Workflow Optimization to Reduce Time to Endovascular Reperfusion for Ultra-fast Stroke Treatment

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Primary objective:• To demonstrate that the DTAS triage workflow involving CBCT results in superior patient outcome in ischemic stroke patients with confirmed Large Vessel Occlusion (LVO) as compared to the conventional CT/MR triage workflow….

Ethical review	Approved WMO
Status	Completed
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON55141

Source
ToetsingOnline

Brief title
WE-TRUST

Condition

- Central nervous system vascular disorders

Synonym
Cerebrovascular accident (CVA), stroke

Research involving
Human

Sponsors and support

Primary sponsor: Philips
Source(s) of monetary or material Support: Philips-sponsored clinical study

Intervention

Keyword: neuroimaging, reperfusion, stroke, workflow

Outcome measures

Primary outcome

The difference in the distribution of ordinal modified Rankin Scale (mRS) scores at 90 ± 14 days follow-up in the ITT population to determine the performance of the DTAS triage imaging workflow involving Stroke CBCT reconstructions by the investigational device in comparison to the conventional CT/MR triage imaging workflow. The 90 day mRS score will be evaluated by a blinded assessor of a pool of blinded assessors (i.e., a specialist with mRS certification) at the local hospital by performing a structured interview of the patient in person using the Rankin Focused Assessment (RFA) structured mRS questionnaire. If subject is unable to return to the clinic for the day 90 ± 14 visit, a (video) call in which the mRS score is assessed by a blinded assessor is preferable to no assessment.

Secondary outcome

Secondary endpoints:

• Median time measurements (and interquartile range) in each study arm for the door-to-arterial puncture time: Time patient arrives at the CSC door to the time the skin of the patient is touched to perform first arterial puncture.

• Median time measurements (and interquartile range) in each study arm for the door-to-reperfusion time: Time patient arrives at the CSC door to the time of successful vessel recanalization (eTICI >= 2b).

• The distribution of ordinal modified Rankin Scale (mRS) scores at 90 ± 14

days follow-up in both arms in the ITD population to determine the difference of the DTAS triage imaging workflow involving Stroke CBCT reconstructions by the investigational device in comparison to the conventional CT/MR triage imaging workflow in all randomized suspected stroke patients

Safety endpoints:

• Report all adverse events, including:

o Mortality and Stroke related mortality at 90 days.

o Symptomatic ICH rates at 24 (-12/+24) hours after randomization. All intracerebral hemorrhages will be classified by the blinded Core Lab using the Heidelberg Bleeding Classification. Symptomatic ICH will be defined as per a modified SITS-MOST definition: Symptomatic intracerebral hemorrhage is defined as local or remote parenchymal hemorrhage type 2, subarachnoid hemorrhage, and/or intraventricular hemorrhage on the 24 (-12/+24) hours post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death.

o Asymptomatic ICH rates at 24 (-12/+24) hours after randomization. All intracerebral hemorrhages will be classified by the blinded Core Lab using the Heidelberg Bleeding Classification. All the intracerebral hemorrhages which are not symptomatic, are classified as asymptomatic.

o Adverse events of special interest are Emboli to Uninvolved territory, Vessel perforation and Vessel dissection. The incidence of these adverse events will be summarized by probability of relationship to investigational device,

comparator (CT/MR), procedure or stroke.

o Adverse events, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational device, comparator (CT/MR) or procedure will be summarized for safety information.

o Adverse device effects, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices or procedure will be summarized for safety information.

o Device deficiencies that could have led to Serious Adverse Events, including any corrective actions taken during the study, if any, will be summarized for safety information.

• For patients that are not part of the Intention-To-Treat population:

• Analysis in the DTAS arm and Control arm to include the following:

o Door-to-diagnostic picture time: Time patient arrives at the Comprehensive Stroke Center door to the time of triage imaging acquisition on which the final diagnosis of the patient is based

o Final diagnosis of the patient (e.g. Non-LVO Stroke, ICH, Stroke Mimics)

o Patient radiation exposure

o For patients with an occlusion not qualifying for the ITT Population:

• Any significant adverse events related to intravenous thrombolysis and/or mechanical thrombectomy

Exploratory endpoints:

• Report median time measurements (and interquartile range) in each study arm (ITT population):

o Door-to-randomization time: Time patient arrives at the CSC door to the time of randomization

o Door-to-imaging time: Time patient arrives at the CSC door to the time of initial triage imaging acquisition (i.e. non-contrast CBCT or CT/MR)

o Randomization-to-imaging time: Time of randomization to the time of initial triage imaging acquisition (i.e. non-contrast CBCT or CT/MR)

o Randomization-to-puncture time: Time of randomization to the time the skin of the patient is touched to perform first arterial puncture

o Door-to-thrombolytics administration time: Time patient arrives at the CSC door to the time of start of thrombolytics administration.

