study, so our cohort seems representative for the Dutch population.

Prospective validation studies are scarce and were mainly performed in small and selected populations.[9-15, 24] Some studies only included ischemic stroke patients and excluded patients without neurovascular imaging.[12-14, 20-22, 24,

[30] RACE is the only scale that has been extensively validated in the field.[9-11, 15] The substantial variability in the design of previous validation studies makes a direct comparison of its results with our findings difficult.[15, 20-22] Two large retrospective studies used similar outcome measures and inclusion criteria. These studies included suspected stroke patients in the ambulance and reported similar sensitivity and specificity for the PASS, G-FAST, C-STAT and RACE.[27, 31]

Our study has some limitations. We have no data about non-included patients and some selection bias might have occurred. For example, we might have missed unstable patients with severe neurologic deficit, or patients with minor deficit because paramedics did not suspect these patients of having an LVO. However, our study population consists of patients that prompted paramedics to assess prehospital stroke scales and is probably a reflection of patients that would be subjected to prehospital triage in the future. In the prehospital assessment, arm drift was not separately assessed. In an exploratory analysis, the overall performance of the scales was not relevantly affected by the merge. Only for G-FAST, PASS and CPSS, sensitivity might have been underestimated in our study. Even though our national guideline advises CTA in every patient with a clinical diagnosis of ischemic stroke within six hours after LKW, in part of the ischemic stroke patients CTA was not performed. Because ischemic stroke patients without CTA had low NIHSS scores, and the likelihood of aLVO in ischemic stroke patients with a low NIHSS is small, we assume the impact on our results is limited. Another limitation might be the relatively high number of prehospital items to be assessed. However, because all participating paramedics received thorough training prior to the study and the mobile application and pocket cards served as guiding tools, we do not expect this to have affected the quality of the assessment. We were not able to validate other published prehospital stroke scales, such as the Field Assessment Stroke Triage for Emergency Destination scale[32] or the Madrid-Direct Referral to Endovascular Center (M-DIRECT) scale[16], because these scales use other items than we included in our prehospital assessments. We do not expect the performance to be much better than the scales validated in our study, because the scales we validated already approached the performance of the physician-assessed NIHSS. Nevertheless, further prehospital validation of scales that hold different items is warranted. In addition to clinical scales, advanced technical tools might be more reliable to detect LVO. These tools, such as transcranial doppler-based devices, volume impedance phase shift spectroscopy or serum biomarkers are currently under development.[33]

Our study has direct implications for clinical practice. Our previous modelling study showed that in most regions a prehospital stroke scale with a PPV threshold of 0.40 would justify bypassing an IVT-capable hospital to directly drive to an intervention center.[34] Our finding that the field-assessed RACE score ≥5 corresponds to a ≥40% risk of aLVO (PPV=0.40), supports the implementation

of RACE or one of the other prehospital stroke scales with similar thresholds in clinical practice in most regions. However, in rural areas with longer driving times to the intervention center, higher PPV thresholds should be considered.

Further research on the effects of the implementation of prehospital stroke scales in triage of suspected stroke patients is needed. In Catalonia, Spain, a randomized trial investigating the effect of direct transfer to an intervention center based on the RACE score is ongoing.[35] Although this trial will provide important insights in the performance of RACE in the Catalonia area, it will be difficult to generalize the findings to other regions with different characteristics, such as the distribution of suspected stroke patients, driving times and workflow times. To optimize outcomes of ischemic stroke patients, model-based approaches should be used to explore the optimal transportation strategy for each specific region.[34, 36-38] In our region in the Southwest of the Netherlands, we are currently preparing the implementation of a prehospital triage strategy which incorporates the risk of aLVO estimated with RACE. We will evaluate its real-world effects by comparing numbers of treated patients and the relevant workflow times in a cohort of patients before and after the implementation.

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Table 1. Prehospital stroke scales and their corresponding items.

	Scored in PRESTO	RACE	G-FAST	CG-FAST	LAMS	CPSS	PASS	C-STAT	FAST-PLUS
Answering questions (age and current month)									
0 – answers correctly	0			0			0	0	
1 – incorrect answer to one question	1			1			1		
2– incorrect answer to at least one question	2							1^	
Following commands ('close your eyes', 'make a fist')									
0 – performs both tasks	0	0*						0	
1 - performs one task	1	1*						1^	
2- performs neither task	2	2*							
Eye deviation									
0 - normal	0	0	0	0			0	0	
1 – partial gaze palsy	1	1	1	1			1	2	
2 – forced deviation									
Facial palsy									
0 – normal	0	0	0	0	0	0			0
1 – minor paralysis	1	1	1	1		1			1
2 – partial paralysis	2	2			1				
3 – complete paralysis									

Table 1. *Continued.*

	Scored in PRESTO	RACE	G-FAST	CG-FAST	LAMS	CPSS	PASS	C-STAT	FAST-PLUS
Arm									
0 – no drift	0	0	0	0	0	0	0	0	0	0#
1 – drift			1		1	1	1		1	
2 – some effort against gravity	1	1		1	2			1		1#
3 – no effort against gravity 4 – no movement	2	2								
Grip strength									
0 – normal	0				0				
1 – weak grip	1				1				
2 – no grip	2				2				
Leg									
0 – no drift 1 – drift	0	0							0#
2 – some effort against gravity	1	1							
3 – no effort against gravity 4 – no movement	2	2							1#
Speech changes									
0 – absent	0		0	0		0			0

Table 1. *Continued.*

	Scored in PRESTO	RACE	G-FAST	CG-FAST	LAMS	CPSS	PASS	C-STAT	FAST-PLUS
1 – mild to moderate	1		1	1		1			1
2 – severe									
3 - mute									
Neglect									
0 – recognizes his/her arm and impairment	0‡	0‡							
1 – does not recognize his/her arm or the impairment	1‡	1‡							
2 – does not recognize his/her arm nor the impairment	2‡	2‡							

* only scored if right hemiparesis
‡ only scored if left hemiparesis
^ 1 point if at least one of the questions is answered incorrectly and at least one command performed incorrectly
# only scored if Face-Arm-Speech-Time test is positive, together with a severe paresis in an arm, leg or both, FAST PLUS[13] is considered positive.
RACE[15]= Rapid Arterial oCclusion Evaluation. G-FAST[20]= Gaze-Face-Arm-Speech-Time. CG-FAST[22]= Conveniently-Grasped Field Assessment Stroke Triage. LAMS[18]= Los Angeles Motor Scale. CPSS[23, 24]= Cincinnati Prehospital Stroke Scale. PASS[21] = Prehospital Acute Stroke Severity. C-STAT[19]= Cincinnati Stroke Triage Assessment Tool.

Table 2. Reasons aLVO patients were not treated with EVT.

	Untreated aLVO patients (n=31)
Reason not treated with EVT	
LVO missed by local observer	21 (68%)
Patient recovered/minor deficit	3 (10%)
Outside treatment window and ineligible for MR CLEAN LATE or randomized for no EVT	2 (7%)
Old or asymptomatic occlusion	2 (7%)
Decision relatives	1 (3%)
Occluded vessel toward ischemic territory	1 (3%)
Occlusion location considered not treatable	3 (10%)

EVT = Endovascular Thrombectomy.

Table 3. Performance of the prehospital stroke scales expressed as AUCs with 95% confidence intervals, and p-values of the comparison of AUCs based on the DeLong test.

	AUC (95% CI)	NIHSS	RACE	G-FAST	CG-FAST	LAMS	CPSS	PASS	C-STAT	FAST PLUS
NIHSS	0.86 (0.83-0.89)	x								
RACE	0.83 (0.79-0.86)	0.05	x							
G-FAST	0.80 (0.76-0.84)	0.003	0.13	x						
CG-FAST	0.80 (0.76-0.84)	0.001	0.09	0.53	x					
LAMS	0.79 (0.75-0.83)	0.002	0.01	0.53	0.72	x				
CPSS	0.79 (0.75-0.83)	<0.0001	0.03	0.03	0.27	0.88	x			
PASS	0.76 (0.72-0.80)	<0.0001	<0.0001	0.007	0.004	0.05	0.12	x		
C-STAT	0.75 (0.71-0.80)	<0.0001	<0.0001	0.002	0.005	0.01	0.07	0.50	x	
FAST PLUS	0.72 (0.67-0.76)	<0.0001	<0.0001	0.0001	0.0004	0.0001	0.003	0.06	0.09	x

CI = confidence interval. NIHSS = National Institute of Health Stroke Scale. RACE= Rapid Arterial oCclusion Evaluation. G-FAST= Gaze-Face-Arm-Speech-Time. CG-FAST = Conveniently-Grasped Field Assessment Stroke Triage. LAMS=Los Angeles Motor Scale. CPSS= Cincinnati Prehospital Stroke Scale. PASS= Prehospital Acute Stroke Severity. C-STAT= Cincinnati Stroke Triage Assessment Tool.

Table 4. Performance of the prehospital stroke scales at each possible cut point.

RACE	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.97 (0.93-0.99)	0.34 (0.31-0.37)	0.16 (0.15-0.17)	0.99 (0.97-1.00)
≥2	0.88 (0.82-0.93)	0.54 (0.51-0.58)	0.20 (0.19-0.22)	0.97 (0.96-0.98)
≥3	0.78 (0.71-0.86)	0.73 (0.70-0.76)	0.27 (0.25-0.3)	0.96 (0.95-0.97)
≥4	0.71 (0.63-0.79)	0.81 (0.78-0.83)	0.32 (0.29-0.36)	0.95 (0.94-0.97)
≥5*	**0.67 (0.58-0.75)**	**0.87 (0.85-0.89)**	**0.40 (0.35-0.45)**	**0.95 (0.94-0.96)**
≥6	0.59 (0.51-0.68	0.90 (0.88-0.92)	0.44 (0.38-0.50)	0.94 (0.93-0.96)
≥7	0.40 (0.62-0.49)	0.93 (0.92-0.95)	0.44 (0.37-0.53)	0.92 (0.91-0.93)
≥8	0.22 (0.15-0.29)	0.96 (0.95-0.98)	0.44 (0.33-0.56)	0.90 (0.90-0.91)
9	0.08 (0.03-0.13)	0.98 (0.98-0.99)	0.38 (0.19-0.58)	0.89 (0.89-0.90)
G-FAST				
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.98 (0.94-1.00)	0.24 (0.21-0.26)	0.14 (0.14-0.15)	0.99 (0.97-1.00)
≥2	0.87 (0.80-0.93)	0.58 (0.55-0.61)	0.21 (0.20-0.23)	0.97 (0.96-0.98)
≥3*	**0.67 (0.58-0.74)**	**0.82 (0.79-0.84)**	**0.32 (0.28-0.36)**	**0.95 (0.94-0.96)**
4	0.28 (0.21-0.37)	0.95 (0.94-0.97)	0.44 (0.34-0.55)	0.91 (0.90-0.92)
CG-FAST				
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.98 (0.94-1.00)	0.22 (0.20-0.25)	0.14 (0.13-0.15)	0.99 (0.97-1.00)
≥2	0.89 (0.83-0.94)	0.50 (0.47-0.54)	0.19 (0.18-0.20)	0.97 (0.96-0.99)
≥3	0.73 (0.66-0.81)	0.76 (0.73-0.79)	0.29 (0.25-0.32)	0.96 (0.94-0.97)
≥4*	**0.50 (0.41-0.59)**	**0.89 (0.87-0.91)**	**0.38 (0.32-0.44)**	**0.93 (0.92-0.94)**
5	0.15 (0.09-0.22)	0.97 (0.96-0.98)	0.39 (0.25-0.54)	0.90 (0.89-0.90)
LAMS				
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.89 (0.83-0.94)	0.50 (0.46-0.53)	0.19 (0.17-0.20)	0.97 (0.96-0.99)
≥2	0.84 (0.78-0.90)	0.60 (0.57-0.63)	0.22 (0.20-0.23)	0.97 (0.95-0.98)
≥3	0.79 (0.72-0.86)	0.65 (0.62-0.68)	0.23 (0.21-0.25)	0.96 (0.95-0.97)
≥4*	**0.63 (0.55-0.72)**	**0.84 (0.82-0.87)**	**0.35 (0.30-0.39)**	**0.95 (0.93-0.96)**
5	0.28 (0.21-0.37)	0.94 (0.93-0.96)	0.40 (0.30-0.49)	0.91 (0.90-0.92)
CPSS				
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.98 (0.94-1.00)	0.24 (0.22-0.27)	0.14 (0.14-0.15)	0.99 (0.97-1.00)
≥2	0.86 (0.79-0.93)	0.61 (0.58-0.64)	0.22 (0.20-0.24)	0.97 (0.96-0.98)

Table 4. *Continued.*

RACE	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
≥3*	**0.57 (0.48-0.66)**	**0.85 (0.83-0.87)**	**0.33 (0.28-0.38)**	**0.94 (0.93-0.95)**
PASS				
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.88 (0.82-0.93)	0.48 (0.45-0.51)	0.18 (0.17-0.19)	0.97 (0.95-0.98)
≥2*	**0.59 (0.51-0.68)**	**0.83 (0.81-0.85)**	**0.31 (0.27-0.35)**	**0.94 (0.93-0.95)**
3	0.20 (0.13-0.27)	0.95 (0.94-0.97)	0.35 (0.25-0.45)	0.90 (0.89-0.91)
C-STAT				
≥0	1.00 (1.00-1.00)	0 (0-0)	0.12 (0.12-0.12)	-
≥1	0.85 (0.78-0.91)	0.55 (0.51-0.58)	0.20 (0.18-0.21)	0.97 (0.95-0.98)
≥2*	**0.50 (0.42-0.59)**	**0.85 (0.82-0.87)**	**0.30 (0.25-0.35)**	**0.93 (0.92-0.94)**
≥3	0.39 (0.30-0.48)	0.91 (0.89-0.93)	0.36 (0.30-0.44)	0.92 (0.91-0.93)
4	0.14 (0.08-0.21)	0.96 (0.95-0.97)	0.32 (0.20-0.44)	0.90 (0.89-0.90)
FAST PLUS				
positive	**0.60 (0.52-0.68)**	**0.83 (0.81-0.86)**	**0.32 (0.28-0.37)**	**0.94 (0.93-0.95)**

* Original cut point. PPV = positive predictive value. NPV = negative predictive value. RACE = Rapid Arterial oCclusion Evaluation. G-FAST= Gaze-Face-Arm-Speech-Time. CG-FAST = Conveniently-Grasped Field Assessment Stroke Triage. LAMS = Los Angeles Motor Scale. CPSS = Cincinnati Prehospital Stroke Scale. PASS= Prehospital Acute Stroke Severity. C-STAT = Cincinatti Stroke Triage Assessment Tool.

Chapter 4.3

On the use of prehospital stroke scales

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Lancet Neurology, 2021

In Response:

We thank Fabio Bandini and colleagues for their interest in our recent Article reporting results of the PRESTO study.[1] They highlight that some patients with ischemic stroke did not receive CT angiography to formally exclude large-vessel occlusion in the anterior circulation (aLVO). As shown in our results, these patients had a very low National Institutes of Health Stroke Scale (NIHSS) and are therefore unlikely to have had aLVO, which limits any potential overestimation of the reported sensitivity. We also emphasize that the proportion of intracerebral hemorrhages among all stroke patients in our study (12%) is similar to the proportion reported in the Dutch Acute Stroke Registry (11%).[2] This finding supports that our study provides reliable estimates of the in-field performance of prehospital stroke scales in a population of patients with suspected stroke.

Bandini and colleagues further state that the positive predictive value (PPV) of 0.40 for a Rapid Arterial oCclusion Evaluation (RACE) score of 5 or greater might not be clinically significant for prehospital triage. They express concern about patients who have a RACE score equal to or higher than 5 but do not have aLVO, who might be harmed by the delay caused by direct transportation to an intervention center. We fully agree with these concerns and reiterate that the trade-off between potential harm and benefit should be made at the patient-level, as demonstrated in our previously developed personalized decision model.[3] This model estimates the probability of a good outcome for the drip-and-ship versus mothership strategy based on the onset time, driving times, likelihood of aLVO, and hospital-specific workflow times. With this model, we showed that a PPV of 0.40 can justify direct transport to an intervention center in certain regions, as the treatment benefit for aLVO patients outweighs the harm caused by delaying intravenous thrombolysis in patients with non-aLVO ischemic stroke.[3] Because the optimal pathway is context-specific, health policy makers should estimate the impact and feasibility of prehospital triage strategies in their region before implementation, preferably using modelling-based approaches. We are currently preparing our prehospital personalized decision model for implementation in a mobile application, which will be evaluated in PRESTO-II. This application incorporates the RACE scale (range 0-9), time since symptom onset, real-time driving times and hospital-specific workflow times.

Before additional interventions such as mobile stroke units or advanced large-vessel occlusion detection tools are sufficiently substantiated, validated prehospital stroke scales are our best option to improve personalized prehospital triage of ischemic stroke patients.

References:

1. 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
2. Katz BS, Adeoye O, Sucharew H, Broderick JP, McMullan J, Khatri P, et al. Estimated impact of emergency medical service triage of stroke patients on comprehensive stroke centers: An urban population-based study. *Stroke*. 2017;48:2164-2170
3. Venema E, Lingsma HF, Chalos V, Mulder M, Lahr MMH, van der Lugt A, et al. Personalized prehospital triage in acute ischemic stroke. *Stroke*. 2019;50:313-320

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Chapter 5

Prehospital stroke triage: a modeling study on the impact of triage tools in different regions

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Abstract

Background and purpose
Direct transportation to a thrombectomy-capable intervention center is beneficial for patients with ischemic stroke due to large vessel occlusion (LVO), but can delay intravenous thrombolytics (IVT). The aim of this modeling study was to estimate the impact of prehospital triage strategies on treatment delays and overtriage in different regions.

Methods
We used data from two prospective cohort studies in the Netherlands: the Leiden Prehospital Stroke Study and the PRESTO study. We included stroke code patients within six hours from symptom onset. We modeled outcomes of RACE triage and triage with a personalized decision tool, using drip-and-ship as reference. Main outcomes were overtriage (stroke code patients incorrectly triaged to an intervention center), reduced delay to endovascular thrombectomy (EVT), and delay to IVT.

Results
We included 1798 stroke code patients from four ambulance regions. Per region, overtriage ranged from 1-13% (RACE triage) and 3-15% (personalized tool). Reduction of delay to EVT varied by region between 24±5 minutes (n=6) to 78±3 (n=2), while IVT delay increased with 5 (n=5) to 15 minutes (n=21) for non-LVO patients. The personalized tool reduced delay to EVT for more patients (25±4 minutes (n=8) to 49±13 (n=5)), while delaying IVT with 3-14 minutes (8-24 patients). In region C, most EVT patients were treated faster (reduction of delay to EVT 31±6 minutes (n=35), with RACE triage and the personalized tool.

Conclusion
In this modeling study, we showed that prehospital triage reduced time to EVT without disproportionate IVT delay, compared to a drip-and-ship strategy. The impact of triage strategies and the associated overtriage varied between regions. Implementation of prehospital triage should therefore be considered on a regional level.

