Statistical analysis plan

Prehospital triage of patients with a suspected acute stroke (PRESTO-2)



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List of abbreviations and relevant definitions

CE	Conformité Européene
CTA	Clinical Trial Agreement
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
EVT	Endovascular thrombectomy
Exception consent	Form Care for data Template, in Dutch: Formulier uitzondering toestemming
FAST	Face Arm Speech Time
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation in Dutch: Algemene Verordening Gegevensbescherming
GPS	Global Positioning System
IC	Informed Consent
IVT	Intravenous thrombolytics
IFU	Instruction For Use
LVO	Large vessel occlusion
mRS	modified Rankin Scale
MTA	Material Transfer Agreement
NIHSS	National Institutes of Health Stroke Scale
NWTC	Non-WMO Review Committee; in Dutch: Niet WMO Toetsingscommissie
PSC	Primary stroke center
STA	**Stroke Triage App**
RACE	Rapid Arterial oCclusion Evaluation
ROAZ	Regionaal Overleg Acute Zorg

1. Introduction and rationale

In current practice, patients with a suspected stroke are transported by ambulance to the nearest stroke center capable of administering intravenous thrombolytics (IVT). Patients presenting with a large vessel occlusion (LVO) at presentation in a primary (=non-intervention) stroke center are transferred to an intervention center for endovascular treatment (EVT). Such transfers delay the start of EVT and adversely affect functional recovery. An alternative strategy is to transport all patients with suspected stroke directly to an intervention center. However, this approach may delay treatment with IVT. Triage of patients eligible for EVT in the prehospital setting may reduce the need for interhospital transfers, thereby expediting the time to EVT and improving long-term functional outcomes. The Stroke Triage App (STA) has been developed to provide a substantiated transportation advice to paramedics. The STA provides personalized prehospital triage advice by integrating stroke severity, onset time, GPS-based driving times, hospital-specific workflow metrics, and time-dependent treatment effects. It compares two transportation strategies (transfer to the nearest primary stroke center and transfer to an intervention center) and identifies the strategy which yields the highest estimated probability of achieving a favorable long-term functional outcome.

2. Objective(s)

The overall objective of the PRESTO-2 study is to evaluate the implementation of the Stroke Triage App, a decision support tool designed for individualized prehospital triage of patients with suspected stroke. We defined the following objectives:

1. To assess whether implementation of prehospital triage with the Stroke Triage App reduces the onset-to-groin time in patients with ischemic stroke due to large vessel occlusion, and whether implementation of the Stroke Triage App impacts the onset-to-needle time in patients without a large vessel occlusion.

2. To evaluate implementation of the Stroke Triage App in the intervention region, regarding (1) logistic measures, such as percentage over- and undertriage and patient distribution, (2) patient measures, such as the percentage of IVT/EVT within 4.5 and 6 hours respectively, complications and the distribution of diagnoses such as

intracerebral hemorrhage and the corresponding triage advice, distribution of functional outcome measured with the modified Rankin Scale (mRS) and (3) user measures, such as the number of monthly users of the Stroke Triage App, and compliance amongst paramedics.

3. Study type

For the first specific objective, we will perform an implementation study using a before-and-after intervention design with difference-in-differences analysis. We will use data from an intervention region and a control region.

For the second specific objective, we will describe the prospective observational cohort of patients with a suspected stroke for which the STA is used.

4. Study population

1. All consecutive adult patients (≥18 years) with a clinical diagnosis of ischemic stroke in the 24 months prior and 24 months after implementation of the Stroke Triage App, in the intervention region and the control region.

2. All consecutive adult patients (≥18 years) with a suspected stroke with onset of symptoms within the last 24 hours for whom the Stroke Triage App was utilized by paramedics to facilitate prehospital triage in the 24 months after implementation of the Stroke Triage App in the intervention region.

6. Methods

Paramedics use the Stroke Triage App in the ambulance to obtain routing advice for the patient transport. The primary outcome in objective 1 is the reduction in onset-to-groin time, assessed by calculating the difference-in-differences estimator with a difference-in-differences linear regression model with data from the national Dutch Audit (DASA) registry. With this data, the intervention region will be compared with a control region to adjust for time-dependent improvements in doo- to-groin times. The intervention region consists of the ambulance regions Rotterdam-Rijnmond and Zuid-Holland Zuid. The control region is defined as the ambulance regions

Zaanstreek-Waterland, Kennemerland, Amsterdam-Amstelland and Noord-Holland-Noord. A more detailed description is found in the appendix I of the nWMO protocol.

Regarding objective 2, descriptive analysis will be performed for all suspected stroke patients for whom the Stroke Triage App is used. Prehospital data will be enriched with data from the ambulance call reports and hospital electronic files. Outcomes that will be investigated, are:

1. Logistic metrics
    - Patient distribution, percentage under- and overtriage, correctly bypassed patients
2. Patient metrics
    - Percentage of EVT, IVT, and percentage of treatments within conventional treatment windows (IVT: <4,5 hours, EVT: <6 hours), door- to-groin, door-to-needle times
    - Complications and the distribution of diagnoses such as intracerebral hemorrhage and the corresponding triage advice
    - Distribution of functional outcome measured with the modified Rankin Scale (mRS)
3. User metrics
    - Monthly users of the Stroke Triage App, number of monthly triages, user compliance

7. Burden and risks

The burden on participants is minimal. The study procedures are conducted in the prehospital setting and consist of a brief neurological examination (with two additional items compared to current clinical practice) and transport to a hospital. There is a small risk that standard treatment with intravenous thrombolysis will be minimally delayed, but it is expected that this is outweighed by the time gained to standard treatment with endovascular thrombectomy.