o Onset-to-door time: Time patient last seen well to the time the patient arrives at the CSC door

o Onset-to-arterial puncture time: Time patient last seen well to the time the skin of the patient is touched to perform first arterial puncture

o Onset-to-successful reperfusion (eTICI >= 2b) time: Time patient last seen well to the time of successfull vessel recanalization (based on angiogram).

o EMS call-to-door time: Time from the call to EMS to the time the patient arrives at the CSC door (total ambulance service time)

o CSC notification call-to-door time: Time from notification call to the CSC stroke team to the time the patient arrives at the CSC door

o Imaging-to-thrombolytics administration time: Time from initial triage

imaging acquisition (i.e. non-contrast CBCT or CT/MR) to the time of start of thrombolytics administration.

o Imaging-to-arterial puncture time: Time from initial triage imaging acquisition (i.e. non-contrast CBCT or CT/MR) to the time the skin of the patient is touched to perform first arterial puncture

o Door-to-device deployment (first pass) time: Time patient arrives at the CSC door to the time of device deployment (first pass).

o Imaging-to-successful reperfusion (eTICI >= 2b) time: Time from initial triage imaging acquisition (i.e. non-contrast CBCT or CT/MR) to time of successful vessel recanalization (based on angiogram).

o Arterial puncture-to- successful reperfusion (eTICI >= 2b) time: Time the skin of the patient is touched to perform first arterial puncture to the time of successful vessel recanalization.

o Arterial puncture-to-catheter out time: Time the skin of the patient is touched to perform first arterial puncture to the time of the catheter is taken out (total EVT procedure time)

• Report other clinical outcome related results in each study arm:

o Degree of disability defined as modified Rankin Scale score (scores 0-6) distribution at discharge or 5-7 days post-procedure, whichever comes first, and at 90 ± 14 days

o NIHSS on admission (baseline), 24 hour follow-up, at discharge or 5-7 days post-procedure, whichever comes first, and at 90 ± 14 days

o Functional independence defined as mRS <= 2 at 90 ± 14 days

o Utility-Weighted modified Rankin Scale (UW-mRS) score at 90 ± 14 days

o Dichotomized mRS score (0-2 versus 3-6) at 90 ± 14 days

o Infarct volume evaluated on CT or MRI at 24 hours (-12/+24 hours) after randomization as measured by the blinded Core Lab

o Dramatic early favorable response as defined as an NIHSS score of 0-2 or NIHSS improvement >= 8 points at 24 (+/-12 hours) hours

o Vessel recanalization post procedure defined as expanded Thrombolysis in Cerebral Infarction (eTICI) grade on the end-procedure angiogram as measured by the blinded Core Lab. Successful recanalization is defined as eTICI grade 2b, 2c or 3.

o X-ray radiation exposure used for triage imaging (rule out intracerebral hemorrhage and confirm the LVO) based on CBCT and other imaging (DTAS triage workflow) and CT (conventional triage workflow)

Study description

Background summary

The safety and efficacy of endovascular treatment (EVT) in acute ischemic stroke (AIS) have been demonstrated in several trials [1-6]. The relevance of rapid reperfusion was confirmed in these trials: for each 9 minutes delay in achieving reperfusion, one in every hundred patients undergoing EVT will present a worse outcome measured by modified Rankin scale (mRS) [7]. Other studies determined that for each 30 minutes delay, the chances to achieve a 90 days favorable outcome decrease by 10 to 15% [8]. For this reason, strategies are being developed focused on improving the workflow.

The main hypothesis of our study is that, in patients with suspected large vessel occlusion (NIHSS >=10) within 6 hours from symptoms onset, an ultra-fast triage in the angiography suite involving Cone-Beam CT (CBCT) results in improved long term outcome by reducing workflow times and avoiding over-selection (i.e. inappropriate exclusion of patients who might benefit from

treatment) as compared to the traditional CT or MRI triage workflow.