Introduction

Rapid reperfusion treatment is essential to optimize functional outcome of ischemic stroke patients.[1, 2] Treatment with intravenous thrombolytics (IVT) is available at all primary stroke centers (PSCs), while endovascular thrombectomy (EVT) is restricted to specialized intervention centers. Only patients with ischemic stroke due to large vessel occlusion (LVO), approximately 24% to 46% of all ischemic strokes, are eligible for EVT.[3] Several strategies can be used to allocate patients with suspected stroke in the ambulance (stroke code patients). In the drip-and-ship strategy, all stroke code patients are allocated to the nearest stroke center to start IVT as soon as possible, followed by transfer to an intervention center in case of eligibility for EVT. However, these interhospital transfers often lead to EVT delay and are associated with worse outcome.[4, 5] In the mothership strategy, all stroke code patients are allocated to the nearest intervention center, consequently delaying IVT for patients who bypass a closer PSC. Furthermore, several prehospital stroke scales have been suggested to select patients with a higher likelihood of LVO stroke for direct allocation to an intervention center.[6, 7]

The key objective of an allocation strategy is to optimize the overall outcome of stroke patients, taking into account that improved outcomes by reduced time to EVT should outweigh the harm caused by delayed IVT for non-LVO stroke patients. Previous studies demonstrated that the effect of allocation strategies depends not only on the likelihood of LVO stroke, but also on delays related to driving times and in-hospital workflow times.[8-12] Consequently, the optimal allocation strategy likely differs between regions.[13]

Our aim was to estimate the impact of prehospital triage strategies for LVO on treatment delays and overtriage in different regions, using two large prehospital stroke code cohorts.

Methods

Study design

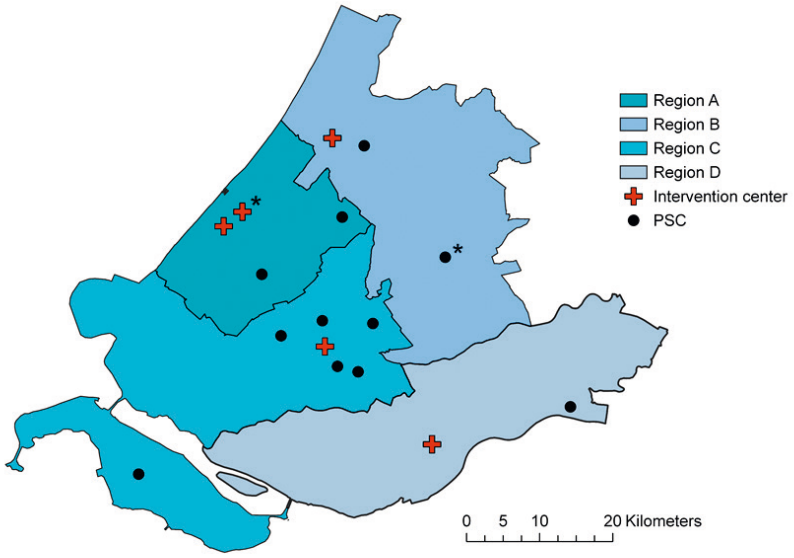
We performed a modeling study with data from the Leiden Prehospital Stroke Study (LPSS) and the Prehospital triage of patients with suspected stroke (PRESTO) study.[14, 15] Both are multi-center, observational prospective cohort studies that included stroke code patients transported by ambulance between July 2018 and October 2019. The Institutional Review Boards of the Leiden University Medical Center and Erasmus MC University Medical Center Rotterdam reviewed the study protocols and confirmed that the Dutch Medical Research Involving Human Subjects Act is not applicable. The need for informed consent was waived because the studies met the exceptions of informed

consent regulations. Detailed information regarding the LPSS and PRESTO study is described elsewhere.[14-16]

Study region and population

Patients from four regions in the Netherlands were included by emergency medical services (EMS) paramedics (Figure 1, Table 1). Emergency medical services in the Netherlands are organized within 25 safety regions, of which four are included in this study. Dispatch of ambulances is coordinated from a control room. Region A (Haaglanden) and B (Hollands-Midden) have their own control room. Region C (Rotterdam-Rijnmond) and D (Zuid-Holland Zuid) have a shared control room. Dispatch and routing is not restricted to the borders of the safety regions and control rooms are in close contact with each other. The destination hospital of patients is decided by the handling EMS paramedic based on standardized ambulance allocation protocols only requiring online medical control in very specific cases. The ambulance allocation protocol always allocates the stroke code patient to the nearest hospital.

Figure 1. Geography of the study region.



PSC: Primary Stroke Center. All PSCs refer for EVT to an intervention center within their region, except for the marked PSC (*), this PSC refers to the marked intervention center (*). Ambulances were allowed to drive outside their region to adhere the allocation strategy.

Table 1. Regional characteristics.

Region	A (n=373)	B (n=386)	C (n=543)	D (n=496)
Name	Haaglanden	Hollands-Midden	Rotterdam-Rijnmond	Zuid-Holland Zuid
Population size	1,000,000	800,000	1,200,000	480,000
Total area (km²)	404	831	863	720
Population density (inhabitants/km²)	2400	950	1540	670

The LPSS was performed in region A with two PSCs and two intervention centers, and region B with two PSCs and one intervention center. The PRESTO study was performed in region C with six PSCs and one intervention center, and region D with one PSC and one intervention center. Inclusion criteria for the LPSS were: stroke code patients (age ≥18 years) with a positive Face-Arm-Speech-Time (FAST) test or other neurological deficits suspected of stroke as considered by EMS paramedics. Inclusion criteria for PRESTO were: stroke code patients (age ≥18 years) with a positive FAST test and blood glucose >2.5 mmol/L. During the inclusion period, all regions applied a drip-and-ship strategy that was not restricted by region borders (i.e. if the closest center was in a different region, then the patient was allocated to that center). EMS paramedics assessed items from different prehospital stroke scales before arrival at the emergency department, including the Rapid Arterial oCclusion Evaluation (RACE) scale.[17] Patients who presented more than six hours after stroke onset or the time that they were last seen well and patients without complete RACE scores were excluded from the current analysis. LVO was defined as an occlusion of the intracranial part of the internal carotid artery, M1 or M2 segment of the middle cerebral artery or A1 or A2 segment of the anterior cerebral artery, as assessed on CT angiography by the local stroke team.

Allocation strategies

We modeled the outcome of individual patients according to different allocation strategies:

- *Drip-and-ship*: all stroke code patients are transported to the nearest stroke center. EVT-eligible patients who first presented in a PSC are subsequently transferred to the nearest intervention center;
- *RACE triage*[17]: stroke code patients with a positive RACE scale (≥5 points) are transported to the nearest intervention center; others to the nearest stroke center
- *Triage by a personalized decision tool*[8]: for each stroke code patient a personalized decision tool is used to optimize allocation. We used a

previously developed decision tree model that estimates and advises the destination center with the highest probability of a good outcome, defined as a modified Rankin Scale (mRS) score ≤2 at three months.[8, 18] An existing script of this model was used to estimate individual patients outcomes of this allocation strategy with R statistical software. This decision tree model used time-dependent effects of IVT and EVT extrapolated from the results of large clinical trials.[1, 19] Input parameters are center-specific workflow times, driving times and the likelihood of an LVO or non-LVO stroke as estimated by the RACE scale score (supplemental material Table 1). For the current analysis, the probability of receiving IVT for ischemic stroke patients who presented within 4.5 hours was adjusted to 0.61 and the probability of receiving EVT for LVO stroke patients who presented within 6 hours to 0.81, calculated based on the pooled data of both studies. All other treatment assumptions and treatment effect estimates remained similar to the original model (supplemental material Table 1).

The drip-and-ship strategy served as a reference. We used ESRI ArcGIS Pro (version 2.0.0) to estimate driving times with geospatial analysis for the fastest possible route, without regarding time or week of day. For each allocation strategy, the expected onset-to-treatment times were calculated from the onset to departure time of the ambulance on site, with the addition of the estimated driving time and center-specific workflow times (supplemental material Table 1).

Outcome measures

The main outcomes were reported separately for each region, these include:

- Stroke code patients directly transported to an intervention center
- Patients incorrectly triaged to an intervention center (overtriage) and the number-needed-to-bypass (NNB), defined as the number of non-LVO patients (including patients with intracranial hemorrhage and non-stroke patients) who bypassed a PSC for each correctly triaged LVO stroke patient. Non-LVO patients that were transported to an intervention center because it was the closest hospital, were considered correctly triaged.

For LVO patients:

- Correctly triaged patients (i.e. LVO patients directly transported to an intervention center).
- Time to EVT (minutes, mean±SD) and treatment number.
- Reduction of delay to EVT due to correct triage.

For non-LVO ischemic stroke patients:

- Incorrectly triaged patients (i.e. non-LVO ischemic stroke patients bypassing a PSC. Also, IV fibrinolytic contraindications were not assessed by the EMS paramedics and these patients were handled as non-LVO ischemic stroke patients).
- Time to IVT (minutes, mean±SD) and treatment number
- Delay to IVT due to incorrect triage

For all ischemic stroke patients:

- Overall probability of good functional outcome (modified Rankin Scale (mRS) 0-2), calculated based on treatment eligibility and treatment times per strategy.

Secondary outcomes included the total number of patients receiving IVT and EVT and the number of interhospital transfers. Treatment eligibility was based on a time window of <4.5 hours for IVT and <6 hours for EVT. Each LVO patient who could be treated within six hours, was considered to be treated with EVT.

Additionally, we performed a post-hoc sensitivity analysis in which we adjusted the threshold of the personalized tool to bypass the PSC (estimated benefit of direct transportation to an intervention center >0.1% or >0.2%).

This study was performed according to the STROBE guidelines.

Results

Patient and regional characteristics

Of 3321 recruited stroke code patients, 1798 were included in the current analysis (Figure 2). We excluded 1523 patients because of presentation more than 6 hours after last seen well (n=995), age less than 18 years (n=1), or an incomplete RACE score (n=527). Regions A and B had a higher percentage of patients with a stroke mimic and (consequently) a lower percentage of stroke code patients treated with IVT compared with C and D (Table 2). The percentage of patients with LVO stroke from the total number of stroke codes ranged from 7% to 11% between the regions.

Figure 2. Inclusion flowchart.

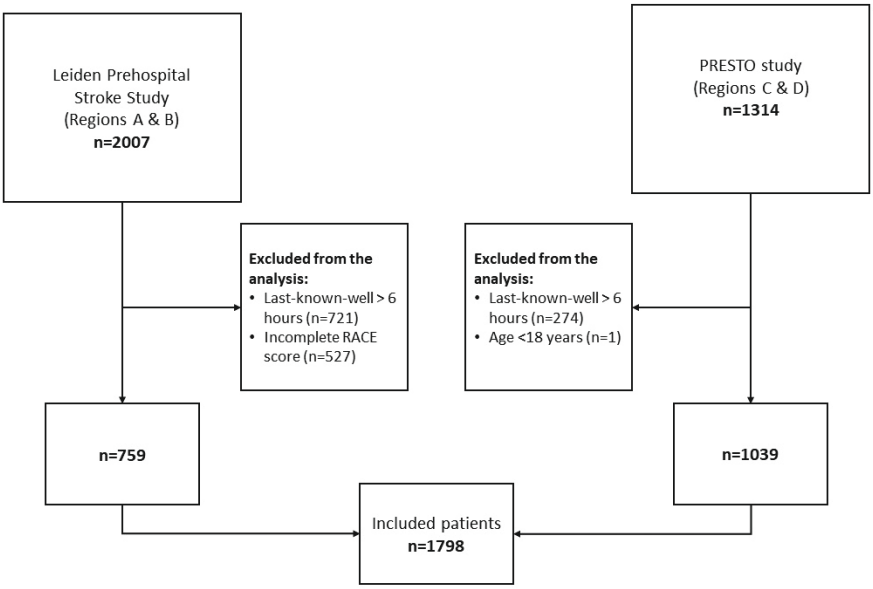


Table 2. Patient characteristics stratified by region.

Region	A (n=373)	B (n=386)	C (n=543)	D (n=496)	Total cohort (n=1798)
Age, years	70 (58-79)	72 (59-80)	71 (60-80)	73 (63-82)	72 (60-80)
Sex, (women)	180 (48%)	175 (45%)	256 (47%)	223 (45%)	834 (46%)
Clinical assessment					
Prehospital RACE score	1 (0-2)	1 (0-2)	2 (0-4)	1 (0-3)	1 (0-3)
Prehospital RACE ≥ 5	33 (9%)	42 (11%)	120 (22%)	81 (16%)	276 (15%)
Admission NIHSS score	2 (1-4)	1 (0-4)	2 (1-7)	2 (0-6)	2 (0-5)
Workflow times (minutes)					
Onset-to-alarm	51 (17-137)	53 (21-132)	49 (15-121)	55 (19-146)	52 (18-134)
Onset-to-door	82 (57-138)	86 (50-153)	80 (52-151)	90 (55-176)	85 (54-155)
Final diagnosis					
Ischemic stroke	144 (39%)	167 (43%)	267 (49%)	255 (51%)	833 (46%)
LVO stroke	29 (8%)	27 (7%)	62 (11%)	39 (8%)	157 (9%)
Non-LVO stroke	115 (31%)	140 (36%)	205 (38%)	216 (44%)	676 (38%)
Intracranial hemorrhage	21 (6%)	25 (7%)	37 (7%)	35 (7%)	118 (7%)
TIA	70 (19%)	76 (20%)	95 (18%)	96 (19%)	337 (19%)
Stroke mimic	138 (37%)	118 (31%)	144 (27%)	110 (22%)	510 (28%)

Table 2. *Continued.*

Region	A (n=373)	B (n=386)	C (n=543)	D (n=496)	Total cohort (n=1798)
Treatment received					
Intravenous thrombolytics	66 (18%)	102 (26%)	165 (30%)	160 (32%)	493 (27%)
Endovascular thrombectomy	13 (3%)	18 (5%)	54 (10%)	37 (8%)	122 (7%)

Data are median (IQR) or n (%), unless otherwise indicated. RACE = Rapid Arterial oCclusion Evaluation. NIHSS = National Institutes of Health Stroke Scale. LVO was defined as an occlusion of the intracranial part of the internal carotid artery (ICA), the middle cerebral artery segment M1 or M2 or the anterior cerebral artery segment A1 or A2, assessed on CTA. TIA = Transient Ischemic Attack. Number of missings: Leiden Prehospital Stroke Study data: NIHSS n=182, onset-to-door and onset-to-alert n=12, PRESTO data: NIHSS n=6, onset-to-alert n=112, onset-to-door n=32.

Outcomes

As can be seen in Table 3, with the triage strategies, the number of strokes code patients primarily allocated to an intervention center increased, most with the personalized tool: (18% in region A to 257% increase in region C). With RACE triage this was somewhat smaller in all regions (4% in region A to 241% in region C). The NNB was highest with the personalized tool (2.3 in region C to 53.0 in region B), and more modest with RACE triage (1.8 in region C to 10.5 in region B).

The number of correctly transported LVO patients increased with prehospital triage strategies. This was most pronounced in region C (15% to 79% with RACE triage and 73% with the personalized tool). Mean time to EVT decreased in all regions, except for region A. This was caused by one additional patient that did not fall out the six hour time window due to correct triage and could therefore be treated with EVT. RACE triage reduced delay to EVT of correctly triaged patients between 24±5 minutes for six patients (15%) in region D (mean time to EVT 188±76 minutes) and 78±3 minutes for two patients (7%) in region A (mean time to EVT 166±72 minutes). Delay to EVT was reduced for more patients when using the personalized tool: 25±4 for eight patients (21%) in region D (mean time 187±77 minutes) and 41±12 for four patients (14%) in region A (mean time 170±76 minutes).

With RACE triage, incorrectly transported non-LVO ischemic stroke ranged from 3% (region A) to 17% (region C). This was somewhat higher across the regions with the personalized tool, from 11% (region B) to 23% (region A). The mean IVT delay due to incorrect triage was smallest with the personalized tool: from 3±3 minutes (for eight patients) in region A to 14±3 (for 24 patients) in region C. With RACE triage this was somewhat higher: 5±4 minutes (for five patients) in region A, to 15±3 minutes (for 21 patients) in region C. Overall, the probability of a good outcome for ischemic stroke patients improved minimally with prehospital triage in all regions compared to the drip-and-ship strategy ($p<0.001$).

Treatment percentages of IVT (for all ischemic strokes) ranged from 46 to 62% (supplemental material Table 2). The number of interhospital transfers decreased mostly in region C, from 48 in the drip-and-ship scenario to 13 with both prehospital triage strategies.

The sensitivity analysis showed that overtriage with the personalized decision tool can be reduced when the threshold to bypass a PSC is increased (supplemental material Table 3).

Table 3. Impact of allocation strategies per region.

