Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke (CASES)

Statistical Analysis Plan

1 Administrative information

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2 Introduction

The aim of the *Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke* (CASES) trial is to assess the efficacy and safety of immediate carotid artery stenting (CAS) in patients undergoing endovascular treatment (EVT) for intracranial large vessel occlusions (LVOs) and concomitant carotid artery atherosclerotic stenosis.

In this statistical analysis plan (SAP), we describe the design and methodology of the trial and the statistical procedures that will be applied to answer the research questions. The SAP was written before database lock and final analysis. All members of the Steering Committee and SAP writing/review group are blinded to the results of the trial at the time of writing. Please note that, due to word count restrictions, not all pre-specified analyses listed in this SAP may be included in the publication of the primary outcomes of the CASES trial. For instance, certain or all subgroup analyses may be made available in subsequent publications or online.

2.1 Background & rationale

The background and rationale of this trial have been previously described (1). All relevant trial documents, including the research protocol, are accessible on the trial's dedicated website (https://cases-trial.eu/).

2.2 Research questions

The primary objective is to assess the efficacy of immediate CAS among patients with acute ischemic stroke treated with EVT and a severe ipsilateral proximal carotid artery stenosis (>50%) or occlusion of atherosclerotic origin and compare this with the strategy of deferred treatment (including carotid endarterectomy, elective CAS or best medical treatment alone) of the proximal carotid artery stenosis according to the guidelines.

The secondary objective is to compare the safety of the two strategies (immediate CAS versus deferred treatment) regarding the incidence of symptomatic intracranial hemorrhage, recurrent stroke, mortality and early proximal carotid artery re-occlusion.

The tertiary objective is to compare the quality of life and cost-effectiveness of both strategies. A separate, detailed analysis plan will be provided for this latter analysis.

3 Study methods

3.1 Trial design

The CASES trial is a phase 3 international multicenter prospective randomized open-label blinded outcome assessment (PROBE) non-inferiority trial. The study will be performed among EVT-capable stroke centers in the Netherlands and Belgium.

3.2 Randomization

Following verification of eligibility, patients will be randomized by the treating physician before endovascular treatment has started based on the findings on the computed tomography angiography (CTA), or in case of significant doubt or inconclusive CTA results, after the first angiographic run of the carotid artery that confirms the cervical atherosclerotic lesion. Randomization will be performed by a web-based procedure using permuted blocks. Back-up by telephone will be provided. Randomization is stratified by center.

3.3 Blinding

The trial features a PROBE design. Both the patient and treating physicians are aware of the treatment assignment. The 90 days follow-up will be performed by certified research personnel blinded to the treatment allocation. Hence, the primary endpoint will be assessed blindly. The assessment of some secondary endpoints will not be blinded, since imaging will reveal whether

the patient was treated with CAS or not. Information on treatment allocation will be kept separate from the main study database. An independent trial statistician will combine the data on treatment allocation with the clinical data in order to report to the data safety monitoring board (DSMB). The trial steering committee will be kept unaware of the exact results of the interim analyses on efficacy and safety. Only the recommendation to continue, modify or stop the trial will be communicated.

3.4 Replacement of individual subjects after withdrawal

The medical ethical committee approved the use of deferred consent, recognizing that the CASES trial involves the investigation of an acute intervention in an emergency setting for a life-threatening disorder. A deferred written informed consent procedure is foreseen in the study. That is, written informed consent is only asked after the treatment procedure. For every patient without consent, an additional patient will be included. Patients who die before informed consent can be asked for will not be replaced.

3.5 Sample Size

For the sample size calculation, we used data from the Dutch MR CLEAN registry, a nationwide cohort of EVT-treated patients between 2014-2018 (2). Based on the modified Rankin Scale (mRS) distributions in the immediate CAS group (mRS 0: 17.9%, mRS 1: 22.3%, mRS 2: 16.7%, mRS 3: 14.4%, mRS 4: 12.3%, mRS 5: 5.0%, mRS 6: 11.4%) and in the deferred treatment group (mRS 0: 6.9%, mRS 1: 20.2%, mRS 2: 17.9%, mRS 3: 16.4%, mRS 4: 17.2%, mRS 5: 8.0%, mRS 6: 13.4%), we calculated the assumed effect size to be a common odds ratio (cOR) of 1.15 for a shift in favorable direction on the full mRS. The non-inferiority margin was set to a cOR of 0.8, corresponding to an absolute difference of approximately 5% in favorable outcome (mRS 0-2). This is a generally accepted margin in the stroke research community and has recently been used in comparable EVT trials (3, 4). We used Monte Carlo simulations with 5000 runs to calculate the required sample size based on the assumptions above showing that a sample size of 610 patients, would provide 80% power (at a two-sided alpha level of 0.05) to determine that the lower bound of the cOR 95% confidence interval (CI) does not cross the non-inferiority margin of 0.8. Covariate adjustment for major prognostic variables that include age, pre-stroke mRS score, stroke severity, collateral score and time from symptom onset to randomization results in a reduction of at least 15% in the required sample size (n=520) (5, 6). Assuming a crossover rate of 3% in each arm (6% for both groups), necessitates an increase in sample size by factor $1/(1- \%\ \text{crossover})^2 = 1/(1 - 0.06)^2 = 1.13$ (7). Taking crossovers into account, the sample size increases to 588 (520*1.13). Based on the experience of the MR CLEAN NO-IV trial and MR CLEAN-MED trial (8, 9), the number of patients lost to follow-up is expected to be low (0 in both recently completed trials). Assuming a combined percentage of 2% due to loss to follow-up and to erroneous inclusions (for example, the inclusion of patients who appear to have carotid dissection or carotid pseudo-occlusion), the sample size will need to be increased to a total sample size of 600 patients (n= 300 per group).