References:
1. Berkhemer, O.A., et al., A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. New England Journal of Medicine, 2014. 372(1): p. 11-20.
2. Goyal, M., et al., Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. New England Journal of Medicine, 2015. 372(11): p. 1019-1030.
3. Saver, J.L., et al., Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med, 2015. 372(24): p. 2285-95.
4. Campbell, B.C.V., et al., Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. New England Journal of Medicine, 2015. 372(11): p. 1009-1018.
5. Jovin, T.G., et al., Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. New England Journal of Medicine, 2015. 372(24): p. 2296-2306.
6. Goyal, M., et al., Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet, 2016. 387(10029): p. 1723-31.
7. Saver, J.L., et al., Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. Jama, 2016. 316(12): p. 1279-88.
8. Mazighi, M. et al. Impact of Onset-to-Reperfusion Time on Stroke Mortality. Circulation 127, 1980-1985, doi:10.1161/circulationaha.112.000311 (2013).

Study objective

Primary objective:
• To demonstrate that the DTAS triage workflow involving CBCT results in superior patient outcome in ischemic stroke patients with confirmed Large Vessel Occlusion (LVO) as compared to the conventional CT/MR triage workflow.

Secondary objectives:
• To demonstrate that the DTAS triage workflow involving CBCT results in faster door-to-arterial puncture time in ischemic stroke patients with confirmed LVO compared to the conventional CT/MR triage workflow.
• To demonstrate that the DTAS triage workflow involving CBCT results in faster door-to-reperfusion (eTICI >= 2b) time in ischemic stroke patients with confirmed LVO compared to the conventional CT/MR triage workflow.
• To asses the difference in patient outcome between the DTAS triage workflow involving CBCT and the conventional CT/MR triage workflow in all suspected stroke patients

Safety objectives:
• Report all adverse events, including:
o Mortality and stroke-related mortality at 90 ± 14 days
o Symptomatic ICH rates at 24 (-12/+24) hours
o Asymptomatic hemorrhage rates at 24 (-12/+24) hours
o Emboli to uninvolved territory
o Vessel Perforation

o Vessel Dissection
• Report all adverse device effects
• Report all device deficiencies that could have led to a serious adverse event

Safety objectives for patients that are not part of the Intention-To-Treat population:
• Analysis in the DTAS arm and Control arm to include the following:
o Time from Comprehensive Stroke Center door to diagnosis
o Final diagnosis of the patient (e.g. Non-LVO Stroke, ICH, Stroke Mimics)
o Radiation exposure
o For patients with an occlusion not qualifying for the ITT Population:
• Any significant adverse events related to intravenous thrombolysis and/or mechanical thrombectomy

Exploratory objectives:
• To assess whether the DTAS triage workflow involving CBCT results in different time metrics mentioned below in ischemic stroke patients with confirmed LVO compared to the conventional CT/MR triage workflow:

o Door-to-randomization time
o Door-to-imaging time
o Randomization-to-imaging time
o Randomization-to-puncture time
o Door-to-thrombolytics administration time
o Onset-to-door time
o Onset-to-arterial puncture time
o Onset-to-successful reperfusion (eTICI >= 2b) time
o EMS call-to-door time
o CSC notification call-to-door time
o Imaging-to-thrombolytics administration time
o Imaging-to-arterial puncture time
o Door-to-device deployment (first pass) time
o Imaging-to-successful reperfusion (eTICI >= 2b) time
o Arterial puncture-to-successful reperfusion (eTICI >= 2b) time
o Arterial puncture-to-catheter out time

• Report other clinical outcome related results in each study arm:
o Degree of disability defined as modified Rankin Scale score (scores 0-6) distribution at discharge or 5-7 days post-procedure, whichever comes first, and at 90 ± 14 days
o NIHSS on admission (baseline), 24 hour follow-up, at discharge or 5-7 days post-procedure, whichever comes first, and at 90 ± 14 days
o Functional independence defined as mRS <= 2 at 90 ± 14 days
o Utility-Weighted modified Rankin Scale (UW-mRS) score at 90 ± 14 days
o Dichotomized mRS score (0-2 versus 3-6) at 90 ± 14 days
o Infarct volume evaluated on CT or MRI at 24 hours (-12/+24 hours) after randomization as measured by the blinded Core Lab

o Dramatic early favorable response as defined as an NIHSS score of 0-2 or NIHSS improvement >= 8 points at 24 (+/-12 hours) hours
o Vessel recanalization post procedure defined as expanded Thrombolysis in Cerebral Infarction (eTICI) grade on the end-procedure angiogram as measured by the blinded Core Lab. Successful recanalization is defined as eTICI grade 2b, 2c or 3.
o X-ray radiation exposure used for triage imaging (rule out intracerebral hemorrhage and confirm the LVO) based on CBCT and other imaging (DTAS triage workflow) and CT (conventional triage workflow).