Region A (n=373)	**Drip-and-ship**	**RACE triage**	**Personalized tool**
Directly transported to intervention center, % (n)	61% (226)	63% (235)	72% (267)
Overtriage to intervention center, % (n)	-	1% (4)	3% (11)
Number-needed-to-bypass (NNB)	-	2.0	7.4
LVO ischemic stroke patients (n=29			
Correctly transported to intervention center, % (n)	69% (20)	79% (23)	86% (25)
Time to EVT, mean±SD	167±67 (n=25)	166±72 (n=26)	170±76 (n=26)
Reduction of delay to EVT due to correct triage, mean±SD	-	78±3 (n=2)	41±12 (n=4)
Non-LVO ischemic stroke patients (n=115)			
Overtriage to intervention center, % (n)	0% (0)	3% (4)	23% (27)
Time to IVT, mean±SD	114±62 (n=50)	114±62 (n=50)	114±62 (n=50)
Delay to IVT due to incorrect triage, mean±SD*	-	5±4 (n=5)	3±3 (n=8)
All ischemic stroke patients (n=144)			
Overall probability of good outcome (mRS 0-2)	48.7%	48.8%	48.8%
Region B (n=386)	**Drip-and-ship**	**RACE triage**	**Personalized tool**
Directly transported to intervention center, % (n)	41% (158)	47% (181)	53% (205)
Overtriage to intervention center, % (n)	-	3% (10)	5% (18)
Number-needed-to-bypass (NNB)	-	10.5	53.0
LVO ischemic stroke patients (n=27)			
Correctly transported to intervention center, % (n)	74% (20)	81% (22)	78% (21)
Time to EVT, mean±SD	169±64 (n=27)	163±68 (n=27)	163±66 (n=27)
Reduction of delay to EVT due to correct triage, mean±SD	-	39±36 (n=4)	49±13 (n=5)
Non-LVO ischemic stroke patients (n=140)			
Overtriage to intervention center, % (n)	0% (0)	6% (16)	11% (29)
Time to IVT, mean±SD	101±46 (n=81)	103±46 (n=81)	103±46 (n=81)

Delay to IVT due to incorrect triage, mean±SD*	-	10±4 (n=9)	8±3 (n=16)
All ischemic strokes (n=167)			
Overall probability of good outcome (mRS 0-2)	48.7%	48.8%	48.8%
Region C (n=543)	**Drip-and-ship**	**RACE triage**	**Personalized tool**
Directly transported to intervention center, % (n)	8% (46)	29% (157)	30% (164)
Overtriage to intervention center, % (n)	-	13% (71)	15% (82)
Number-needed-to-bypass (NNB)	-	1.8	2.3
LVO ischemic stroke patients (n=62)			
Correctly transported to intervention center, % (n)	15% (9)	79% (49)	73% (45)
Time to EVT, mean±SD	179±61 (n=57)	163±66 (n=58)	163±66 (n=58)
Reduction of delay to EVT due to correct triage, mean±SD	-	31±6 (n=35)	31±6 (n=35)
Non-LVO ischemic stroke patients (n=205)			
Overtriage to intervention center, % (n)	0 (0%)	17% (34)	20% (40)
Time to IVT, mean±SD	114±60 (n=125)	116±59 (n=125)	116±59 (n=125)
Delay to IVT due to incorrect triage, mean±SD*	-	15±3 (n=21)	14±3 (n=24)
All ischemic strokes (n=267)			
Overall probability of good outcome (mRS 0-2)	48.4%	48.6%	48.6%
Region D (n=496)	**Drip-and-ship**	**RACE triage**	**Personalized tool**
Directly transported to intervention center, % (n)	68% (338)	74% (367)	85% (422)
Overtriage to intervention center, % (n)	-	5% (23)	15% (76)
Number-needed-to-bypass (NNB)	-	3.8	9.5
LVO ischemic stroke patients (n=39)			
Correctly transported to intervention center, % (n)	77% (30)	92% (36)	97% (38)
Time to EVT, mean±SD	191±76 (n=39)	188±76 (n=39)	187±77 (n=39)
Reduction of delay to EVT due to correct triage, mean±SD	-	24±5 (n=6)	25±4 (n=8)

Non-LVO ischemic stroke patients (n=216)			
Overtriage to intervention center, % (n)	0% (0)	6% (12)	18% (38)
Time to IVT, mean±SD	120±61 (n=130)	120±61 (n=129)**	120±61 (n=130)
Delay to IVT due to incorrect triage, mean±SD*	-	7±7 (n=6)	4±5 (n=17)
All ischemic stroke patients (n=255)			
Overall probability of good outcome (mRS 0-2)	48.6%	48.6%	48.6%
Total cohort (n=1798)	**Drip-and-ship**	**RACE triage**	**Personalized tool**
Directly transported to intervention center, % (n)	43% (768)	52% (940)	59% (1058)
Overtriage to intervention center, % (n)	-	6% (108)	10% (187)
Number-needed-to-bypass (NNB)	-	2.4	4.8
LVO ischemic stroke patients (n=157)			
Correctly transported to intervention center, % (n)	50% (79)	83% (130)	82% (129)
Time to EVT, mean±SD	178±66 (n=148)	170±70 (n=150)	170±71 (n=150)
Reduction of delay to EVT due to correct triage, mean±SD	-	33±8 (n=47)	33±7 (n=52)
Non-LVO ischemic stroke patients (n=676)			
Overtriage to intervention center, % (n)	0% (0)	10% (66)	20% (134)
Time to IVT, mean±SD	113±58 (n=386)	114±57 (n=385)**	114±57 (n=386)
Delay to IVT due to incorrect triage, mean±SD*	-	12±4 (n=41)	9±3 (n=65)
All ischemic stroke patients (n=833)			
Overall probability of good outcome (mRS 0-2)	48.4%	48.7%	48.7%

* Not all non-LVO ischemic stroke patients were treated with IVT due to contraindications, this explains the difference between the number of delayed IVT patients with the number of overtriaged patients.
** in this scenario, one patient arrived outside the treatment window for IVT due to incorrect triage.
Because results regarding treatment and treatment times in Table 3 were modelled based on predefined assumptions, results might show differences between the results from Table 2.

Discussion

In this modeling study, we used individual patient data to estimate the impact of allocation strategies in four different regions. We found that prehospital triage with the RACE scale or a personalized tool expedites EVT without a disproportionate delay to IVT, though this differed between regions. Importantly, RACE triage resulted in relatively modest overtriage rates and thereby limited effect on patient flows. The estimated differences in patient outcome between the allocation strategies were small, though we expect that these differences could become clinically relevant on a population level. Prehospital triage will always be a trade-off between expediting EVT and delaying IVT for those patients bypassing a closer PSC. In this respect it is important to realise that large meta analyses demonstrated that every 10 minutes of decrease in time to EVT results in an increase of 1% on the probability of good functional outcome, while 10 minutes of delay in IVT results in a decrease of 0.33% on the probability of good functional outcome.[1, 20] Furthermore, it is important that the impact of prehospital triage strategies differs per region.

This difference can partly be explained by differences in case mix of the stroke code populations. Regions A and B (LPSS) used broader inclusion criteria than regions C and D (PRESTO study), which probably resulted in fewer RACE-positive patients and consequently in a lower percentage of LVO strokes. Differences in geographical characteristics also play a role and can explain differences in outcome, for example the NNB. In region C, centers are located closely together in a densely populated area with six PSCs and only one intervention center. Therefore, prehospital triage strategies led to an increase in direct transportation of LVO patients to intervention centers while delay to IVT remained relatively small. However, this also resulted in a substantial increase of incorrectly triaged stroke code patients presented primarily in the intervention center. In regions A, B and D, the geographic position of the centers, triage with the personalized tool led to considerably more overtriage and a higher NNB compared to RACE triage because all patients with a (small) potential benefit of faster EVT were allocated to an intervention center. Direct allocation to an intervention center will be favored in these regions even when the likelihood of LVO is low, because the potential effect of EVT delay is large when the PSCs are relatively distant from the intervention center.

The RACECAT trial, situated in a nonurban region with much larger travel times between PSC and intervention center (average transfer time 45 minutes), randomized 1401 patients between mothership and drip-and-ship in patients with a positive RACE scale.[21] Their results indicate that RACE triage did not improve nor worsen clinical outcomes.[22, 23] However, these findings are not generalizable to other regions with different geographical characteristics and workflow times. Previous modeling studies demonstrated differences in optimal

allocation strategies based on geographic characteristics, workflow times and LVO likelihood. However, these studies were mostly conducted in simulated cohorts or geographies and often excluded non-LVO patients, thus lacking the important data to estimate overtriage.[9, 11, 24-27] In contrast, we used data from a prehospital stroke code cohort (also including non-stroke patients) with patient-specific and center-specific time metrics.

Limitations of our study include the use of some assumptions for model-based approaches. Travel times were modelled with a geographic system, but could have differed in real-life due to traffic congestion or speeding by the ambulance. Furthermore, different inclusion criteria of stroke code patients and EMS paramedic expertise with the use of RACE scale between the regions probably explain some differences that cannot merely be attributed to the allocation strategies or geographies. However, these differences also reflect clinical practice. Next, we could only include patients with complete RACE scales, which could have introduced some selection bias. However, in the LPSS population we found no differences in baseline characteristics, LVO status, final diagnosis or clinical outcome in patients with or without complete RACE (data not shown). Furthermore, because stroke code patients with symptom onset exceeding six hours were excluded extrapolating our results to this subgroup has to be done with caution. Lastly, our study was not powered to demonstrate differences in clinical outcome. However, based on our modeling it seems likely that the implementation of prehospital triage strategies on a larger scale can improve clinical outcomes of ischemic stroke patients.[13]

Implementation of RACE triage is straightforward, but it does not take into account other variable factors such as local driving times or workflow times. The personalized tool takes these factors into account and is adaptive to a specific region. For example, real-time driving times can be used and workflow times can be adjusted if in-hospital workflows are improved. Currently, this decision tool has been processed into the Stroke Triage app, which is planned to be implemented in region C and D soon. This application uses a route planner to estimate real-time driving times. Of note, the negative effects of overtriage are not necessarily limited to non-LVO ischemic stroke patients, as crowding in intervention centers might affect local health care. On the other hand, we regarded patients with (severe) intracranial hemorrhage that bypassed a PSC as overtriage, where it could be argued that these patients might benefit from direct transport to a center with neurosurgical facilities. Potential capacity issues might also differ between regions or hospitals, so this is important to consider before implementing prehospital triage strategies. To minimize overtriage, the sensitivity of this personalized tool to bypass PSCs can be adjusted, as shown in our sensitivity analysis. We want to emphasize that prehospital triage strategies have different impact between regions, and decisions on prehospital triage should ultimately be taken on a regional level. This study is a demonstration

on how to estimate the impact of prehospital triage strategies, which can aid local health policy makers in making better-informed decisions.

Conclusion

In two large cohorts of stroke code patients, prehospital triage with the RACE scale or the personalized decision tool reduced the time to EVT in all regions without disproportionate delay of IVT compared to the drip-and-ship model. The impact of triage strategies and the associated overtriage varied between regions. Implementation of prehospital triage should therefore be considered on a regional level.

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Supplemental Material

Table 1. Input parameters used for the allocation strategies.

	Value	Source
Median door-to-needle times, minutes		
Hospital A	20	Local median 2017-2019
Hospital B	24	Local median 2017-2019
Hospital C	24	Local median 2017-2019
Hospital D	25	Local median 2017-2019
Hospital E	20	Local median 2017-2019
Hospital F	22	Local median 2017-2019
Hospital G	30	Local median 2017-2019
Hospital H	23	Local median 2017-2019
Hospital I	17	Local median 2017-2019
Hospital J	24	Local median 2017-2019
Hospital K	21	Local median 2017-2019
Hospital L	23	Local median 2017-2019
Hospital M	22	Local median 2017-2019
Hospital outside region	24	National median DASA 2017-2019
Median door-to-groin-time, minutes (primary presented patient)		
Intervention center A	78	Local median 2017-2019
Intervention center B	53	Local median 2017-2019
Intervention center C	59	Local median 2017-2019
Intervention center D	67	Local median 2018-2019
Intervention center E	72	Local median 2018-2019
EVT-center outside region	69	National median DASA 2017-2019
Median door-to-groin-time, minutes (transferred patient)		
Intervention center A	21	Local median 2017-2019
Intervention center B	17	Local median 2017-2019
Intervention center C	24	Local median 2017-2019
Intervention center D	29	Local median 2018-2019
Intervention center E	25	Local median 2018-2019
Median door-in-door-out-time, minutes	62	PRESTO study - median

Table 1. *Continued.*

	Value	Source
Probability of receiving IVT if presenting <4.5h with an ischemic stroke	0.61	Pooled data Leiden Prehospital Stroke Study & PRESTO study
Likelihood of an LVO ischemic stroke		Pooled data Leiden Prehospital Stroke Study & PRESTO study
RACE = 0	0.02	
RACE = 1	0.04	
RACE = 2	0.05	
RACE = 3	0.08	
RACE = 4	0.09	
RACE = 5	0.23	
RACE = 6	0.37	
RACE = 7	0.39	
RACE = 8	0.48	
RACE = 9	0.39	
Likelihood of a non-LVO ischemic stroke		Pooled data Leiden Prehospital Stroke Study & PRESTO study
RACE = 0	0.31	
RACE = 1	0.37	
RACE = 2	0.43	
RACE = 3	0.46	
RACE = 4	0.46	
RACE = 5	0.41	
RACE = 6	0.37	
RACE = 7	0.32	
RACE = 8	0.16	
RACE = 9	0.14	

DASA = Dutch Acute Stroke Audit. RACE = Rapid Arterial oCclusion Evaluation.
IVT = Intravenous thrombolysis.
Door-to-needle time was defined as the minutes from presentation to the stroke center up to the administration of IVT. Door-to-groin-time was defined as the minutes from presentation to the intervention center up to the groin puncture for EVT. Door-in-door-out-time was defined as the minutes from presentation to the primary stroke center up to the time of departure from the primary stroke center for transfer to the intervention center. LVO was defined as an occlusion of the intracranial part of the internal carotid artery (ICA), the middle cerebral artery segment M1 or M2 or the anterior cerebral artery segment A1 or A2, assessed on CTA.

Table 2. Secondary outcomes.

	Drip-and-ship (reference)	RACE triage	Personalized tool
Region A (n=373)			
Ischemic stroke patients treated with IVT, n (%)	65/144 (46%)	65/144 (46%)	65/144 (46%)
LVO stroke patients treated with EVT, n (%)	25/29 (86%)	26/29 (90%)	26/29 (90%)
Number of interhospital transfers	3	2	1
Region B (n=386)			
Ischemic stroke patients treated with IVT, n (%)	102/167 (61%)	102/167 (61%)	102/167 (61%)
LVO stroke patients treated with EVT, n (%)	27/27 (100%)	27/27 (100%)	27/27 (100%)
Number of interhospital transfers	5	3	2
Region C (n=543)			
Ischemic stroke patients treated with IVT, n (%)	165/267 (62%)	164/267 (61%)	165/267 (62%)
LVO stroke patients treated with EVT, n (%)	57/62 (92%)	58/62 (94%)	58/62 (94%)
Number of interhospital transfers	48	13	13
Region D (n=496)			
Ischemic stroke patients treated with IVT, n (%)	157/255 (62%)	155/255 (61%)	157/255 (62%)
LVO stroke patients treated with EVT, n (%)	39/39 (100%)	39/39 (100%)	39/39 (100%)
Number of interhospital transfers	9	3	1

Percentages are rounded to whole numbers. IVT = intravenous thrombolysis.
EVT = endovascular thrombectomy.

Table 3. Sensitivity analysis with the adjusted thresholds of the personalized model

	Region A (n=373)	Region B (n=386)	Region C (n=543)	Region D (n=496)
Probability of good outcome intervention center > PSC (original model)				
Directly transported to intervention center, % (n)	72% (267)	53% (205)	30% (164)	85% (422)
Overtriage to intervention center, % (n)	3% (11)	5% (18)	15% (82)	15% (76)
Number-needed-to-bypass	7.4	53.0	2.3	9.5
Increase in probability of good outcome intervention center vs PSC > 0.1 %				
Directly transported to intervention center, % (n)	66% (246)	52% (201)	27% (146)	76% (379)
Overtriage to intervention center, % (n)	2% (9)	4% (15)	12% (66)	7% (35)
Number-needed-to-bypass	5.4	43.0	1.9	5.8
Increase in probability of good outcome intervention center vs PSC > 0.2 %				
Directly transported to intervention center, % (n)	63% (235)	47% (180)	25% (133)	73% (362)
Overtriage to intervention center, % (n)	2% (9)	3% (13)	10% (53)	4% (20)
Number-needed-to-bypass	2.0	*not available	1.6	5.0

*In this region no LVO patients bypassed a PSC if the threshold was > 0.2%.

Chapter 6.1

Accuracy of CTA evaluations in daily clinical practice for large and medium vessel occlusion detection in suspected stroke patients

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European Stroke Journal, 2021

Abstract

Introduction
Early detection of large vessel occlusion (LVO) is essential to facilitate fast endovascular treatment. CT angiography (CTA) is used to detect LVO in suspected stroke patients. We aimed to assess the accuracy of CTA evaluations in daily clinical practice in a large cohort of suspected stroke patients.

Patients and methods
We used data from the PRESTO study, a multi-center prospective observational cohort study that included suspected stroke patients between August 2018 and September 2019. Baseline CTAs were re-evaluated by an imaging core laboratory and compared to the local assessment. LVO was defined as an occlusion of the intracranial internal carotid artery, M1 segment, or basilar artery. Medium vessel occlusion (MeVO) was defined as an A1, A2 or M2 occlusion. We calculated the accuracy, sensitivity and specificity to detect LVO and LVO+MeVO, using the core laboratory evaluation as reference standard.

Results
We included 656 patients. The core laboratory detected 89 LVOs and 74 MeVOs in 155 patients. Local observers missed 6 LVOs (7%) and 28 MeVOs (38%), of which 23 M2 occlusions. Accuracy of LVO detection was 99% (95% CI: 98-100%), sensitivity 93% (95% CI: 86-97%), and specificity 100% (95% CI: 99-100%). Accuracy of LVO+MeVO detection was 95% (95% CI: 93-96%), sensitivity 79% (95% CI: 72-85%), and specificity 99% (95% CI: 98-100%).

Discussion and Conclusion
CTA evaluations in daily clinical practice are highly accurate and LVOs are adequately recognized. The detection of MeVOs seems more challenging. The evolving EVT possibilities emphasize the need to improve CTA evaluations in the acute setting.

Introduction

Endovascular thrombectomy (EVT) has become the standard of care for patients with an intracranial large vessel occlusion (LVO) in the anterior circulation up to 6 hours after onset, and in selected patients even up to 24 hours after onset.[1-3] Because the effect of EVT is time-dependent, early detection of LVO is essential for good clinical outcome.[4] In most stroke centers, CT angiography (CTA) is used to detect LVOs during the acute work-up of suspected stroke patients.[5, 6] Interrater agreement of LVO detection on CTA has been reported ranging from 0.48 to 0.97.[7-10] However, this has only been assessed in a limited number of small studies (sample size range 15-100) that were focused on proximal LVOs and performed in retrospective, controlled, and experimental settings.[7-10] Most suspected stroke patients are referred to stroke centers without EVT-capabilities and half of the patients present outside office hours.[11] Consequently, presence and location of LVO will often not be assessed by neuroradiologists or interventionalists, but by radiologists, neurologists or residents with less experience in vascular neuroradiology. So far, the accuracy of CTA evaluations in the acute setting is unknown. We aimed to assess the accuracy of CTA evaluations in daily clinical practice in a large representative cohort of suspected stroke patients in different hospitals.

Methods

Study design

We used data from the Prehospital triage of patients with suspected stroke (PRESTO) study, a multicenter prospective observational cohort study that included suspected stroke patients in the ambulance between August 13, 2018 and September 2, 2019.[12, 13] Inclusion criteria were new neurological deficit defined as at least one point on the Face-Arm-Speech-Time test, age 18 years or older, and blood glucose of at least 2.5 mmol/L. For the current analysis, we included patients with baseline CTA. Patients with intracranial hemorrhage on baseline NCCT were excluded. The Institutional Review Board of the Erasmus MC University Medical Center Rotterdam has reviewed the study protocol and confirmed that the Dutch Medical Research Involving Human Subjects Act was not applicable. Because this study met the exceptions of informed consent regulations, the need for informed consent was waived. Detailed information regarding the study is described elsewhere.[13]

Local procedures

The eight participating hospitals had an emergency department and stroke unit and were equipped for rapid diagnosis of ischemic stroke. Three hospitals had a radiology residency training program, of which two centers were intervention

centers capable of EVT, including one academic hospital. During the PRESTO study, Non-Contrast CT (NCCT), CTA, CT perfusion (CTP), magnetic resonance imaging or digital subtraction angiography could be performed as part of the regular work-up, based on the assessment of the treating physician. CTAs were performed according to local clinical acquisition protocols. Directly after imaging acquisition, the radiology resident or radiologist on call reviewed the NCCT and CTA. CTA evaluations by radiology residents were always supervised by a radiologist. In clinical practice, especially during the night shift, this supervision was at a later moment. For this analysis, the final supervised imaging report was used as local evaluation. Dutch national guidelines recommend CTA if a diagnosis of ischemic stroke is clinically suspected in patients without EVT contra-indications. Regional protocols advised EVT in all patients with an occlusion of the intracranial part of the internal carotid artery (ICA), the middle cerebral artery segment (M1 or M2), or the anterior cerebral artery segment (A1 or A2), if EVT is possible within 6 hours after last-seen-well, irrespective of stroke severity. During the course of the study, patients with basilary artery occlusions were evaluated for inclusion in the BASilar artery International Cooperation Study.[14]

Central imaging storage and evaluation

All neuro-imaging was de-identified and stored in an imaging database (XNAT; Neuroinformatics Research Group, St Louis, MO). All baseline CTAs were reviewed by an imaging core laboratory using RadiAnt DICOM Viewer software (Medixant, Poland). Baseline NCCT was provided with the CTA. CTP (if performed) was not provided to the imaging core laboratory. Core laboratory observers were blinded to the final diagnosis or severity of the symptoms, but were informed about the following clinical symptoms at baseline: presence and side of the hemiparesis, presence of aphasia, or non-localizing symptoms in case of absence of hemiparesis and aphasia.

