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

Esmee Venema,[1,2] Martijne H C Duvekot,[2,3] Hester F Lingsma,[1] Anouk D Rozeman,[3] Walid Moudrous,[4] Frederique H Vermeij,[5] Marileen Biekart,[6] Aad van der Lugt,[7] Henk Kerkhoff,[3] Diederik W J Dippel,[2] Bob Roozenbeek,[2,7] on behalf of the PRESTO investigators

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For numbered affiliations see end of article.

**Correspondence to**
Esmee Venema;
e.venema@erasmusmc.nl

## ABSTRACT

**Introduction** The efficacy of both intravenous treatment (IVT) and endovascular treatment (EVT) for patients with acute ischaemic stroke strongly declines over time. Only a subset of patients with ischaemic 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** Prehospital triage of patients with suspected stroke symptoms (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 ischaemic 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.

**Trial registration number** NTR7595.

## 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 treatment (IVT) is effective for patients with an ischaemic stroke of <4.5 hours after onset.[1 2] However, the effect of IVT is limited for ischaemic 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 onset of symptoms, but this treatment can only be performed in specialised 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

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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 Severity (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 ischaemic stroke caused by an intracranial LVO in the prehospital setting.

## METHODS AND ANALYSIS

### Study design

Prehospital triage of patients with suspected stroke symptoms (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 ischaemic 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).

### 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 (LimeSurvey GmbH/Carsten Schmitz, https://www.limesurvey.org). 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 (eg, 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 (eg, 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 ischaemic 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 ischaemic 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

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

| Item | 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 |
| 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 | | | 1 | 1 | |
| C. Mild palsy (arm drifts down within 10 s) | | 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 s) | | 1 | | | | 1 |
| D. Severe palsy (not able to lift leg) | | 2 | | | | 2 |
| 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‡ |

*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.
C-STAT, Cincinnati Stroke Triage Assessment Tool; G-FAST, Gaze-Face-Arm-Speech-Test; LAMS, Los Angeles Motor Scale; PASS, Prehospital Acute Stroke Severity scale; RACE, Rapid Arterial oCclusion Evaluation.

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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 (ie, intracranial LVOs) are required for the external validation of predictive models.[24 25] The annual incidence of suspected ischaemic 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 ischaemic stroke due to an LVO, 31% an ischaemic stroke without the presence of an LVO, 9% a transient ischaemic attack (TIA), 10% an intracerebral haemorrhage 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 <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 (eg, ischaemic stroke, haemorrhagic stroke, TIA or stroke mimic) and, if applicable, the location of the intracranial LVO. For ischaemic stroke patients, we will report the given treatment (IVT, EVT or both) and corresponding treatment times, the number of interhospital transfers and the functional outcome after 90 days. Missing values will be imputed with simple imputation based on the mean or mode (if <5% missing) or multiple imputations based on relevant covariates and outcome (if >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 dichotomised, 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 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 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 11 November 2018 under number NTR7595 (www.trialregister.nl). The study started on 13 August 2018 in the region Zuid-Holland Zuid and on 1 September 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,

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will spread towards different directions after presentation in the hospital, a disproportionate number of healthcare providers from a variety of specialisms (eg, 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 healthcare 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 participate as coauthor, 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 interhospital transfers will lead to more efficient use of EMS resources.

**Author affiliations**
[1]Public Health, Erasmus MC University Medical Centre, Rotterdam, The Netherlands
[2]Neurology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands
[3]Neurology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
[4]Neurology, Maasstad Hospital, Rotterdam, The Netherlands
[5]Neurology, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands
[6]Ambulance Service Rotterdam-Rijnmond, Barendrecht, The Netherlands
[7]Radiology & Nuclear Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

**Collaborators** PRESTO Investigators: Diederik WJ Dippel; Bob Roozenbeek; Aad van der Lugt; Hester F Lingsma; Henk Kerkhoff; Anouk D Rozeman; Walid Moudrous; Frederique H Vermeij; Esmee Venema; Martijne HC Duvekot; Cees L Alblas; Laus JJM Mulder; Bruno JM van Moll; Lisette Maasland; Roeland PJ van Eijkelenburg; Marileen Biekart; Frits GJ Weijschede; Bianca Buijck; Amber Hoek; Jeanette Bakker; Erick Oskam; Rezan Demir; Mandy MA van der Zon; Egon D Zwets; Mirjam Woudenberg; Anja Noordam-Reijm; Timo Bevelander; Vicky Chalos; Eveline JA Wiegers.

**Contributors** EV contributed to study conception and design and wrote the manuscript. HFL, DWJD and BR contributed to study conception and design and critical review of the manuscript. MHCD, ADR, HK, WM, FHV, MB and AvdL contributed to study design and critical review of the manuscript.

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