Study design

The Workflow Optimization to REduce Time to Endovascular Reperfusion for Ultra-fast Stroke Treatment or WE-TRUST study is a prospective, multi-center, randomized, controlled, open-label, blinded-endpoint trial with an adaptive design. The randomization employs a 1:1 ratio to either
1) Direct To Angiography Suite (DTAS) triage workflow arm involving non-contrast CBCT using Butterfly Recontructor to rule out intracerebral hemorrhage. To select stroke patients with a large vessel circulation ischemic stroke (due to intracranial ICA and/or MCA-M1 occlusion with or without Cervical ICA involvement, excluding MCA-M2 or more distal occlusions) upon the discretion of the physician, imaging with CBCT-A and/or cerebral arteriography and/or DSA and/or any other imaging will be acquired within 6 hours from time last seen well (TLSW) and are potential candidates for mechanical thrombectomy (MT) as per local protocols and guidelines. These patients are part of the Intention-To-Treat population (ITT), in which mechanical thrombectomy (MT) is then directly performed in the same angio suite using a stent retriever if consistent with institutional and regional guidelines and physician*s judgement. Administration of thrombolytics is given according to institutional and regional guidelines.
or:
2) Conventional triage workflow (Comparator) involving CT/MR, CTA/MRA, CT/MR perfusion, as per local standards, i.e., the control arm. Non-contrast CT/MR imaging will be acquired to rule out intracerebral hemorrhage and e.g. CTA/MRA is acquired to select stroke patients with a large vessel circulation ischemic stroke (due to intracranial ICA and/or MCA-M1 occlusion with or without Cervical ICA involvement, excluding MCA-M2 or more distal occlusions) within 6 hours from time last seen well (TLSW) and are potential candidates for mechanical thrombectomy (MT) as per local protocols and guidelines. These patients are part of the Intention-To-Treat population (ITT) and are directly sent to the angio suite to perform mechanical thrombectomy (MT) using a stent retriever if consistent with institutional and regional guidelines and physician*s judgement. Administration of thrombolytics is given according to institutional and regional guidelines.

The randomization process will be performed at the door of the Emergency Department of the Comprehensive Stroke Center, right before sending the patient

to stroke triage. In the randomization process the subjects will be stratified according to:
• Age (<70, >=70)
• Baseline NIHSS (<=15 moderate stroke, >15 severe stroke)
• TLSW (<3 vs. 3-6 hours from symptom onset)
• Type of patient presentation and Thrombolytics previously administered:
o Mothership patients of the Comprehensive Stroke Center, no thrombolytics previously administered
o Transfer patients from Primary Stroke Center, thrombolytics previously administered in primary stroke center
o Transfer patients from Primary Stroke Center, no thrombolytics previously administered in primary stroke center

Mothership patients of the Comprehensive Stroke Center are defined as patients that did not receive prior triage imaging. Transfer patients are defined as patients that have received prior triage imaging.

The Clinical Investigation is completed when the last 90 days follow-up visit of the last subject has taken place.

Intervention

In this investigation the Direct-To-Angio-Suite triage workflow will be studied in comparison with the currently conventional triage workflow involving the CT/MR suite. The patients randomized to the DTAS triage arm will undergo CBCT (and optional CBCT-A) triage imaging, which deviates from normal clinical practice (CT/MR triage workflow).

Patients in the Intention-To-Treat (ITT) population will undergo a CT or MRI scan at 24 (-12/+24) hours to evaluate the infarct volume. At discharge or 5-7 days post-procedure and at 90 ± 14 days post-procedure, the study outcome endpoints (mRS score, NIHSS) are recorded. Patients that do not fulfill the criteria for acute stroke patients with confirmed LVO (i.e. i.e. not fulfill the criteria of the ITT population) will receive treatment as per local clinical practice and will be included in the safety population, which includes assessments at 5-7 days post-procedure and at 90 ± 14 days post-procedure to obtain the mRS and NIHSS scores.

Study burden and risks

The WE-TRUST trial focuses on faster triage and faster treatment of acute stroke patients with a large vessel occlusion (LVO) in the anterior circulation eligible for endovascular treatment (EVT) using a Direct To Angio Suite (DTAS) triage workflow. There are scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit to the patients in the DTAS triage arm. Although the majority of the available studies have shown

that the DTAS is safe, feasible and results in a significant reduction in treatment times and potentially improved long term patient outcome, there is clinical equipoise which warrants this multi-center Randomized Controlled Trial (RCT). Patients participating in the study in the control group (CT/MR arm) will follow the standard workflow and will therefore not benefit individually from participation. For the patients in the control group, the benefit is an advancement in medical knowledge. The research is group-related and cannot be performed without subjects of the proposed category.