LVO was defined as an occlusion of the intracranial ICA: infraclinoid, supraclinoid or terminal part of the ICA (ICA-T), the M1 segment or the basilar artery.[15] MeVO was defined as an occlusion of the A1, A2, or M2 segment. We differentiated between proximal and distal M1 occlusions based on the proximal versus the distal half of the M1 segment. The M2 segments were defined as the post-bifurcation branches of the M1 segment. The M2-M3 transition was defined as the location where the arteries rotate to the operculum and return in a horizontal position.

The imaging core laboratory consisted of seven experienced observers (four neuroradiologists and three interventional neuroradiologists). Each scan was evaluated by one of six core laboratory observers (JB, ASP, JJH, ACGMvE, GJL, PJvD). In case of discordant CTA evaluations between the local observer and the imaging core laboratory, the seventh core laboratory member (AvdL) re-

evaluated imaging, blinded to the prior assessments. If the two core laboratory evaluations did not match, disagreements were resolved in consensus by the two co-chairs of the imaging core laboratory (ACGMvE, AvdL).

Statistical analysis

We reported continuous variables as mean and standard deviation or median and interquartile range. We reported categorical variables as numbers and percentages. To calculate the sensitivity, specificity and accuracy for the detection of LVO and MeVO, we created contingency tables with the local CTA evaluation as index test, and the final core laboratory evaluation as reference standard. For the contingency tables, we approached every LVO and MeVO separately in patients with multiple occlusions. Other occlusion locations were reported, but were not used in the analysis. To assess the effect of simultaneous CTP acquisition or presentation in an academic hospital, we calculated the test characteristics for the subgroup of patients with CTP (that was only available to the local observers) and the subgroup of patients that presented in the academic hospital. Test characteristics for these subgroups were compared to the test characteristics of the remaining cohort using Fisher's exact test.

Additionally, we compared two subgroups of patients with a core laboratory confirmed LVO or MeVO: the patients with an LVO or MeVO detected by the local observer and the patients with an LVO or MeVO missed by the local observer. For this comparison, patients with multiple occlusions were categorized in the subgroup of patients with a locally detected occlusion if at least one LVO or MeVO was locally detected. Between-group comparisons were made with independent-samples t-test, Mann-Whitney U test, Chi Square test or Fisher's exact test, as appropriate. To estimate the clinical impact of occlusions missed by the local team, we explored the potential EVT indication of these patients, based on our regional treatment protocols. We assumed all patients with a clinical diagnosis of ischemic stroke and LVO or MeVO were technically treatable. If, in addition, treatment was possible within six hours after last-seen-well and the occlusion was symptomatic (NIHSS>0), we considered the patient eligible for EVT.

We assessed and reported completeness of the data. No data imputation was used for the analyses. All analyses were performed using R software (version 3.6.1) and RStudio (version 1.0.153).

Results

Of the 1334 patients enrolled in the PRESTO study, we included 656 patients for this analysis (Figure 1). Patients had a median age of 73 years (IQR: 62-81), 290/656 (44%) were women and the median NIHSS score was 4 (IQR: 2-9) (Table 1). Patients presented at the emergency department at a median of 94 minutes

(IQR: 54-200) since last-seen-well. Baseline NCCT was performed 9 minutes (median) after arrival at the emergency department (IQR: 6-13), followed by CTA after another 6 minutes (median, IQR: 3-10).

Core laboratory evaluations of 596 CTAs (91%) were consistent with the local evaluations (Figure 2). Sixty CTAs (9%) had to be reviewed by a second core laboratory member. The second core laboratory member agreed with the first core laboratory assessment in 18 CTAs. Disagreement concerning 42 CTAs (70%) was resolved in consensus. Most discordances between the two core laboratory evaluations concerned the presence of an occlusion (30/42, 71%), in particular regarding the M2 segment (21/30, 70%).

Figure 1. Flowchart of the patient inclusion

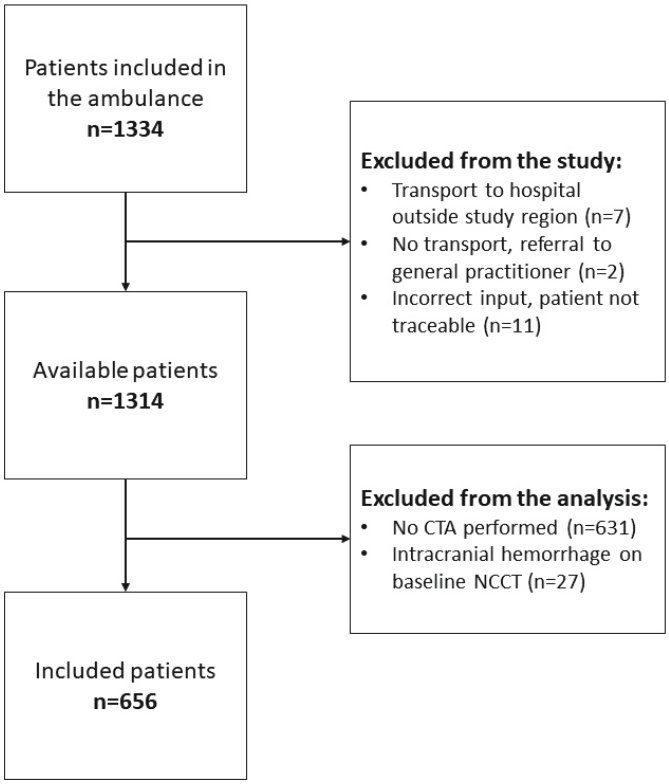
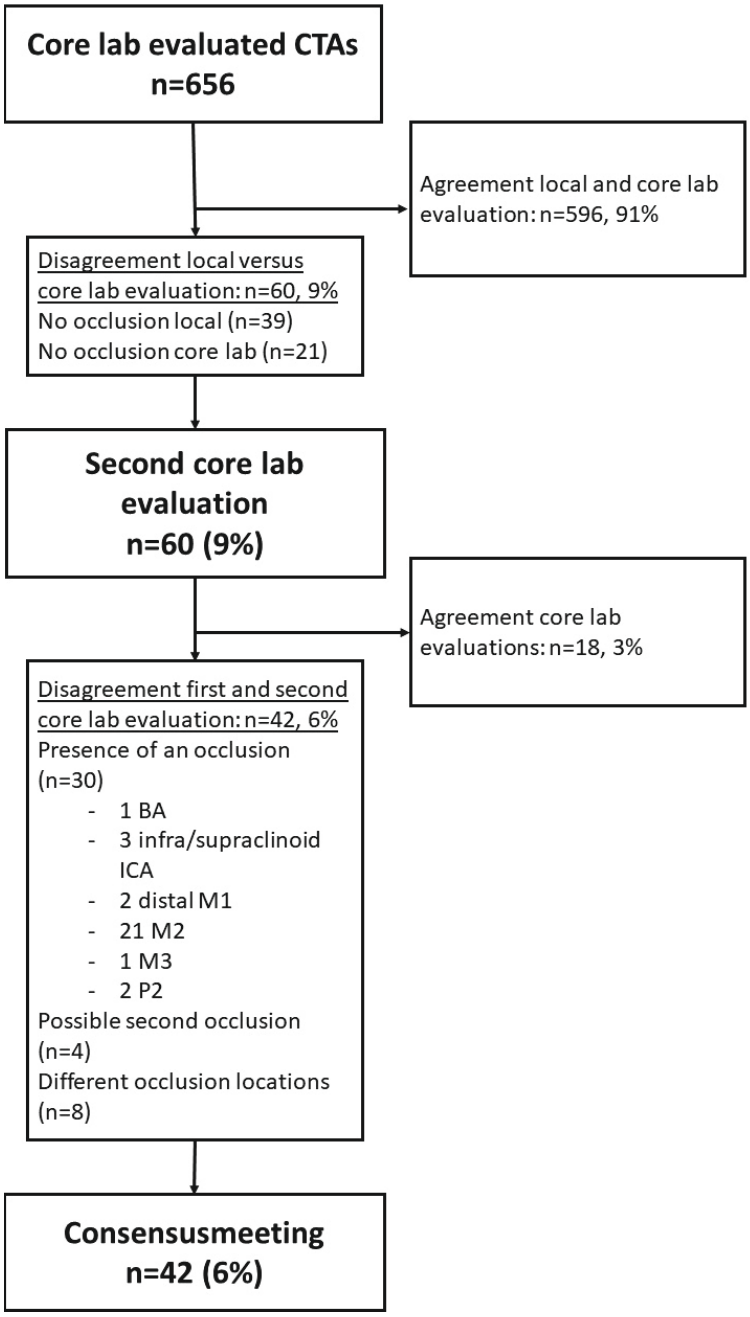


Figure 2: Flowchart of the core laboratory assessments.



BA = basilary artery. ICA = internal carotid artery.

Table 1. Patient characteristics.

	N=656
Age (years)	73 (62-81)
Sex (female)	290 (44%)
Medical history	
Atrial fibrillation	119 (18%)
Hypertension	433 (66%)
Hypercholesterolemia	473 (72%)
Diabetes mellitus	124 (19%)
Ischemic stroke	156 (24%)
Myocardial infarction	82 (13%)
Intracranial hemorrhage	4 (1%)
SBP (mean±SD)	159±28
NIHSS score	4 (2-9)
Workflow times (minutes)	
Onset-to-door	94 (54-200)
Door-to-NCCT	9 (6-13)
CT-to-CTA	6 (3-10)
Hospital	
A (academic hospital and intervention center)	90 (14%)
B (training hospital and intervention center)	233 (36%)
C (training hospital)	86 (13%)
D-I	247 (38%)
Final diagnosis	
Ischemic stroke	513 (78%)
Stroke mimic	86 (13%)
TIA	57 (9%)

Data are median (IQR) or n (%), unless otherwise indicated. SBP = systolic blood pressure. SD = Standard deviation. NIHSS = National Institute of Health Stroke Scale. NCCT = Non-Contrast Computed Tomography. CTA = Computed Tomography Angiography. TIA = Transient Ischemic Attack. Number of missings: SBP: 4 (0.6%), NIHSS: 3 (0.5%), Onset-to-door: 15 (2%), Door-to-NCCT: 16 (2%), CT-to-CTA: 20 (3%).

Performance of local CTA evaluations

The imaging core laboratory detected 89 LVOs and 74 MeVOs in 155/656 (24%) patients (Table 2). Eighteen patients (3%) had occlusions in two different segments (Supplemental Table 1). In total, local observers missed 6 LVOs (7%) and 28 MeVOs (38%), mostly of the M2 segment (23/34, 68%), which was 35% (23/66) of all M2 occlusions (Table 2). The core laboratory did not confirm four locally presumed intracranial occlusions (Supplemental Table 2).

Table 2. Occlusion locations.

	Occlusions detected by the local team	Occlusions missed by the local team
LVO and MeVO	n=129	n=34
Infraclinoid/supraclinoid ICA	7	3
ICA-T	12	0
M1 (proximal)	31	0
M1 (distal)	28	2
M2	43	23
A1	1	0
A2	2	5
Basilar artery	5	1
Other occlusions:	n=6	n=13
M3	0	2
A3	0	2
Vertebral artery (intracranial part)	1	4
P1	1	0
P2	4	5

LVO = Large Vessel Occlusion, defined as an occlusion in the intracranial internal carotid artery, M1 segment or basilar artery. MeVO = Medium Vessel Occlusion, defined as an occlusion of the A1, A2, or M2 segment. ICA = Internal Carotid Artery. ICA-T = Internal Carotid Artery Terminus. 18 of 164 patients had two occlusions, total occlusion count is 182.

The accuracy for the detection of LVO was 99% (95% confidence interval (CI): 98-100%), with a sensitivity of 93 (95% CI: 86-97%) and a specificity of 100 (95% CI: 99-100%). The accuracy for the detection of LVO+MeVO was 95% (95% CI: 93-96%), with a sensitivity of 79% (95% CI: 72-85%) and a specificity of 99 (95% CI: 98-100%). Sensitivity of MeVO detection was 62% (95% CI: 51-73%). Results for the detection of LVO or LVO+MeVO were not significantly different for patients

that underwent CTP or for patients that presented in the academic hospital (Supplemental Table 3-5).

Patients with LVO/MeVO missed by the local observer

In 30/656 (5%) patients, local observers missed an LVO or MeVO (Table 3). Patients with an LVO or MeVO missed by the local observer had lower NIHSS scores, with a median of 4 (IQR: 2-11), compared to the patients in whom the LVO or MeVO was detected locally (NIHSS 14, IQR: 9-18, p<0.001). Patients with a missed LVO or MeVO more often presented after the 6 hours after symptoms onset (8/30 [27%] versus 15/125 [12%], p=0.04). Fifteen of these 30 patients (50%) received intravenous thrombolytics. Two patients of whom the occlusion was missed by the local observer were diagnosed with a transient ischemic attack. In 4/30 (13%) of the patients with a locally missed LVO or MeVO, the symptoms could not be (completely) attributed to the occlusion location, which was more often than in patients with locally detected LVO or MeVO (2/125 [2%], p=0.01). Of all 155 patients with an LVO or MeVO, 102 (66%) were treated with EVT. Reason for omitted EVT was most often because the occlusion was missed by the local observer or the opportunity for treatment within the 6 hour time-window was passed (Supplemental Table 6). Based on our regional guidelines, EVT might have been indicated in 15/30 (50%) patients, if the occlusions would have been detected by the local observer.

Table 3. Clinical and Imaging aspects of patients with intracranial occlusions confirmed by the core laboratory.

	Patients with locally detected LVO/ MeVO n=125	**Patients with locally missed LVO/MeVO n=30**	**p-value**
Clinical aspects			
Age (years)	73 (63-82)	73 (62-83)	0.89
Sex (female)	58 (46%)	17 (57%)	0.31
NIHSS score	14 (9-18)	4 (2-11)	<0.001
Symptom onset			
Witnessed	79 (63%)	18 (60%)	0.18
Wake-up stroke	14 (11%)	7 (23%)	
Unknown, not-witnessed	32 (26%)	5 (17%)	
CTA outside office hours	70 (57%)	14 (45%)	0.54
CTA during night-time	19 (16%)	5 (18%)	0.77

Table 3. *Continued.*

	Patients with locally detected LVO/ MeVO n=125	Patients with locally missed LVO/MeVO n=30	p-value
Presentation beyond 6 hours after symptom onset	15 (12%)	8 (27%)	0.04
Presentation in training hospital	79 (63%)	18 (62%)	0.95
Presentation in EVT-capable center	66 (52%)	15 (52%)	0.95
Presentation in academic hospital	27 (21%)	3 (10%)	0.20
Workflow times (minutes)			
Onset-to-door	85 (47-211)	111 (69-286)	0.08
Door-to-NCCT	8 (6-11)	8 (5-10)	0.78
NCCT-to-CTA	7 (4-11)	7 (4-10)	0.63
Diagnosis			
Ischemic stroke	125 (100%)	28 (93%)	0.004
Transient ischemic attack	0	2 (7%)	
Treated with intravenous thrombolytics	75 (60%)	15 (50%)	0.53
Imaging aspects			
Quality of the CTA – moderate/poor	8 (6%)	4 (13%)	0.45
Acquisition phase			0.45
Early/peak arterial	95 (74%)	24 (80%)	0.75
Equilibrium	23 (18%)	4 (13%)	
Peak/late venous	6 (5%)	2 (7%)	
Thin slices available (≤ 1 mm)	112 (90%)	27 (90%)	0.95
CTP performed	28 (22%)	3 (10%)	0.13

Table 3. *Continued.*

	Patients with locally detected LVO/ MeVO n=125	Patients with locally missed LVO/MeVO n=30	p-value
Clinical symptoms not (completely) attributed to the occlusion	2* (2%)	4† (13%)	0.01

Data are median (IQR) or n (%), unless otherwise indicated. NIHSS = National Institute of Health Stroke Scale. CTA = Computed Tomography Angiography. EVT = Endovascular thrombectomy. NCCT = Non-Contrast Computed Tomography. CTP = Computed Tomography Perfusion.
Number of missings: NIHSS: 2 (1%), CTA outside office hours: 3 (2%), CTA during night-time: 5 (3%), Onset-to-door: 2 (1%), Door-to-NCCT: 3 (2%), NCCT-to-CTA: 5 (3%), Quality of the CTA: 6 (4%), Acquisition phase: 1 (0.6%).
Patients with multiple LVOs/MeVOs were categorized in the subgroup of patients with a locally detected LVO/MeVO if at least one LVO/MeVO was locally detected.
* Two patients were diagnosed with an occlusion in the contralateral (asymptomatic) hemisphere. † Four patients were diagnosed with an occlusion in a different vascular territory than the clinical symptoms suggested (cerebellar versus hemispheric) or the contralateral hemisphere.

Discussion

This study is the first to assess the accuracy of CTA evaluations of suspected stroke patients in daily clinical practice. CTA evaluations to detect LVO are accurate. However, a considerable proportion of MeVOs were not detected in the acute setting. Missed MeVOs were mostly located in the M2 segment.

The imaging core laboratory was not only more experienced, but also benefited from the setting without time pressure. Besides this, the need for a consensus meeting because of discrepancies between core laboratory evaluations confirmed the difficulty of occlusion detection in the M2 segment. Patients with LVO or MeVO missed by the local observer had milder neurologic deficit, which may be explained by the proportion of more distal occlusion locations, but might also be because good collateral circulation made the occlusions hard to detect. Patients with a missed LVO or MeVO more often presented outside the six hour time window. Our core laboratory was instructed carefully before the evaluations, but local observers had a different objective, namely rapidly assess EVT eligibility. In patients that presented beyond six hours after last-seen-well, local observers might have been focusing less on MeVO presence. This because beyond six hours after last-seen-well, only LVOs and proximal M2 occlusions could be included in the MR CLEAN LATE Trial. In some

patients, clinical symptoms could not be fully attributed to the found occlusion location, so these occlusions might have been pre-existent or asymptomatic. However, it remains important to recognize all intracranial occlusions, in case of acute neurological deterioration of the patient, to gain insight in stroke etiology and the international tendency to treat more distal occlusions.[16, 17]

One previous single-center study in which a panel of 2 neuroradiologist re-assessed CTAs of ischemic stroke patients (n=522) concluded that 20% of the intracranial occlusions were missed, mostly M2 occlusions.[18] Other studies focused on the interobserver agreement of CTA assessments, were performed in controlled settings and did not evaluate the CTA evaluation in the acute setting.[7-10] Observers in previous studies ranged from neurologists and radiology trainees to expert radiologists in neuroradiology. These studies demonstrated that interobserver agreement of LVO detection varies from weak to strong.[7-10] Most of these studies were performed in small and selected populations, and some did not include occlusions of the M2 segment at all, or in small numbers.[7, 9]

This study has some limitations. We used our final core laboratory evaluation as reference standard, but since some (mostly distal) occlusions are not easily detected, it is possible there might have been more MeVOs that were even missed by the core laboratory. We have no knowledge regarding the exact training (for example radiological focus area) and working experience of the local observers. It is likely that the level of experience of the observers is an important factor in the accuracy of CTA evaluations.[18] Also, we have no information about the time that was needed to detect the intracranial occlusions. However, it is clear that locally missed occlusions were not always easily detectable, even by an experienced core laboratory. Another limitation is that in a substantial proportion of the patients included in the PRESTO study CTA was not performed. In clinical practice, the indication of a CTA in suspected stroke patients is determined by the treating physician. The Dutch national stroke guidelines recommend that all patients with a diagnosis of acute ischemic stroke undergo CTA. This is most often omitted because the likelihood of ischemic stroke or presence of an intracranial occlusion is considered to be very low. This implies that our cohort reflects the suspected stroke population that would be subjected to CTA.