8. Recruitment and consent

Patients are recruited in the prehospital setting by paramedics. Due to the nature of the study, an appeal is made to the exception of Section 7:458(1)(b) of the Dutch Civil Code, as stated in Chapter 5 Section 5.4 of the 2022 Code of Conduct for Health Research, for an exemption for the need of informed consent in accordance with the code of conduct 2022.

9. Statistical analysis plan

A statistical plan for analysis is developed for both objectives.

9.1 Statistical analysis of objective 1: *To assess whether implementation of prehospital triage with the Stroke Triage App reduces the onset-to-groin time in patients with ischemic stroke due to large vessel occlusion, and whether implementation of the Stroke Triage App impacts the onset-to-needle time in patients without a large vessel occlusion.*

For the primary objective, data will be collected from the national stroke care quality registry (the Dutch Acute Stroke Audit (DASA) of the Dutch Institute of Clinical Auditing (DICA)). This dataset contains all patients with a diagnosis of ischaemic stroke from 2022-2025, from all hospitals in the intervention and control region, for the time period before and after implementation of the Stroke Triage App. The Stroke Triage App only considers a direct transfer/bypass to an intervention center when it is used within the time window of 6 hours after symptom onset. Therefore, for this analysis, we will only select patients who were presented at the emergency department within 6 hours after symptom onset. If symptom onset is unknown, patients will be excluded for analysis of the primary outcome.

Missing data

We will report proportions of missing values for all described variables in the baseline characteristics overview. For descriptive analyses, only the crude, non-imputed data will be presented. For regression analyses, missing data will be imputed, with the choice between single and multiple imputation determined by the proportion of missing values and the presumed underlying mechanism of missingness.

Primary effect analysis

The primary outcome measure in objective 1 is the (reduction in) onset-to-groin time. Therefore, only patients with LVO ischemic stroke who are treated with EVT will be selected from the dataset. To avoid duplicate inclusions, we will delete patient data from primary (= non-intervention) stroke centers collected in the DASA registry. Subsequently, for every patient, we will calculate the time-interval between symptom onset and groin puncture (start of EVT).

The primary effect parameter will be a difference in onset-to-groin time with its 95% confidence interval before and after implementation of the Stroke Triage App, compared to a control region, to account for time-dependent improvements. This will be estimated with a difference-in-differences linear regression model. Before analysis, we will check whether the parallel trends assumption is met in both regions by means of a graphical comparison between onset-to-groin times the two regions before implementation, to support the difference-in-differences analysis.

Adjusted for:

- Age
- Sex
- NIHSS

Secondary effect analysis

The secondary outcome

measure for the primary objective will be the change of onset-to-needle time in patients who are treated with IVT. For this purpose, we will select all patients who underwent IVT, excluding the patients who were referred from primary stroke centers (to avoid duplicate inclusions) collected in the DASA registry. Just as with the primary outcome measure, the effect on the secondary outcome measure will be estimated with a difference-in-differences linear regression model. Model adjustment in the linear differences-in-differences model will be similar for the secondary outcome.

9.2 Statistical analysis of objective 2: *To evaluate implementation of the Stroke Triage App in suspected stroke patients in the intervention region, regarding (1) logistic measures, such as percentage over- and undertriage and patient distribution, (2) patient measures, such as the percentage of IVT/EVT within 4.5 and 6 hours respectively, complications and the distribution of diagnoses such as intracerebral hemorrhage and the corresponding triage advice, and (3) user measures, such as the number of monthly users of the Stroke Triage App, and compliance amongst paramedics.*

For the secondary objective, we will use collected data from the STA cohort. This dataset contains data gathered in the ambulance that is entered into the STA, data which are automatically generated by the STA, and data from the hospital electronic files. After the follow-up of the final patients, the last records of the database will be cleaned and checked for completeness within one month. Upon completion, the database will be locked.

Missing data

We will report proportions of missing values for all collected variables. Because the secondary objective only involves descriptive statistics, imputation of missing values is not applicable. Only the crude, non-imputed data will be presented.

Data analysis

The study protocol specified that the STA should be used for all adult patients (≥18 years) with a suspected stroke (based on a positive FAST-test (≥1 point)) with onset of symptoms within the last 24 hours. For these results, data from all adult patients for whom the app was utilized will be included, following an intention-to-treat analysis mimicking clinical practice. Patients for whom the STA was entered after arrival at the emergency department, were excluded from analysis, as this could distort the results of the primary outcome. Patients without a suspected stroke for which the STA was used, were also excluded.

1. Logistic metrics
    - Patient distribution, percentage under- and overtriage, correctly bypassed patients

2. Patient metrics
    - Percentage of EVT, IVT, and percentage of treatments within conventional treatment windows (IVT: <4,5 hours, EVT: <6 hours), door to groin, door to needle times
3. User metrics
    - Monthly users of the Stroke Triage App, number of monthly triages, user compliance

In this objective, data regarding geographical distribution of patients, treatment characteristics (such as IVT/EVT within time windows) and triage characteristics (percentage under- and overtriage, correctly bypassed patients) will be analyzed. An overview regarding patient characteristics will be developed with e.g. age, NIHSS score, LVO yes/no, tension, age, sex, medical history and medication use. In addition, secondary outcomes such as onset to groin, onset to needle times, percentage of treatment within conventional treatment windows, and mRS score at 90 days will be evaluated. Time to treatment for both IVT and EVT will be analyzed and presented, as well as the number of correctly triaged patients. In addition, organizational outcomes such as workflow times will be analyzed. For user metrics, we will investigate the number of monthly STA users, numbers of monthly triages, and user compliance.