Patients in the Intention-To-Treat (ITT) population will undergo a CT or MRI scan at 24 (-12/+24) hours to evaluate the infarct volume. At discharge or 5-7 days post-procedure and at 90 ± 14 days post-procedure, the study outcome endpoints (mRS score, NIHSS) are recorded. Patients that do not fulfill the criteria for acute stoke patients with confirmed LVO (i.e. not fulfill the criteria of the ITT population) will receive treatment as per local clinical practice and will be included in the safety population, which includes assessments at 5-7 days post-procedure and at 90 ± 14 days post-procedure to obtain the mRS and NIHSS scores.

There are certain risks related to the use of the investigational device (Butterfly Reconstructor):

1) Delay in treatment because no images could be made or because the quality of the images was not sufficient.
2) Exposure to additional X-ray dose because a new scan was needed. Possibly, additional contrast medium had to be administered. This is because the image quality of the first scan was not usable.
3) Wrong diagnosis or measurement leading to the wrong treatment or delay in treatment.

The overall residual safety risk for the investigational device for the purpose of the clinical investigation is assessed to be acceptable. The investigational device is safe for clinical use based on the assessment of the individual risk profiles, the overall residual risks and supported by the earlier clinical studies performed. The outcome of the risk management process for the investigational device is that the residual risks for the investigational device are outweighed by the medical benefits. Risks have been included in the patient information letter.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is 18 years of age or older, or of legal age to give informed consent per state or national law
2. Baseline NIHSS score obtained prior to randomization must be equal or higher than 10 points
3. Subjects with no significant pre-stroke functional disability (modified Rankin scale 0 - 2)
4. Subjects suspected of acute ischemic stroke with an estimated arrival time at a stroke center (clinical investigational site participating in this study) < 6 hours from symptom onset. Symptom onset is defined as point in time the patient was last known well (at baseline).
5. Informed consent obtained from patient or his or her legally designated representative (if locally required)
6. Angiography suite immediately available.
7. Endovascular treatment team immediately available (Neurologist, Neurointerventionist, Anesthesiologist, Nursing, Technicians as per local standard practice)

Exclusion criteria

Clinical exclusion criteria:
1. Known hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 3.0.
2. Known Baseline platelet count < 30.000/µL.
3. Baseline blood glucose of < 50mg/dL (< 2.78mmol/l).
4. For patients receiving thrombolysis: severe, sustained hypertension (SBP > 185 mm Hg or DBP > 110 mm Hg). Note: If the blood pressure can be successfully reduced and maintained at the acceptable level using AHA/ASA guidelines recommended medication (including IV antihypertensive drips) [1], the patient can be enrolled.
5. Patients from a transfer center (Primary Stroke Center) with a CT/MR that is not required to be redone in the Comprehensive Stroke Center as per discretion of the physician or per local standards (e.g. CT/MR less then 90 minutes old).
6. Patients in coma (NIHSS item of consciousness >1) defined as totally unresponsive; responding only with reflexes or being areflexic (Intubated patients for transfer could be randomized only in case an NIHSS is obtained by a neurologist prior transportation).
7. Patients with extreme vomiting.
8. Patients that are extremely agitated.
9. Seizures at stroke onset which would preclude obtaining a baseline NIHSS.
10. Serious, advanced, or terminal illness with anticipated life expectancy of less than one year.
11. Patients acquired stroke while in-hospital.
12. History of life threatening allergy (more than rash) to contrast medium.
13. Cerebral vasculitis.
14. Patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, mRS score at baseline must be <=2. This excludes patients who are severely demented, require constant assistance in a nursing home type setting or who live at home but are not fully independent in activities of daily living (toileting, dressing, eating, cooking and preparing meals, etc.).
15. Unlikely to be available for 90-day follow-up (e.g. no fixed home address, visitor from overseas).
16. Patients with unstable clinical status who require emergent life support care.
17. Any condition that, in the judgment of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.
18. Subject participates in a potentially confounding drug or device trial during the course of the study.
19. Woman of childbearing potential who is known to be pregnant on admission.
20. Subject meets an exclusion criteria according to national law (e.g. age, pregnant woman, breast feeding woman)

21. Subject is Philips employee or their family members residing with this Philips employee.

References:

1. Powers, W.J., et al., Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 2019. 50(12): p. e344-e418.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-02-2023
Enrollment:	27
Type:	Actual

Medical products/devices used

Generic name:	Butterfly Reconstructor R1.0
Registration:	No

Ethics review

Approved WMO

Date:	28-01-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	20-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	ClinicalTrials.gov: NCT04701684
CCMO	NL74939.000.21