In contrast to local practices in our region, EVT of MeVOs is not standardly recommended by all guidelines, especially in patients with low NIHSS scores.[15] Currently, the ENDOLOW trial is being conducted to investigate whether EVT improves clinical outcome of patients with occlusions up to the M2 segment and low NIHSS (0-5). Since the prevalence of ischemic stroke in the population is expected to rise and EVT possibilities are developing, it is crucial to improve the detection of MeVOs. Besides, even if patients with an LVO or MeVO would not be treated, occlusion detection may influence stroke management, for example regarding blood pressure management. The first step towards improvement is

to be aware that in patients with minor deficit, intracranial occlusions can still be present and these occlusions might not always be obvious, especially in the M2 segment. It is also important to thoroughly assess the complete intracranial vasculature, both the anterior as the posterior circulation, and not restrict to the clinically suspected area. Additional training in LVO/MeVO detection might also be helpful. Another possible solution to prevent missing occlusions could be the acquisition of multiphase CTA or additional CTP imaging. There is some evidence that multiphase CTA improves the diagnostic accuracy for occlusion detection.[10] Visible perfusion defects on CTP imaging might guide the observer to the occluded vessel and ease the CTA evaluation.[19, 20] We found no differences in LVO/MeVO detection by local observers in patients with CTP and patients that presented in the academic hospital. However, because these were small subgroup analyses and most CTPs were performed in the academic hospital which was also the only hospital with multiphase CTA, our study is not suitable to assess the added value of either CTP or multiphase CTA. Another development, the use of automated LVO detection software is currently being explored and might also be used to aid the radiologist in rapid detection of LVO.[21]

Conclusions

CTA evaluations in daily clinical practice are highly accurate and in general, LVOs are adequately recognized. The detection of MeVOs seems more challenging. With the evolving endovascular treatment possibilities, this emphasizes the need to improve CTA assessments in the acute setting.

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Supplemental material

Table 1. Occlusion locations of patients with two occlusions.

Most proximal occlusion	Most distal occlusion
Infraclinoid ICA (LVO)	distal M1 (LVO)
Infraclinoid ICA* (LVO)	M2 (MeVO)
Infraclinoid ICA* (LVO)	M2* (MeVO)
Supraclinoid ICA (LVO)	M2 (MeVO)
Supraclinoid ICA (LVO)	P1
ICA-T (LVO)	A1 (MeVO)
Proximal M1 (LVO)	P2*
Proximal M1 (LVO)	A2 (MeVO)
Distal M1 (LVO)	VA*
M2 (MeVO)	A2* (MeVO)
M2 (MeVO)	A3*
M2 (MeVO)	A2* (MeVO)
M2* (MeVO)	P2
M2* (MeVO)	A3*
M2 (MeVO)	VA*
BA (LVO)	P2
VA	BA
P2 right*	P2 left*

* occlusion missed by local observer

Table 2. Locally presumed occlusions, not confirmed by imaging core laboratory

Presumed occlusion location	Treated with EVT	Reason omitted EVT	Imaging core laboratory conclusion
M2 segment	No	Assigned to best medical treatment in the MR CLEAN LATE trial	No occlusion
M2 segment	No	Complete spontaneous neurologic recovery	No occlusion
M3 segment	No	Considered too distal for treatment	No occlusion
Basilar artery	No	Ineligible for BASilar artery International Cooperation Study (BASICS) trial	Persistent trigeminal artery and a hypoplastic basilar artery appearing as an occlusion

Table 3. Performance of local observers to detect intracranial occlusions - subgroup of patients with CTP (n=78)

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
LVO	91% (72-99%)	100% (94-100%)	97% (94-100%)
LVO and MeVO	91% (76-98%)	98% (89-100%)	95% (90-100%)

Table 4. Performance of local observers to detect intracranial occlusions - subgroup of patients presented in the academic hospital (n=90)

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
LVO	90% (70-99%)	100% (95-100%)	98% (95-100%)
LVO and MeVO	91% (75-98%)	98% (91-100%)	95% (91-100%)

Table 5. P-values of Fisher's exact test for the comparison between test characteristic of the occlusion detection by local observers in different strata based on CTP acquisition and presentation in an academic hospital.

	Patients with CTP versus patients without CTP – p-values		Presentation in an academic hospital versus presentation in a non-academic hospital – p-values	
	LVO	LVO+MeVO	LVO	LVO+MeVO
Sensitivity	0.65	0.09	0.62	0.09
Specificity	1.0	0.25	1.0	0.32
Accuracy	0.93	1.0	0.94	0.94

Table 6. Reasons of omitted endovascular thrombectomy in patients with LVO or MeVO.

	Patients with LVO/ MeVO (n=155)
Treated with EVT	102 (66%)
Not treated with EVT	53 (34%)
Reason not treated with EVT	
LVO/MeVO missed by local observer	30 (57%)
Patient recovered/minor deficit	3 (6%)
Ineligible for BASICS or randomized for no EVT	3 (6%)
Outside treatment window and ineligible for MR CLEAN LATE or randomized for best medical treatment	8 (15%)
Pre-existent or asymptomatic occlusion	4 (8%)
Decision relatives	1 (2%)
Occluded vessel toward ischemic territory	1 (2%)
Occlusion considered not treatable by local stroke team*	3 (6%)

EVT = Endovascular Thrombectomy. BASICS = BASilar artery International Cooperation Study

***** Two patients had an M2 occlusion that was considered too distal for treatment. Another patient had a distal M2 occlusion together with an intracranial ICA occlusion. In this patient, treatment was omitted because of the distal location in the M2 segment and concerns to cause more distal emboli by passing the ICA occlusion.

Chapter 6.2

Diagnostic Performance of an Algorithm for Automated Large Vessel Occlusion Detection on Computed Tomography Angiography

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Abstract

Introduction
Machine learning algorithms hold potential to contribute to fast and accurate detection of large vessel occlusion (LVO) in patients with suspected acute ischemic stroke. We assessed the diagnostic performance of an automated LVO detection algorithm on computed tomography angiography (CTA).

Methods
Data from the MR CLEAN Registry and PRESTO were used including patients with and without LVO. CTA data were analyzed by the algorithm for detection and localization of LVO (intracranial internal carotid artery (ICA)/ICA terminus (ICA-T), M1, or M2). Assessments done by expert neuroradiologists were used as reference. Diagnostic performance was assessed for detection of LVO and per occlusion location by means of sensitivity, specificity, and area under the curve (AUC).

Results
We analyzed CTAs of 1,110 patients from the MR CLEAN Registry (median age [IQR], 71 years [60-80]; 584 men; 1,110 with LVO) and of 646 patients from PRESTO (median age [IQR], 73 years [62-82]; 358 men; 141 with and 505 without LVO). For detection of LVO, the algorithm yielded a sensitivity of 89% in the MR CLEAN Registry and sensitivity of 72%, specificity of 78%, and AUC of 0.75 in PRESTO. Sensitivity per occlusion location was 88% for ICA/ICA-T, 94% for M1, and 72% for M2 occlusion in the MR CLEAN Registry and 80% for ICA/ICA-T, 95% for M1, and 49% for M2 occlusion in PRESTO.

Conclusion
The algorithm provided a high detection rate for proximal LVO, but performance varied significantly by occlusion location. Detection of M2 occlusion needs further improvement.

Introduction

Computed tomography angiography (CTA) is currently the most widely used imaging modality for detection of a large vessel occlusion (LVO) in patients presenting with suspected acute ischemic stroke. For acute ischemic stroke due to LVO in the anterior circulation, endovascular treatment (EVT) is considered the most effective therapy.[1] However, technical success and, more importantly, individual patient benefit are strongly dependent on time between symptom onset and initiation of treatment.[2, 3] Fast and accurate detection of LVO on CTA can therefore contribute to the likelihood of a good clinical outcome.

In general, experienced (neuro)radiologists are well-capable of identifying LVOs on CTA, enabling prompt diagnosis of acute ischemic stroke due to LVO.[4, 5] Yet, such expertise is not always readily available, for instance in hospitals with lower caseloads and during off-hours when dedicated neuro-radiologists are not on call. This may hamper fast and accurate CTA assessment.[6, 7] At the same time, the number of CTA examinations for suspected acute ischemic stroke is increasing due to optimization of stroke management and prolonged treatment windows.[8, 9]

To support fast and accurate CTA assessment, diagnostic tools applying artificial intelligence algorithms are being developed. These tools are aimed at screening CTAs for LVOs and, in case of a positive finding, notifying not only local radiologists but also the stroke team at the nearest EVT-capable stroke center.[10-14] Determining the performance of such algorithms is needed to estimate their potential clinical utility.

The aim of this study was to assess the diagnostic performance of an automated LVO detection algorithm in patients with and without anterior circulation LVO, and to assess the impact of scan acquisition parameters on performance.

Methods

Study design and patient selection

This study was performed in accordance with the STARD guidelines for reporting diagnostic accuracy.[15] We used data from the first part of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) Registry[16] and from the Prehospital triage of patients with suspected stroke (PRESTO) study.[17] The MR CLEAN Registry is a multicenter prospective registry including patients (n=1,627) with acute ischemic stroke undergoing EVT from March 18th, 2014 until June 15th, 2016. PRESTO is a multicenter prospective observational cohort study including patients (n=1,334) with suspected stroke in the ambulance from August 13th, 2018 until September 2nd, 2019. All patients who underwent baseline CTA were eligible for inclusion. Imaging parameters

required for inclusion were: axial series; slice thickness 0.2 – 3 mm; slice increment equal to or smaller than slice thickness (i.e. no excess z-spacing); matrix size of 512 x 512 or above; full head coverage. The evaluated algorithm was developed and trained only to detect intracranial internal carotid artery (ICA)/ICA terminus (ICA-T), M1, and M2 occlusions, but not isolated extracranial ICA, A1/A2, M3/M4, and posterior circulation (vertebral artery, basilar artery, or posterior (P1/P2) cerebral artery) occlusions. The latter group will be evaluated when implementing the current algorithm in a clinical setting. Therefore, we chose to include patients from our real-world PRESTO cohort with occlusions other than ICA, ICA-T, M1 or M2, but classified them as patients without LVO in order to assess whether they interfere with real-world diagnostic performance. CTA data that were used for algorithm training were not included in the current assessment of diagnostic performance. A complete overview of patient inclusion and exclusion criteria is outlined per cohort in Supplemental Figure 1.

Reference LVO definition

CTAs were evaluated for presence and location of LVO by imaging core labs consisting of 3 neuroradiologists and 10 interventional neuroradiologists (5-20 years of experience) who were blinded for algorithm output and all clinical data with the exception of symptomatic side of stroke symptoms. The most proximal occlusion sites scored by core lab observers were defined as follows: extracranial ICA from the cervical segment to the clinoid segment; intracranial ICA from the clinoid segment to the ICA terminus; ICA terminus (ICA-T); M1-middle cerebral artery (MCA) from the ICA bifurcation to the MCA bifurcation; M2-MCA from the MCA bifurcation to where the vessels turn from the insula or exit the Sylvian fissure.[18] Proximal occlusion sites used as reference location in this study included the intracranial ICA/ICA-T, M1-MCA, and M2-MCA. In patients with an extracranial ICA occlusion and concomitant intracranial tandem lesion, the most proximal intracranial occlusion site was taken as reference location.

Automated LVO detection

The commercially available LVO detection algorithm (StrokeViewer v2.1.22, NICO.LAB, Amsterdam, The Netherlands) evaluated here is based on a deep learning convolutional neural network and runs within a web-based application hosted on a cloud platform. All CTA series were uploaded in Digital Imaging and Communications in Medicine (DICOM) format and processed separately. The algorithm indicated whether an occlusion was present via a binary output (i.e. LVO detected: 'Yes' or 'No'). In case of a positive LVO finding, an occlusion box was centered around the proximal occlusion site and shown using maximum intensity projection (MIP) reconstructions in axial, coronal, and sagittal views. The threshold for detection of LVO was fixed at a single cut-off value by the developers of the algorithm and could not be adjusted.

Algorithm outcome and image quality assessment

All results generated by the algorithm were inspected by an independent observer who was blinded for all core lab imaging assessments and clinical data. In case of a positive LVO finding, the observer noted the hemisphere and the vessel segment (intracranial ICA/ICA-T, M1, or M2) on which the occlusion box was placed. Cases in which the occlusion box was not correctly placed (e.g. in brain parenchyma or in the unaffected hemisphere) were classified separately. Processing time was recorded as the time between receiving messages that CTA series were successfully uploaded and receiving the results.

CTA scan phase was classified into 1 of 5 phases using a previously described method for which interobserver agreement has also been determined (weighted κ 0.87).[19, 20] For the current study, scans were grouped into arterial (early arterial & peak arterial), equilibrium, or venous (peak venous & late venous) phase. Information on slice thickness, slice overlap, and peak kilovoltage was extracted from DICOM tags.

Statistical analysis

Diagnostic performance for correct detection of LVO and correct assessment of occlusion location was evaluated within each cohort. Performance was reported by means of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) as appropriate. In order to assess the impact of image quality on detection of LVO, we pooled data from the MR CLEAN Registry and PRESTO, and reported diagnostic performance stratified by scan acquisition parameters. Performance per occlusion location stratified by scan acquisition parameters could only be reliably assessed in the MR CLEAN Registry due to the large sample of patients with LVO and heterogeneity of scan protocols used in this cohort. To allow comparison between performance of the current algorithm with those described in prior studies[12-14], we performed a sensitivity analysis in which we excluded patients with M2 occlusions and assessed performance for detection of LVO based on correct identification of the affected hemisphere but not exact occlusion location. Statistical differences in AUC were evaluated using DeLong's method.[21] Results are reported with corresponding 95% confidence intervals (CI). Statistical analyses were performed using R statistical software (version 3.6.1).

Results

CTAs of 1,110 patients in the MR CLEAN Registry (median age [interquartile range], 71 years [60-80 years]; 584 men; 1,110 with LVO) and of 646 patients in PRESTO (median age, 73 [62-81 years]; 342 men; 141 with and 505 without LVO) were successfully processed. Detailed patient and imaging characteristics are summarized per cohort in Supplemental Table 1. Mean processing time of the

algorithm was 4 minutes and 59 seconds (standard deviation: ±1 minute and 12 seconds).

LVO detection

Assessment of diagnostic performance was based on correct identification of the exact location of an LVO or the absence of LVO. In the MR CLEAN Registry, 992/1,110 LVOs were correctly identified by the algorithm resulting in a sensitivity of 89% ([95% CI: 87-91]; Table 1). The algorithm incorrectly indicated absence of LVO in 46 patients, and in 72 patients, the algorithm correctly indicated that LVO was present, but the occlusion box was incorrectly placed (Supplemental Table 2). In PRESTO the algorithm correctly identified 102/141 patients with LVO and 392/505 patients without LVO. This resulted in a sensitivity of 72% (95% CI: 64-80), specificity of 78% (95% CI: 74-81), PPV of 47% (95% CI: 41-54), NPV of 91% (95% CI: 88-93) and AUC of 0.75 ([95% CI: 0.71-0.79]; Table 1). The algorithm incorrectly indicated that LVO was absent in 29 patients with LVO and correctly indicated that LVO was present in 10 patients, but with incorrect placement of the occlusion box (Supplemental Table 3). A total of 113 false positives were counted in patients without LVO, of which the majority M2 occlusions (61/113, 54.0%; Supplemental Table 3).

Table 1. Diagnostic performance for detection of an LVO in the MR CLEAN Registry and PRESTO

	LVO present/ LVO absent	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
MR CLEAN Registry	1110/0	89 (87-91)	n/a	n/a	n/a	n/a
PRESTO	141/505	72 (64-80)	78 (74-81)	47 (41-54)	91 (88-93)	0.75 (0.71-0.79)

Sensitivity, specificity, PPV, and NPV are presented as percentages. LVO: large vessel occlusion; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve.

In the sensitivity analysis, patients with M2 occlusions were excluded and correct identification of the affected hemisphere was used to assess diagnostic performance. By doing so, we report the performance for detection of ICA/ICA-T and M1 occlusion, and correct detection of LVO by the algorithm was based on identifying the affected hemisphere but not the exact occlusion location. This resulted in a sensitivity of 96% (912/952, [95% CI: 94-97]) in the MR CLEAN Registry and, a sensitivity of 93% (71/76, [95% CI: 85-98]) and specificity of 78% (392/505; [95% CI: 87-92]) in PRESTO.

Sensitivity per occlusion location

For ICA/ICA-T occlusions, the algorithm yielded a sensitivity of 88% (243/276, [95% CI: 84-92]) in the MR CLEAN Registry and 80% (12/15, [95% CI: 52-96]) in PRESTO (Table 2). The highest detection rate was observed for M1 occlusions with a sensitivity of 94% (636/676, [95% CI: 92-96]) in the MR CLEAN Registry and 95% (58/61, [95% CI: 86-99]) in PRESTO. For M2 occlusions, a lower detection rate was observed than for other vessel segments and differed between the two study cohorts with a sensitivity of 72% (113/158, [95% CI: 64-78]) in the MR CLEAN Registry and 49% (32/65, [95% CI: 44-79]) in PRESTO. In patients who had an extracranial ICA occlusion with concomitant intracranial tandem lesion, the algorithm correctly detected 35/40 (87.5%) intracranial lesions.

Table 2. Sensitivity per occlusion location in the MR CLEAN Registry and PRESTO

	ICA/ICA-T		**M1**		**M2**	
	N	Sensitivity (95% CI)	N	Sensitivity (95% CI)	N	Sensitivity (95% CI)
MR CLEAN Registry	276	88 (84-92)	676	94 (92-96)	158	72 (64-78)
PRESTO	15	80 (52-96)	61	95 (86-99)	65	49 (37-62)

Sensitivity is presented as percentage. ICA: internal carotid artery; ICA-T: internal carotid artery terminus; M1: M1 segment of the middle cerebral artery; M2: M2 segment of the middle cerebral artery.

Impact of scan acquisition parameters on performance

Slice thickness of ≥2mm had a negative impact on diagnostic performance of the algorithm compared to <1 mm (AUC 0.71 vs. 0.83, p<0.01) and 1-2 mm scans (AUC 0.71 vs. 0.85, p<0.01; Supplemental Table 4). Lower diagnostic performance was also observed for venous scan phase compared to equilibrium (AUC 0.75 vs. 0.87, p=0.02), but not compared to arterial scan phase (AUC 0.75 vs. 0.82, p=0.14). Sensitivity per occlusion location within different subgroups was only evaluated within the MR CLEAN Registry. This revealed that increasing slice thickness, no slice overlap, and later scan phase resulted in a lower sensitivity

for detection of M2 occlusions but not for detection of ICA/ICA-T and M1 occlusions (Supplemental Table 5).

Discussion

This study evaluated the diagnostic performance of an automated LVO detection algorithm based on deep learning in a large cohort of patients with and without LVO, demonstrating overall high performance for the detection of intracranial LVOs. Differences in detection rate were seen between occlusion sites and based on image acquisition parameters.

Studies on the diagnostic performance of human readers generally show a high detection rate for occlusions in the ICA/ICA-T and M1 segments, with sensitivities ranging from 89% to 97%[5, 22], which is comparable to the sensitivity found here. Human diagnostic error for more distal, in particular M2, occlusions is notably higher with a reported sensitivity of only 65% in one study[7], similar to the sensitivity of local radiologists in PRESTO.[23] This indicates a large potential for improvement of detection of M2 occlusion. For the algorithm evaluated here, we found a clear difference in detection of M2 occlusion between both cohorts. This was most likely the result of the selection of the MR CLEAN Registry population, where all occlusions, including M2 occlusions, were already identified by human readers and where patients were referred for EVT. In contrast, PRESTO represents a real-world stroke cohort including patients prior to imaging assessment and reflects the distribution of LVOs as encountered in daily clinical practice. As a consequence a broader spectrum of M2 occlusions is included in PRESTO, even those more difficult to detect for human readers. This makes it a more suitable target population for evaluating the diagnostic performance of the algorithm in a real-world setting.[24] The sensitivity of the algorithm for detection of M2 occlusion in PRESTO was lower than that of human readers.

The algorithm also provided a lower specificity than human readers (78% vs. 86-97%).[5, 22] When evaluating the diagnostic performance of LVO detection algorithms, however, it is important to put performance measures into a clinical context and thereby also consider the prior probability of LVO in patients undergoing CTA due to suspected acute ischemic stroke.[25] For LVO detection, a false positive result means the radiologist and stroke team wrongfully receive an alert of a potential LVO finding on CTA prompting fast imaging assessment. A false negative result wrongfully indicates no LVO is present, potentially providing false reassurance and delaying further CTA evaluation by a radiologist. While false positives may be a nuisance for clinicians, false negatives may delay initiation of treatment and possibly be harmful for patients. Efforts should therefore be aimed at achieving a high sensitivity for detecting LVOs along with an acceptable specificity. On the other hand, previous studies including PRESTO

have shown that the prior probability of anterior circulation LVO on CTA in patients with suspected acute ischemic stroke is relatively low and lies within the range of 16-21%.[23, 26] This means that, despite the specificity of 78% of the current algorithm, true positives will occur just as frequently as false positives when implementing this algorithm in a real-world setting as indicated by the PPV of 47% in PRESTO.

An elegant feature of the current algorithm mitigating this issue is placement of a box around the exact location where it detects an occlusion. This direct detection method allows inspection of what triggered the algorithm to come to its decision, providing users with transparency and directing them to (pathological) features that led to the output.[27] By doing so, users can quickly distinguish true positive from false positive results. Other algorithms notify users in case of a positive LVO finding and provide more indirect information (e.g. brain regions with reduced vessel density) on how the decision was reached.[10, 13, 28] The current algorithm thus has the potential to aid in locating the exact occlusion site. This can be especially useful for less experienced readers and possibly aid in early detection of LVO thereby also accelerating diagnosis. It further allows remote access to output both at the primary stroke center and also the nearest EVT-capable intervention center. This may help to expedite decision-making about EVT and enrollment in clinical trials. Such algorithms thus hold potential to increase patient benefit of EVT as treatment of LVO is known to be highly time sensitive.[3]

Recent studies have reported performance metrics of other commercially available LVO detection algorithms. For detection of LVO, a sensitivity of 96% and specificity of 98% has been reported for the RAPID-LVO[12], a sensitivity of 82% and specificity of 90% for Viz LVO[13], and a sensitivity of 84% and specificity of 96% for e-CTA[14]. However, direct comparisons of performance of these algorithms with the current algorithm are difficult to make due to discrepancies in study design. Studies evaluating RAPID-LVO and Viz LVO excluded M2 occlusions in their analyses, for which it has been shown that these algorithms yield lower detection rates.[13, 28] In addition, diagnostic performance was based on either presence or absence of LVO with[12, 14] or without[13] correct identification of the affected hemisphere, whereas we assessed performance based on correct identification of the exact location of LVO or the absence of LVO. Not including M2 occlusion as LVO and assessment of performance not based on the exact location of the occlusion leads to higher detection rates of LVO as shown in our sensitivity analysis. Other factors contributing to differences in performance are varying inclusion criteria and patient populations. Some studies used curated datasets[12, 14] and others a real-world stroke population.[13] This may lead to differences in the distribution of LVO locations and, because of varying detection rates by occlusion location, overall performance measures. As demonstrated in the current study, the sensitivity of the algorithm for detection

of LVO was considerably higher in the MR CLEAN Registry compared to PRESTO mainly due to the higher proportion and broader spectrum of M2 occlusions in the latter cohort.

However, diagnostic performance of LVO detection algorithms should preferably be assessed in a real-world stroke population such as PRESTO as it provides a more reliable estimation of the potential of the algorithm in a clinical setting. Nevertheless, benefits of using the MR CLEAN Registry here was that CTAs were acquired with a variety of acquisition protocols. This allowed us to show that image acquisition parameters such as slice thickness and CTA scan phase significantly impact algorithm performance, and that high-quality input data is a prerequisite for adequate diagnostic performance. This was most evident for the detection of M2 occlusions, likely due to the smaller caliber, branching pattern, and tortuosity of these vessels, making vascular segmentation more susceptible to errors. Especially for M2 occlusions, it is possible that other acquisition schemes such as multiphase CTA leads to better detection by automated algorithms[10] like what is seen for M2 occlusion detection by human readers.[29]

Strengths of this study include the large sample size of LVOs, allowing us to assess diagnostic performance both for overall detection of an LVO and per individual occlusion location with sufficient precision. By including CTAs from a variety of hospitals (>50) using different acquisition protocols, we were able to investigate the impact of scan acquisition parameters on performance. Also, the current evaluation was conducted independently of commercial developers and their affiliates. A limitation of this study is that the evaluation was carried out retrospectively and we were therefore not able to assess the impact of the current LVO detection algorithm on decision-making and treatment parameters.[30] Also, we were not able to reliably compare performance of the current algorithm to those described by others mainly due to the use of different test sets. If feasible, head-to-head comparisons of different algorithms within the same test set will ultimately allow for more unbiased and reliable comparisons.

Conclusion

The algorithm we evaluated here has a high sensitivity for the detection of proximal anterior circulation LVOs (ICA/ICA-T and M1) on CTA. The sensitivity for M2 occlusion is lower than human assessment in a real-world setting and future efforts should specifically target improvement of M2 occlusion detection. Together with the lower specificity of the algorithm than human readers, critical CTA evaluation by radiologists remains crucial irrespective of algorithm output.

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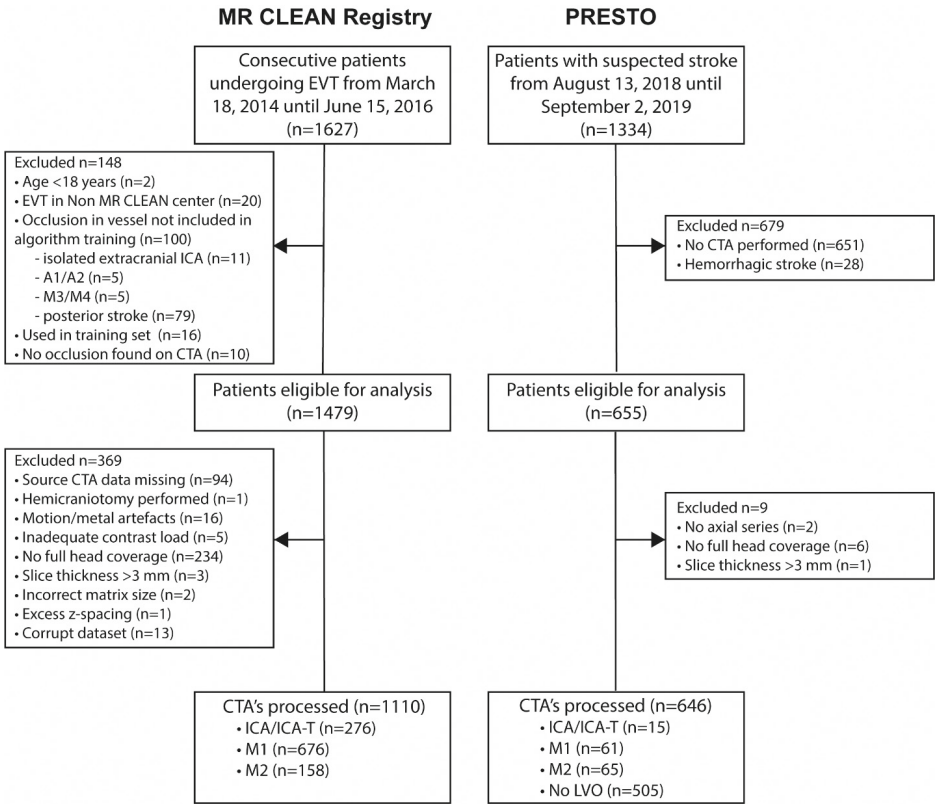
Supplemental material

Figure 1. Patient inclusion and exclusion flowchart



EVT: endovascular treatment; CTA: computed tomography angiography; LVO: large vessel occlusion; ICA: internal carotid artery; ICA-T: internal carotid artery terminus; M1: M1 segment of the middle cerebral artery; M2: M2 segment of the middle cerebral artery; A1/A2: A1 or A2 segment of the anterior cerebral artery; M3/M4: M3 or M4 segment of the middle cerebral artery; MIP: maximum intensity projection; mm: millimeters

Table 1. Patient characteristics per cohort

	MR CLEAN Registry (n=1110)	PRESTO (n=646)
Age, median (IQR)	71 (60-80)	73 (62-82)
Sex, male (%)	584 (52.6)	358 (55.4)
NIHSS at baseline, median (IQR)	16 (12-20)	4 (2-9)
ASPECTS, median (IQR)	9 (7-10)	n/a*
Occlusion side, left (%)	586 (52.8)	74 (45.7)†
Occlusion location (%)		
Extracranial ICA (isolated)	n/a	2 (1.2)†
Extracranial ICA (with tandem lesion)	37 (3.3)	3 (1.9)†
Intracranial ICA	19 (1.7)	5 (3.1)†
ICA-T	256 (23.1)	10 (6.2)†
M1	651 (58.6)	60 (37.0)†
M2	147 (13.2)	63 (38.9)†
M3/M4	n/a	2 (1.2)†
A1/A2	n/a	4 (2.5)†
Vertebral artery	n/a	2 (1.2)†
Basilar artery	n/a	6 (3.7)†
P1/P2	n/a	5 (3.1)†
No occlusion	0 (0.0)	484 (74.9)
Slice thickness, mm (%)		
<1	503 (45.3)	453 (70.1)
1-2	304 (27.4)	128 (19.8)
≥2	303 (27.3)	65 (10.1)
Slice overlap (%)		
Yes	821 (74.0)	481 (74.5)
No	289 (26.0)	165 (25.5)
Peak Kilovoltage, kV (%)		
≥120	553 (49.8)	319 (49.4)
<120	557 (50.2)	327 (50.6)
Scan phase (%)		
Early arterial	295 (26.6)	177 (27.4)
Peak arterial	187 (16.8)	316 (48.9)
Equilibrium	296 (26.7)	120 (18.6)
Peak venous	230 (20.7)	28 (4.3)

Table 1. *Continued.*

	MR CLEAN Registry (n=1110)	PRESTO (n=646)
Late venous	102 (9.2)	5 (0.8)

*ASPECTS was not assessed in PRESTO
†Numbers between parentheses are percentages of total amount of patients with an occlusion (n=162)
NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; ICA: internal carotid artery; ICA-T: internal carotid artery terminus; M1: M1 segment of the middle cerebral artery; M2: M2 segment of the middle cerebral artery; mm: millimeters; kV: kilovoltage.

Table 2. Cross-table with occlusion location indicated by the algorithm (rows) versus reference (columns) in the MR CLEAN Registry

	Intracranial ICA/ICA-T	M1	M2	No LVO	Total
Intracranial ICA/ICA-T	243	5	0	0	248
M1	3	636	4	0	643
M2	0	0	113	0	113
No LVO	8	13	25	0	46
Box in affected hemisphere, but not on vessel	11	14	11	0	36
Box in unaffected hemisphere	11	8	5	0	24
Total	276	676	158	0	1110

ICA: internal carotid artery; ICA-T: internal carotid artery terminus; M1: M1 segment of middle cerebral artery; M2: M2 segment of middle cerebral artery; LVO: large vessel occlusion.

Table 3. Cross-table with occlusion location indicated by the algorithm (rows) versus reference (columns) in PRESTO

	Extracranial ICA	Intracranial ICA/ICA-T	M1	M2	M3/M4	A1/A2	Vertebral artery	Basilar artery	P1/P2	No LVO	Total
Intracranial ICA/ICA-T	1	12	0	0	0	0	0	0	0	4	17
M1	1	0	58	0	0	0	0	0	0	20	79
M2	0	0	0	32	0	1	0	0	0	60	93
No LVO	0	2	0	27	2	3	1	6	4	376	421
Box in affected hemisphere, but not on vessel	0	1	0	3	0	0	0	0	1	0	29
Box in unaffected hemisphere	0	0	3	3	0	0	1	0	0	24†	7
Total	2	15	61	65	2	4	2	6	5	484	646

†Patients without LVO and no affected hemisphere
ICA: internal carotid artery; ICA-T: internal carotid artery terminus; M1: M1 segment of middle cerebral artery; M2: M2 segment of middle cerebral artery; LVO: large vessel occlusion.

Table 4. Diagnostic performance for LVO detection according to imaging quality in pooled cohort (MR CLEAN Registry and PRESTO)

	LVO present/ LVO absent	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Slice thickness, mm				
<1	603/353	86 (83-89)	80 (75-84)	0.83 (0.81-0.86)
1-2	331/101	89 (85-92)	81 (72-88)	0.85 (0.81-0.89)
≥2	317/51	88 (84-91)	55 (40-69)	0.71 (0.64-0.78)
Slice overlap				
Yes	932/370	87 (85-89	80 (75-84)	0.84 (0.81-0.86)
No	319/135	88 (84-91)	72 (63-79)	0.80 (0.76-0.84)
Peak Kilovoltage, kV				
<120	633/251	87 (84-90)	78 (72-83)	0.82 (0.80-0.85)
≥120	618/254	88 (85-90)	78 (72-83)	0.83 (0.80-0.86)
Scan Phase				
Arterial	589/386	88 (85-90)	77 (72-81)	0.82 (0.80-0.85)
Equilibrium	323/93	90 (86-93)	84 (75-91)	0.87 (0.83-0.91)
Venous	339/26	84 (80-88)	65 (44-83)	0.75 (0.65-0.84)

Sensitivity and specificity are presented as percentages. LVO: large vessel occlusion; AUC: area under the curve; mm: millimeters; kV: kilovoltage.

Table 5. Sensitivity per occlusion according to imaging quality in the MR CLEAN Registry

	ICA/ICA-T		M1		M2	
	N	**Sensitivity (95% CI)**	**N**	**Sensitivity (95% CI)**	**N**	**Sensitivity (95% CI)**
Slice thickness, mm						
<1	117	89 (82-94)	303	93 (89-95)	83	78 (68-87)
1-2	78	83 (73-91)	187	96 (92-98)	39	72 (55-85)
≥2	81	89 (80-95)	186	94 (90-97)	36	56 (38-72)
Slice overlap						
Yes	191	87 (82-92)	508	94 (92-96)	122	75 (66-82)
No	85	89 (81-95)	168	93 (89-97)	36	61 (43-77)
peak Kilovoltage, kV						
<120	132	86 (79-92)	344	94 (90-96)	81	74 (63-83)
≥120	144	90 (83-94)	332	95 (92-97)	77	69 (57-79)
Scan phase						
Arterial	108	89 (81-94)	298	96 (93-98)	76	79 (68-87)
Equilibrium	68	91 (82-97)	183	95 (90-97)	45	73 (58-85)
Venous	100	85 (76-91)	195	91 (86-95)	37	54 (37-71)

Sensitivity is presented as percentage. ICA: internal carotid artery; ICA-T: internal carotid artery terminus; M1: M1 segment of middle cerebral artery; M2: M2 segment of middle cerebral artery; mm: millimeters; kV: kilovoltage

Chapter 7

General Discussion

The overall aim of the research described in this thesis was to improve the prehospital triage and diagnostic work-up of patients with suspected stroke. In this final chapter, I discuss the main findings of this thesis, the strengths and limitations, clinical implications and future perspectives.

Interpretation of main findings

1. Which factors influence the direct notification of emergency medical services by patients with acute stroke?

To facilitate fast presentation in the hospital and thereby fast reperfusion treatment, rapid notification of emergency medical services (EMS) after noticing stroke symptoms is crucial. Chapter 2 demonstrated that the majority of patients with suspected stroke in the PRESTO study do not call EMS directly after noticing stroke symptoms, but instead call the general practitioner (GP). Higher scores on the FAST test, notification outside office hours and more rapidly seeking medical attention were associated with directly alerting EMS. In Dutch clinical practice, GPs are often familiar to the patient and easily approachable, which might be the reason patients most often call the GP first, despite awareness campaigns to call EMS.[1, 2] EMS are more often called outside office hours, probably because the GP practice is closed at that time. A higher FAST score was associated with directly alerting EMS and shorter onset-to-alarm times whereas the National Institutes of Health Stroke Scale (NIHSS), a more extensive clinical tool to quantify stroke symptom severity, was not. FAST symptoms might be recognized more easily or experienced as a medical emergency compared to other deficits captured by the NIHSS but not by FAST.

2. How sensitive are prehospital stroke scales for the detection of different intracranial large vessel occlusion locations?

Patients with ischemic stroke due to large vessel occlusion (LVO) often have more severe neurologic deficits with more often cortical signs compared to ischemic stroke patients without LVO.[3] In Chapter 3, I showed that prehospital stroke scales are less sensitive to detect more distal occlusions in a retrospective cohort of patients treated with endovascular thrombectomy (EVT). This suggests that M2 occlusions will often be missed in a prehospital setting if stroke scales are used for triage of suspected stroke patients to be brought directly to an intervention center.[4]

3. What is the in-field performance of prehospital stroke scales?

"The Mission: Lifeline-Severity-based Stroke Triage Algorithm for EMS" of the American Heart Assocation/American Stroke Association (AHA/ASA) recommends direct transport to an intervention center in patients with suspected LVO based on a validated prehospital stroke scale if the travel time to the closest intervention center is less than 30 minutes.[5] The AHA/ASA guidelines of 2019 stated: "there is insufficient evidence to recommend one scale over the other or a specific threshold of additional travel time for which bypassing a general hospital is justified."[6] At that time, only the Rapid Arterial oCclusion Evaluation (RACE) Scale was validated in the field.[7-10] In Chapters 4.1 and 4.2, I described the protocol and results of the PRESTO study, a multicenter, prospective, observational cohort study in which eight prehospital stroke scales were validated.[11, 12] Chapter 4.2 showed that RACE, Gaze-Face-Arm-Speech-Time (G-FAST) and Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST) were the best performing scales and approached the performance of the physician-assessed NIHSS. The scales' performance was slightly better in PRESTO compared to a similar Dutch study, the Leiden Prehospital Stroke Study (LPSS), performed in an adjacent region.[13] This could be caused by different inclusion criteria and a different approach to the analysis of neuro-imaging data. The investigators of the LPSS included all suspected acute stroke patients and did not exclude patients who presented more than six hours after last-seen-well. PRESTO restricted inclusions to suspected stroke patients with a positive Face-Arm-Speech-Time (FAST) test who presented within six hours after last-seen-well. Moreover, neuro-imaging of PRESTO patients was reassessed by expert neuroradiologists to validate the prehospital stroke scales on the true LVO status, whereas in the LPSS cohort occlusion status was based on local imaging assessments. Nonetheless, both studies confirmed prehospital stroke scales are able to detect LVO with acceptable-to-good accuracy and provided valid estimates about the in-field performance of prehospital stroke scales.

4. What is the impact of prehospital transportation strategies on treatment times and patient flows?

In Chapter 4.3, I emphasized that in decision making about the optimal destination you should balance the potential benefit of expediting EVT by driving directly to an intervention center farther away against the potential harm of delayed treatment with intravenous thrombolytics (IVT) by bypassing the nearest hospital. With prehospital stroke scales, you can estimate the likelihood of having an LVO. However, the optimal destination should be the destination where the patient has the highest likelihood of a good functional outcome. This outcome depends on multiple factors: the likelihood of having an LVO, driving times, in-hospital workflow times and time-dependent treatment effects of IVT and EVT.[14, 15] Therefore, I argue that the ideal strategy for prehospital triage

should not solely be based on a prehospital stroke scale. Instead, a personalized decision model should be used that also considers regional characteristics and the time-dependent treatment effects, for example with a personalized decision tool. In Chapter 5, two approaches of prehospital triage were modeled in a pooled analysis of the PRESTO cohort and LPSS cohort: triage with the RACE score and triage with a personalized decision tool. Their impact was compared with the drip-and-ship strategy in four Dutch ambulance regions. Both triage strategies expedited EVT and decreased interhospital transfers with a relatively small delay in IVT. However, I found that the personalized decision tool that combines a prehospital stroke scale with regional characteristics seems to come with higher rates of overtriage - patients incorrectly triaged to intervention centers - in most regions. Differences in overtriage between these strategies can be explained by geographical characteristics. As every minute EVT expedite yields more treatment benefit than the delay of IVT costs in terms of treatment effect, the model will advise an intervention center more easily in regions with longer (between-hospital) driving times, causing higher rates of overtriage. Only in region Rotterdam-Rijnmond overtriage was similar to the RACE triage. Here, most centers are located closely together in a densely populated area with multiple general hospitals referring for EVT to one intervention center.

5. What is the diagnostic performance of CTA evaluations in daily clinical practice and of an automated LVO detection algorithm in patients with suspected stroke?

Accurate detection of LVO on CTA is crucial to recognize ischemic stroke patients eligible for EVT. In Chapter 6.1, all CTAs performed in the PRESTO study were re-assessed by experienced neuroradiologists or neuro-interventionalists and compared with the assessments of local radiologists to determine the accuracy of LVO detection in clinical practice. Proximal intracranial occlusions located in the internal carotid artery, M1 segment of the middle cerebral artery or basilar artery were detected with a high accuracy. However, occlusions of the M2 segment of the middle cerebral artery were often missed.

Machine learning algorithms could be a potential solution for missing LVOs in EVT-eligible patients. In Chapter 6.2, an automated detection algorithm tool was validated on CTAs from the MR CLEAN Registry and PRESTO study. The algorithm showed a high sensitivity in the MR CLEAN Registry and a moderate sensitivity and specificity in the PRESTO data. In both cohorts, the detection rate of proximal LVO was high, but the detection rate for M2 occlusions was lower. In the MR CLEAN Registry, only patients who underwent EVT were included. In the PRESTO study, all CTAs were re-assessed by experienced radiologists. A lot more M2 occlusions were detected during the second reading of experienced radiologists in the PRESTO study. These occlusions were apparently more

difficult to detect for local radiologists. Therefore, a larger number of M2 occlusions was included in the PRESTO study compared to the MR CLEAN Registry. This probably explains the difference in sensitivity of the algorithm between the MR CLEAN Registry and PRESTO.

Strengths and limitations

The analyses in this thesis were performed with data from the PRESTO study, MR CLEAN Registry and LPSS. The MR CLEAN Registry is a large, representative cohort of patients treated with EVT. The PRESTO study and LPSS are large representative cohorts of suspected stroke patients. All neuro-imaging of the PRESTO study and MR CLEAN Registry was re-assessed by imaging core laboratories that consisted of experienced neuroradiologists or neuro-interventionalists. Therefore, most data, except for the pooled data from PRESTO and LPSS, from this thesis were based on the true occlusion status and pre-set definitions regarding the occlusion locations.

Some general limitations need to be considered for this thesis. For the MR CLEAN Registry data, it is important to note that only patients treated with EVT were included. It is likely that some patients with LVO were not treated because the occlusion was not recognized, or because stroke symptoms were too mild to consider treatment. PRESTO was originally designed to validate prehospital stroke scales. Most substudies were post-hoc analyses and were limited to the data that were available. For example, in Chapter 2 - about medical attention seeking by suspected stroke patients - all patients from ambulance region Rotterdam-Rijnmond had to be excluded because the type of ambulance request (patient, GP or other) was often not reported in the ambulance call reports. Finally, both studies were conducted during a time that EVT outside six hours after symptom onset was not implemented yet. Only during the last part of the PRESTO study, EVT was performed beyond six hours in patients that complied to strict perfusion imaging criteria. Therefore, most results described in this thesis only apply to suspected stroke patients in the early time-window of maximally six hours after symptom onset or last seen well.

Clinical implications and future perspectives

Medical attention seeking by suspected stroke patients

Most suspected stroke patients still call the GP as first caregiver, despite awareness campaigns to urgently call EMS. Several studies have shown that campaigns increase the public's stroke knowledge without any effect on the delay between stroke onset and seeking of medical assistance.[16, 17] A time-series study from the United Kingdom showed that repeated television campaigns reduced this delay, because EMS was contacted earlier and more often.[18] I showed there is still room to improve awareness of stroke symptoms and to seek

help immediately by contacting EMS. Since most patients with stroke symptoms have one or more cardiovascular comorbidities, GP visits for cardiovascular risk management might be used to educate patients about stroke alerts on a patient level, but further research is warranted.

Prehospital stroke scales and prehospital triage

Several prehospital stroke scales have been prospectively compared in this thesis and the RACE scale turned out as the best performing scale. However, despite the high AUCs (>0.80), prehospital stroke scales are far from perfect. An AUC >0.80 is considered high and implies excellent performance. However, prehospital stroke scales are in general designed to be used as either positive or negative based on a predefined cut point.[19] In the field, prehospital stroke scales will yield a certain score, which results in a concomitant sensitivity and specificity to detect LVO, based on the chosen cut point. Even though sensitivity and specificity are important test characteristics, the positive predictive value (PPV) and negative predictive value (NPV) are also important to take into account. PPV, the chance that a patient with a positive scale is truly positive for an LVO, is influenced by the prevalence of LVO in the investigated population. This can be calculated with the following formula:

$$PPV = \frac{sensitivity\ x\ prevalence}{sensitivity\ x\ prevalence + (1 - specificity)\ x\ (1 - prevalence)}$$

The sensitivity and specificity of a test can be very high (for example: both 90%), but if the prevalence of a disease is very low (for example: 1%), the PPV of this test is: (0.9*0.01) / 0.9*0.01 + (1-0.9) * (1-0.01) = 0.08, which implies only 8% of the patients with a positive test truly have the disease. If the prevalence is higher (for example: 10%), the PPV of this test is: (0.9*0.1) / 0.9*0.1 + (1-0.9) * (1-0.1) = 0.5, which implies 50% of the patients with a positive test truly have the disease. The PPV of a test greatly affects the efficiency of a triage strategy and should be taken into account. Besides, by dichotomizing prehospital stroke scales, valuable information on the LVO likelihood will be lost. For example, the RACE scale ranges from 0 to 9 and the usual cut point is 5. The LVO likelihood of patients with RACE 0 is lower compared to patients with RACE 4, but both patient groups will be treated in the same way if one cut point is used. The highest PPV reached with the RACE scale is 0.44, which means the highest likelihood to detect LVO with a prehospital stroke scale in the field is merely 44%. The optimal destination hospital in which a suspected stroke patient has the highest likelihood of a good outcome, depends not only on the prehospital stroke scale score, but also on other variables: driving distances, workflow times

(such as the door-to-needle time, door-to-groin time, door-in-door-out time, and transfer time) and time since symptom onset.[15] The decision for an optimal transportation strategy should be made at the patient level, as previously shown in modeling studies.[14, 15, 20-22] A previously developed personalized decision model showed prehospital triage based on a prehospital stroke scale is justified in most urban and suburban regions.[15] On the other hand, in rural regions with long distances to hospitals, a PPV of 44% does not provide enough certainty of LVO to justify bypassing a primary stroke center with potentially delaying IVT. Implementing a prehospital stroke scale in this context might be harmful. The usefulness of transportation strategies in such circumstances have to be determined prior to implementation to prevent negative effects on outcome. The previously developed decision model can be used to assess this.

The potential impact on patient flows should be determined prior to the implementation of a transportation strategy. Intervention centers should be prepared to receive an increased number of patients, in order to prevent a negative impact on workflows. Modeling based approaches, preferably based on real-world cohorts of suspected stroke patients, can be used to estimate the impact of different transportation protocols, as shown in Chapter 5. Prehospital triage by a personalized decision model is preferred over the use of solely a prehospital stroke scale, to account for multiple factors that influence the optimal transportation choice. An advantage of a personalized decision model over other "rigid" strategies, is that it is adaptive and can be adjusted based on new developments in the field. For example, if the model is built in an application with a connection to the Global Positioning System, real-time driving times can be considered. Also, workflow times can change over time and should be adjusted based on the most recent hospital-specific workflow times. To prevent large shifts in patient flows, the sensitivity of the personalized model can be adjusted to bypass only if the chance of a good clinical outcome (modified Rankin Scale 0-2) is estimated to improve with a predefined level. After implementing a transportation strategy, it is important to evaluate its effect. Prehospital triage data should be linked to hospital data to gain insight in how many patients were triaged, if triage recommendations were adhered to and why paramedics deviated. This will provide additional insight in the changes in patients flows, provided treatment and treatment times. Such a personalized decision model will soon be enrolled in Rotterdam-Rijnmond and Zuid-Holland Zuid within the PRESTO-2 study.

Prehospital stroke scales have only limited detection accuracy. More accurate LVO detection tools might aid prehospital decision-making in the future. Currently, more advanced LVO detection tools are investigated, such as dry-electrode electroencephalography (EEG), transcranial doppler ultrasound, and volumetric impedance phase shift spectroscopy.[23, 24] These tools might be able to provide a more reliable LVO certainty. The ELECTRA-STROKE study, in

which dry-electrode EEG is investigated to detect LVO, is ongoing. The results of the first 100 patients that underwent EEG-recordings in the emergency department showed EEG data were sufficient in only 65/100 patients due to EEG artifacts.[23] However, in the 65 patients with sufficient quality the EEG showed a sensitivity of 100% and specificity of 84% for LVO stroke. Validation in the prehospital setting is ongoing and should be awaited, but it appears EEG recordings is not feasible in a substantial proportion of suspected stroke patients. However, if EEG artifacts can be resolved, this could be a promising tool. Transcranial doppler ultrasound is another tool suggested to detect LVO in the prehospital setting. The main difficulty of this technique is the density of the skull resulting in signal attenuation. So far, few experimental studies have explored the accuracy, but all ultrasound assessments were performed by trained technicians or neurologists, which is not representative for the average paramedic.[25, 26] Volumetric impedance phase shift spectroscopy uses bioimpedance asymmetry scores to predict LVO. Only one study has shown a high accuracy to detect severe stroke, but unfortunately this technique does not seem to be able to distinguish LVO stroke from intracranial hemorrhages.[27] When an alternative LVO detection tool is validated and has been shown to be more accurate than prehospital stroke scales, this can be incorporated in the decision model for more precision. However, until alternative and more advanced LVO detection tools are sufficiently validated and proven feasible in the prehospital setting, clinical scales are the most effective, simple and rapid solutions available at this time.

Maybe the most promising development in the prehospital field is the implementation of mobile stroke units with onboard vascular imaging. No doubt, this will provide the highest accuracy to detect LVO in the prehospital setting and mobile stroke units have already shown to be able to expedite IVT and EVT.[28, 29] However, the implementation of mobile stroke units is costly and though there is evidence MSUs are cost-effective, the cost-effectiveness might be considered on a regional level.[30, 31] Also, unless a few mobile stroke units per region are operational at the same time, mobile stroke units will not be able to cover all stroke alerts and transportation strategies as discussed in this thesis remain necessary.

Imaging assessment of intracranial occlusions

After the patient is transported to the hospital, it is crucial to rapidly assess the presence of an intracranial occlusion. Proximal LVOs were detected by local radiologists with a high accuracy but the difficulty is in detecting M2 occlusions. In Dutch clinical practice, M2 occlusions are often eligible for EVT, so it is crucial to detect all M2 occlusions.[32] All emergency radiologist and neurologists should be regularly educated on LVO detection. To further improve LVO detection, imaging quality should be improved. Photon-counting CT is an

upcoming technology to reduce imaging noise and increase spatial resolution.[33] Multiphase CTA instead of single-phase CTA might improve the diagnostic accuracy for occlusion detection.[34] Also, additional CT perfusion imaging can aid, as perfusion defects might support the CTA evaluation.[35, 36] The machine learning algorithm showed a high sensitivity to detect proximal LVOs such as ICA and M1 occlusions, but low sensitivity for detecting M2 occlusions. At this point, machine learning algorithms cannot replace the clinician's CTA reading, but might be used to support the clinician in the future, especially if algorithms are improving over time.

Conclusion

Most suspected stroke patients still call the GP as first caregiver, despite awareness campaigns to urgently call EMS. Prehospital stroke scores are feasible and can easily be implemented for prehospital triage but they have limited LVO detection accuracy. Prehospital triage strategies have a positive effect on acute stroke treatment when implemented correctly and should always be considered by regional health policy makers. The optimal prehospital triage strategy is context-specific and depends on multiple factors, among which driving times, treatment capabilities of hospitals, hospital-specific workflow times, time since symptom onset, and the likelihood of an LVO. Occlusions of the M2 segment of the middle cerebral artery were often missed by local radiologist and the machine learning algorithm.

Recommendations on future research

Medical attention seeking by suspected stroke patients
There is still room to improve awareness of stroke symptoms and to seek help immediately by contacting emergency medical services. Since most suspected stroke patients have one or more cardiovascular comorbidities, GP visits for cardiovascular risk management might be used to educate patients about stroke alerts on a patient level, but further research is warranted.

Prehospital stroke scales and prehospital triage
Prehospital stroke scales are feasible and can easily be implemented for prehospital triage. Prehospital triage strategies have a positive effect on acute stroke treatment and should always be considered by regional health policy makers. A personalized decision tool is preferred over the use a single prehospital stroke scale because it is adaptive and multiple factors can be taken into account. Because the impact of prehospital triage strategies is context-specific, prehospital triage strategies should be considered with care on a regional level. Feasibility and effectiveness of advanced LVO detection tools and mobile stroke units should be further studied to improve the accuracy of LVO detection in the field and can be incorporated in the personalized decision model. After the implementation of a transportation strategy, it is important to evaluate its effect.

Imaging assessment of intracranial occlusions
LVO detection should be improved, especially of M2 segment occlusions. Neurologists and radiologists should be educated on LVO detection regularly. To improve visibility of occlusions, imaging quality should be improved by the use of photon-counting CT imaging, multiphase CTA, and additional CT perfusion imaging.

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Chapter 8

Summary & Samenvatting

Summary

Ischemic stroke can be effectively treated with acute reperfusion treatments: intravenous thrombolytics (IVT) and endovascular thrombectomy (EVT). However, the effects of both IVT and EVT strongly decline over time. Early recognition of stroke and rapid initiation of these treatments are essential to maximize chances of recovery. This thesis addresses three ways to shorten the time from stroke onset to the start of reperfusion therapy are: 1) preventing patient delay after stroke onset, 2) transportation of suspected stroke patients to the right destination, and 3) improving diagnosis of EVT-eligible stroke with vessel imaging.

A large part of delay in the prehospital setting consists of the time from symptom onset to the first medical contact. Direct notification of emergency medical services (EMS) by patient or bystanders after onset of stroke symptoms helps to facilitate rapid arrival at the hospital and subsequent treatment. Public stroke campaigns instruct people to alert EMS as soon as possible after noticing stroke symptoms, but still several patients with suspected stroke call their general practitioner (GP) first.

Endovascular thrombectomy in patients with an intracranial proximal large vessel occlusion (LVO) can only be performed in specialized intervention centers capable of EVT. IVT can be administered in all stroke centers. Several strategies are proposed for the ambulance transportation of suspected stroke patients. With the drip-and-ship strategy, a patient is presented to the closest hospital for rapid IVT. In case of EVT-eligibility, a subsequent interhospital transfer to an intervention center is arranged. Prehospital stroke scales can be used for prehospital triage to distinguish between patients with a high and a low LVO likelihood for direct transportation to an intervention center or the closest hospital. Using these scales, a more personalized approach is proposed: with the use of a personalized prehospital decision tool, multiple factors can be taken into account to determine the optimal transportation strategy.

Crucial in the treatment of LVO patients is the rapid and accurate detection of LVOs on vessel imaging. However, the accuracy of CTA evaluations in daily clinical practice has never been investigated. In addition, to aid fast CTA evaluation and LVO detection, diagnostic tools with artificial intelligence algorithms have been developed, but their clinical utility has not been evaluated yet.

The overall aim of this thesis was to improve the prehospital triage and diagnostic work-up of patients with suspected stroke. The specific research questions were:

1. Which factors influence the direct notification of emergency medical services by patients with suspected stroke?

2. How sensitive are prehospital stroke scales for the detection of different intracranial large vessel occlusion locations?

3. What is the in-field performance of prehospital stroke scales?

4. What is the impact of prehospital transportation strategies on patient flows and treatment times?

5. What is the diagnostic performance of CTA evaluations in daily clinical practice and of an automated LVO detection algorithm in patients with suspected stroke?

To explore patient and notification characteristics that influence direct notification of emergency medical services and the time to alert, I performed a substudy in the PRESTO data (**Chapter 2**). More than half (52%) of the included patients called the GP instead of EMS. Patients with higher FAST scores, alert outside office hours, and a rapid alert, more often call EMS directly. Patients with diabetes mellitus waited longer to alert. Despite national awareness campaigns, patients with suspected stroke often wait to alert and then call their general practitioner. GP-visits for cardiovascular risk management might be used to educate patients about stroke alerts, but the effectiveness of such an intervention should be investigated.

In **Chapter 3**, I focused on the sensitivity of prehospital stroke scales for different occlusion locations with data from the MR CLEAN Registry. Prehospital stroke scales were most sensitive to detect ICA-T occlusion (sensitivity of 21 to 97% for the different scales), and less sensitive to detect M2 occlusions (sensitivity of 8 to 84%). This implies that prehospital stroke scales are less useful to detect distal occlusions.

Chapters 4.1 and 4.2 describe the design and results of the PRESTO study. In the PRESTO study, I prospectively validated eight prehospital stroke scales in the field in a multicenter observational cohort study. The RACE, G-FAST and G-FAST were the scales with the highest performance to detect LVO. Their performance approached the performance of the physician-assessed National Institutes of Health Stroke Scale. With this study, I provide valuable data on the performance of prehospital stroke scales, when used in the field in an unselected cohort of suspected stroke patients. The results of this study can be used by healthcare professionals and policy makers to decide on the most suitable prehospital stroke scale and threshold to customize prehospital triage to the characteristics of their region. This was further elaborated in **Chapter 4.3**, in which the advantages of a multivariable prehospital decision tool compared to merely a prehospital stroke scale were explored. Prehospital stroke scales

are often used as dichotomized tests, in which triage is performed based on a certain threshold. Multivariable decision models are able to take more factors into account, such as driving times, time since symptom onset, hospital-specific workflow times and the LVO likelihood based on the full range of a prehospital stroke scale.

In **Chapter 5,** I showed prehospital triage with the RACE scale or a personalized decision tool lead to a considerable change in time-to-EVT, against a limited delay for patients receiving IVT. In the evaluated regions, RACE triage was associated with relatively modest overtriage. The impact of transportation strategies depends on multiple factors, such as the distribution of hospitals and their stroke treatment capabilities, population density and regional workflow times. Regional health policy makers should evaluate the optimal strategy prior to implementation.

In **Chapter 6.1**, I compared the CTA evaluations of the local radiologists by the evaluation of the core laboratory, which I used as reference standard. I used imaging data from the PRESTO study, which was evaluated by the local radiologists but also by an expert imaging core laboratory. The accuracy to detect proximal occlusions was high, but distal occlusions were often missed and seemed more challenging to detect. Because of the quickly evolving EVT possibilities, CTA evaluations in the acute setting need to be improved. Furthermore, I investigated the diagnostic performance of an artificial intelligence algorithm for the detection and localization of LVO in **Chapter 6.2.** I used data from the MR CLEAN Registry and PRESTO study and used the expert imaging core lab evaluations as reference standard. The algorithm showed a high sensitivity to detect LVO in the MR CLEAN Registry (89%), and a modest sensitivity in the PRESTO data (72%). The algorithm had a high detection rate for proximal LVOs, but performance varied significantly by occlusion location. Detection of distal occlusions is not sufficient and needs to be improved.

In the general discussion (**Chapter 7**), the results that were presented in this thesis were discussed and the research questions were answered. Based on this thesis, recommendations for clinical practice and future research were formulated. These recommendations include:

Medical attention seeking by suspected stroke patients

- Since most suspected stroke patients have one or more cardiovascular comorbidities, GP visits for cardiovascular risk management might be used to educate patients about stroke alerts on a patient level, but further research is warranted.

Prehospital stroke scales and prehospital triage

- Prehospital stroke scales are feasible and can easily be implemented for prehospital triage.

- A personalized decision tool is preferred over the use a single prehospital stroke scale because it is adaptive and multiple factors can be taken into account.
- Because the impact of prehospital triage strategies is context-specific, prehospital triage strategies should be considered with care on a regional level.
- Feasibility and effectiveness of advanced LVO detection tools and mobile stroke units should be further studied to improve the accuracy of LVO detection in the field and can be incorporated in the personalized decision model.
- After the implementation of a transportation strategy, it is important to evaluate its effect.

Imaging assessment of intracranial occlusions

- LVO detection should be improved, specifically of M2 segment occlusions.
- Neurologists and radiologists should be educated on LVO detection regularly.
- To improve visibility of occlusions, imaging quality should be improved by the use of photon-counting CT, performing multiphase CTA, and CT perfusion imaging.

Samenvatting

Een herseninfarct kan effectief behandeld worden door acute reperfusie behandelingen: intraveneuze trombolyse (IVT) en endovasculaire trombectomie (EVT). Echter, het effect van zowel IVT als EVT neemt snel af over de tijd. Snelle herkenning van een beroerte en snelle initiatie van deze behandelingen zijn essentieel om de kans op herstel te vergroten. Dit proefschrift bespreekt 3 manieren om de tijd van het optreden van een beroerte tot het starten van behandeling te verkorten: 1) het voorkomen van 'patient delay' na het optreden van een beroerte, 2) transport van patiënten met de verdenking op een beroerte naar de juiste bestemming, en 3) het verbeteren van de diagnose van herseninfarcten die in aanmerking komen voor EVT middels beeldvorming.

Prehospitaal bestaat het grootste deel van de vertraging uit de tijd van het optreden van symptomen tot het eerste medische contact. Directe alarmering van 112 door patiënten of omstanders na het optreden van beroerte symptomen versnelt de aankomst in het ziekenhuis en de hierop volgende behandeling. Publieke voorlichtingscampagnes instrueren mensen om zo snel mogelijk contact op te nemen met 112 na het bemerken van beroerte symptomen, maar er zijn nog steeds veel patiënten met de verdenking op een beroerte die eerst hun huisarts bellen.

Endovasculaire trombectomie bij patiënten met een intracraniële proximale occlusie kan alleen verricht worden in gespecialiseerde interventiecentra. IVT kan toegediend worden in alle ziekenhuizen. Er zijn verschillende strategieën voorgesteld voor het transport van patiënten met de verdenking op een beroerte door de ambulance. Met de drip-and-ship strategie, wordt een patiënt naar het dichtstbijzijnde ziekenhuis gebracht voor snelle behandeling met IVT. Indien de patiënt in aanmerking komt voor EVT, wordt de patiënt overgeplaatst naar een interventiecentrum. Prehospitale stroke scores kunnen worden gebruikt als prehospitale triage om patiënten met een hoge kans op een proximale occlusie te onderscheiden van patiënten met een lage kans op een proximale occlusie voor direct transport naar een interventiecentrum. Met behulp van deze scores wordt een gepersonaliseerde benadering voorgesteld: met een gepersonaliseerd prehospitaal beslismodel kunnen meerdere factoren meegewogen worden voor de optimale transport strategie.

Cruciaal voor het behandelen van patiënten met een proximale occlusie is het snel en accuraat detecteren van occlusies op beeldvorming. Echter, de nauwkeurigheid van CTA beoordelingen in de dagelijkse klinische praktijk is nooit onderzocht. Daarnaast zijn er voor het bespoedigen van occlusie detectie diverse 'artificial intelligence' algoritmes ontwikkeld, maar hun klinische betekenis is nog niet onderzocht.

Het doel van dit proefschrift was het verbeteren van prehospitale triage en diagnostische work-up van patiënten met de verdenking op een beroerte. Specifieke onderzoeksvragen waren:

1. Welke factoren beïnvloeden het direct alarmeren van 112 door patiënten met de verdenking op een beroerte?

2. Hoe gevoelig zijn prehospitale stroke scores voor de detectie van verschillende intracraniële proximale occlusie locaties?

3. Hoe presteren prehospitale stroke scores in het veld?

4. Wat is de impact van prehospitale transport strategieën op patiëntenstromen en behandeltijden?

5. Wat is de diagnostische prestatie van CTA beoordelingen in de dagelijkse klinische praktijk en van geautomatiseerde occlusie detectie algoritmes bij patiënten met de verdenking op een beroerte?

Om patiënt- en notificatie karakteristieken te onderzoeken die de directe alarmering van 112 en de tijd tot alarmering beïnvloeden, heb ik een substudie uitgevoerd in de PRESTO data (**Hoofdstuk 2**). Meer dan de helft (52%) van de geïncludeerde patiënten belde eerst de huisarts in plaats van 112. Patiënten met hogere FAST scores, patiënten die alarmeerden buiten kantooruren of die snel alarmeerden, belden vaker direct naar 112. Patiënten met diabetes mellitus wachtten langer tot alarmering. Ondanks nationale voorlichtingscampagnes wachten patiënten met de verdenking op een beroerte vaak af en bellen vervolgens hun huisarts. Huisarts afspraken voor cardiovasculair risico management kunnen gebruikt worden om voorlichting te geven over het optreden van beroerte symptomen, maar de effectiviteit hiervan zal moeten worden onderzocht.

In **Hoofdstuk 3** heb ik mij gefocust op de gevoeligheid van prehospitale stroke scores voor verschillende occlusie locaties in de MR CLEAN Registry. Prehospitale stroke scores waren het meest gevoelig voor carotistop occlusies (sensitiviteit van 21 tot 97% voor de verschillende scores), en minder gevoelig voor M2 occlusies (sensitiviteit van 8 tot 84%). Dit impliceert dat prehospitale stroke scores minder bruikbaar zijn om distale occlusies te detecteren.

Hoofdstukken 4.1 en 4.2 beschrijven de opzet en de resultaten van de PRESTO studie. In de PRESTO studie zijn acht prehospitale stroke scores gevalideerd in het veld in een multicenter observationele cohort studie. De RACE, G-FAST en CG-FAST kunnen een proximale occlusie het best detecteren. Hun prestatie benadert die van de National Institutes of Health Stroke Scale,

uitgevoerd door artsen. Met deze studie toon ik waardevolle data van de prestatie van prehospitale stroke scores in het veld in een ongeselecteerd cohort van patiënten met de verdenking op een beroerte. De resultaten van deze studie kunnen gebruikt worden door zorgprofessionals en beleidsmakers om de beste passende prehospitale stroke score en afkappunt om prehospitale triage aan te passen aan hun regio. Dit is verder toegelicht in **Hoofdstuk 4.3**, waarin de voordelen van een multivariabel prehospitaal beslismodel worden besproken ten opzichte van enkel een prehospitale stroke score. Prehospitale stroke scores worden vaak gebruikt als gedichotomiseerde test, waarbij triage wordt uitgevoerd op basis van een bepaald afkappunt. Multivariabele beslismodellen kunnen meer factoren meewegen, zoals rijtijden, tijd sinds het optreden van symptomen, ziekenhuis specifieke doorlooptijden en de kans op een proximale occlusie op basis van de volledige prehospitale stroke score.

In **Hoofdstuk 5** toon ik dat prehospitale triage met de RACE score of een gepersonaliseerd beslismodel leidt tot een aanzienlijke verandering in tijd-tot-EVT, ten koste van een beperkte vertraging voor patiënten die IVT ontvangen. In de bestudeerde regio's leidde triage middels de RACE score tot relatief bescheiden overtriage. De impact van transport strategieën hangt af van meerdere factoren, zoals de verdeling van ziekenhuizen en hun behandelmogelijkheden, bevolkingsdichtheid en regionale doorlooptijden. Regionale beleidsmakers zouden de optimale strategie moeten evalueren voor de implementatie.

In **Hoofdstuk 6.1** vergeleek ik lokale CTA beoordelingen met de core lab beoordelingen. Hiervoor gebruikte ik de beeldvorming verricht in de PRESTO studie, welke zowel door lokale radiologen als een expert core lab waren beoordeeld. De accuratesse voor de detectie van proximale occlusies was hoog, maar distale occlusies werden vaker gemist en blijken lastiger te detecteren. Vanwege de snelle ontwikkeling van EVT mogelijkheden, is er ruimte voor verbetering van CTA beoordelingen in de acute setting. Daarnaast onderzocht ik de diagnostische prestatie van 'artificial intelligence' algoritmes voor de detectie en lokalisatie van proximale occlusies in **Hoofdstuk 6.2**. Hiervoor gebruikte ik data van de MR CLEAN Registry en PRESTO studie en gebruikte ik de expert core lab beoordelingen als gouden standaard. Het algoritme had een hoge sensitiviteit voor de detectie van occlusies in de MR CLEAN Registry (89%), en een matige sensitiviteit in de PRESTO data (72%). Het algoritme had een hoge detectiekans voor proximale occlusies, maar de prestatie verschilde significant per occlusie locatie. De detectie van distale occlusies door dit algoritme is niet voldoende en moet verbeterd worden.

In de algemene discussie (**Hoofdstuk 7**), worden de resultaten van dit proefschrift bediscussieerd en de onderzoeksvragen beantwoord. Gebaseerd op dit proefschrift werden aanbevelingen voor de klinische praktijk en verder onderzoek geformuleerd. Deze aanbevelingen zijn:

Alarmering van patiënten met de verdenking op een beroerte

- Aangezien de meeste patiënten met de verdenking op een beroerte een of meer cardiovasculaire comorbiditeiten hebben, zouden huisarts bezoeken in het kader van cardiovasculair risicomanagement gebruikt kunnen worden om op patiënt niveau voorlichting te geven over het alarmeren bij beroerte symptomen, maar hier dient verder onderzoek naar gedaan te worden.

Prehospitale stroke scores en prehospitale triage

- Prehospitale stroke scores zijn makkelijk uitvoerbaar en kunnen geïmplementeerd worden voor prehospitale triage.
- Een gepersonaliseerd beslismodel heeft de voorkeur boven het gebruik van een prehospitale stroke score alleen, omdat het meerdere factoren mee kan wegen en aan te passen is.
- Omdat de impact van prehospitale triage strategieën context-specifiek is, moeten prehospitale triage strategieën overwogen worden op regionaal niveau.
- De haalbaarheid en effectiviteit van geavanceerde occlusie detectie tools en mobile stroke units dient verder onderzocht te worden om de accuratesse van occlusie detectie in het veld te verbeteren en op te nemen in gepersonaliseerde beslismodellen.
- Na de implementatie van een transport strategie is het belangrijk om het effect hiervan te evalueren.

Beoordeling van intracraniële occlusies op beeldvorming

- Er is ruimte voor verbetering van occlusie detectie, specifiek voor M2 occlusies.
- Neurologen en radiologen dienen regelmatig bijgeschoold te worden op het gebied van occlusie detectie.
- Om de zichtbaarheid van occlusies te verbeteren, dient de kwaliteit van beeldvorming verbetert te worden middels photon-counting CT, multiphase CTA en CT perfusie.

Appendices

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Other publications

A. Ganesh, R.M. van de Wijdeven, J.M. Ospel, **M.H.C. Duvekot**, E. Venema, A.D. Rozeman, W. Moudrous, K.R.I.S. Dorresteijn, J.J. Hensen, A.C.G.M. van Es, A. van der Lugt, H. Kerkhoff, D.W.J. Dippel, M. Goyal, and B. Roozenbeek; PRESTO Investigators. Evaluating the Diagnostic Performance of Prehospital Stroke Scales Across the Range of Deficit Severity: Analysis of the Prehospital Triage of Patients With Suspected Stroke Study. *Stroke.* 2022 Dec;53(12):3605-3615.

F. Kremers, E. Venema, **M.H.C. Duvekot**, L. Yo, R. Bokkers, G. Lycklama À Nijeholt, A. van Es, A. van der Lugt, C. Majoie, J. Burke, B. Roozenbeek, H. Lingsma, D. Dippel; MR CLEAN Registry Investigators. Outcome Prediction Models for Endovascular Treatment of Ischemic Stroke: Systematic Review and External Validation. *Stroke.* 2022 Mar;53(3):825-836.

M. Goyal, J.M. Ospel, B.J. Kim, N. Kashani, **M.H.C. Duvekot,** B. Roozenbeek, A. Ganesh. A Bayesian Framework to Optimize Performance of Pre-Hospital Stroke Triage Scales. *Journal of Stroke.* 2021 Sep;23(3):443-448.

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* † equal contribution

PhD portfolio

Name:	Martijne H.C. Bansraj-Duvekot
Erasmus MC Department:	Neurology
Albert Schweitzer ziekenhuis Department:	Neurology
Research school:	COEUR
PhD period:	July 2018 – October 2021
Promotor:	Prof.dr. D.W.J. Dippel
Copromotors:	Dr. H. Kerkhoff & dr. B. Roozenbeek

PhD training	Year	Workload (ECTS)
General academic courses		
Principles of Research in Medicine & Epidemiology	2018	0.7
Conceptual Foundation Epidemiologic Study Design	2018	0.7
Introduction to Data-analysis	2018	1.0
Fundamentals of Medical Decision Making	2018	0.7
Biostatistical Methods I: Basic Principles	2018	5.7
Openclinica	2018	0.3
Advanced Topics in Decision-making in Medicine	2019	2.4
Advanced Analysis of Prognosis Studies	2019	0.9
Biomedical English Writing Course for MSc and PhD students	2019-2020	2.0
Research Integrity	2019	0.3
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2019	1.0
CTA course (Rotterdam Stroke Center)	2020	0.3
Presentation at (inter)national conferences		
European Stroke Organisation Conference; Milan (oral and poster presentation)	2019	1.5
Wetenschapsdag Albert Schweitzer Hospital (oral and poster presentation)	2019	1.5
European Stroke Organisation Conference; Vienna (oral and poster presentation)	2020	1.5
Wetenschapsdag Albert Schweitzer Hospital (oral presentation)	2021	1.0
Workshops, research meetings and symposia		
Research meetings neurology, neurovascular research group, radiology	2018-2021	4.0
Workshop MR CLEAN Registry	2018	0.3

PhD training	Year	Workload (ECTS)
COEUR course “Imaging for Ischemic Heart and Brain Disease and symposium “Stroke Center meets Cardiology: Differences between acute interventions in ischemic heart and brain disease”	2018	0.5
Wetenschappelijke vergadering NNW&NNG	2018	0.3
Masterclass Mayank Goyal	2018	0.2
Wetenschappelijke vergadering NNW&NNG	2019	0.3
Workshop MR CLEAN Registry	2019	0.3
CONTRAST Consortium meeting	2019	0.3
Masterclass Michael Hill	2019	0.2
Masterclass James F. Burke	2019	0.2
COEUR course “Advanced Decision making in Vascular Care”	2020	0.5
CONTRAST Consortium meeting	2021	0.3
Teaching activities		
Supervising Master Thesis Dennis van Kalkeren	2019	1.5
Supervising Master Thesis Jasper Daems	2020-2021	1.5
Teaching paramedics (Stroke knowledge and study procedures)	2018-2019	1.0
Teaching medicine students (The neurological examination)	2018-2021	1.0
Other activities		
Peer reviewer International Scientific Journals	2020-2021	1.5

About the author

Martijne Bansraj-Duvekot was born June 19th, 1992 in Rotterdam, the Netherlands. She graduated 'cum laude' from the Erasmiaans Gymnasium in Rotterdam. In 2010, she started studying Medicine at the Erasmus Medical Center in Rotterdam. In 2017 she obtained her medical degree and started working as a neurology resident at the Albert Schweitzer hospital in Dordrecht. As of January 2018, she changed hospitals and started working as a neurology resident at the Erasmus Medical Center in Rotterdam.

In 2018 she was given the opportunity to start her PhD research on prehospital triage of patients with suspected stroke under supervision of professor Diederik Dippel and her copromotors Henk Kerkhoff and Bob Roozenbeek of the departments of Neurology at the Albert Schweitzer hospital and Erasmus University Medical Center. During her PhD research, she coordinated the PRESTO study, of which the results are described in this thesis.

Since 2022, Martijne is in training as a radiologist at the Maasstad hospital in Rotterdam. She lives in Pijnacker (really close to Rotterdam!) with her husband Dyaran and son Daan.