3.6 Framework

A non-inferiority design will be used. If immediate CAS is not less effective compared to deferred treatment, immediate CAS will become the new standard of care in this group of stroke patients. The justification for a non-inferiority design is as follows: If immediate CAS is not worse compared to the deferred treatment strategy, it will be implemented as standard practice because: 1) it will be highly cost-effective, as no second hospitalization is needed for a carotid revascularization procedure, and 2) the immediate CAS approach is a more patient-friendly approach.

4 Trial population

Inclusion criteria:

To be eligible to participate in this study, a subject must meet all of the following inclusion criteria:

- Acute ischemic stroke due to proximal intracranial occlusion in the anterior circulation (intracranial ICA, M1, proximal M2) on CTA
- Stenosis ≥ 50% according to the North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) criteria (10) or acute occlusion of the ipsilateral cervical carotid artery of presumed atherosclerotic origin on baseline CTA or first DSA run of the common carotid artery
- Eligible for EVT according to the guidelines: EVT within 6 hours of onset or EVT between 6-24 hours after onset based on perfusion CT imaging selection (conform local guidelines)
- Baseline National Institute of Health Stroke Scale (NIHSS) score ≥ 2
- Age >18 years
- Written informed consent (deferred consent)

Exclusion criteria:

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Any intracranial hemorrhage
- Cervical carotid artery stenosis or occlusion due to causes other than presumed atherosclerosis (e.g. carotid artery dissection, floating thrombus, carotid web)
- Any exclusion criterion for EVT according to the guidelines
- Pre stroke disability (defined as a modified Rankin Scale score >2)
- Gastro-intestinal or urinary tract hemorrhage in the preceding 6 weeks
- Severe head trauma in the preceding 6 weeks
- Recent infarction on baseline brain CT in the same vascular territory within the preceding 6 weeks
- Known allergy to aspirin and/or clopidogrel
- Pregnancy
- Participation in another randomized controlled intervention (EVT) trial
- Alberta Stroke Program Early CT Score (ASPECTS) < 6

5 Analysis populations

Three analysis sets will be defined:

1) A **Full Analysis Set (FAS)** which will include all randomized patients who provided informed consent or died before consent could be obtained. Patients will be analyzed according to the intention-to-treat (**ITT**) principle, that is, in the group to which they were randomized.

2) A **Per Protocol set (PPS)** which will include all randomized patients who provided informed consent or died before consent could be obtained and had no major protocol violations. Crossovers will be considered as major protocol violations regardless of the reason provided to crossover. Patients will be analyzed in the group to which they were randomized.

3) A **Safety Set (SS)** which will include all randomized patients. Patients will be analyzed according to the as-treated principle, that is, in the group based on which treatment they actually received.

In a blinded-to-outcome review meeting just before the interim analysis for efficacy and the final database lock, it will be determined which patients will be included in each set. All major protocol deviations that lead to exclusion from the PP set or any other exclusions will be fully documented in the Analysis Sets Specification Document which will be dated and signed before database lock.

The primary and secondary endpoints will be analyzed for the FAS and PPS. In addition, the data from the safety registry will used for a sensitivity analysis of the treatment effect estimates of EVT and CAS vs no CAS on symptomatic intracranial hemorrhage and mortality in the SS.

6 Procedure for accounting for missing, unused and spurious data

We will report the proportion of missing values for all collected variables. For descriptive analyses, only the crude, non-imputed data will be presented. For the efficacy and safety endpoints, a multiple imputation approach is foreseen. Only patients from the FAS will be imputed, the data from the safety registry will not be imputed.

For patients who died within the study period, we will in the first step assign the worst score for the following unassessed clinical outcome measures and use those for analyses:

- For subjects with unassessed National Institute of Health Stroke Scale (NIHSS) scores due to death at the time of assessment, we will assign the worst score (i.e. 42).
- The value “0” will be assigned to unassessed EQ-5D-5L health index that is missing due to death at the time of assessment.

In the second step, a while-alive strategy will be applied to the following endpoints for patients who died within the study period:

- For subjects with unassessed thrombolysis in cerebral infarction (TICI) scores at the time of assessment, we will assign the score TICI 2a such that the endpoint adequate recanalization after EVT will be set to non-adequate.
- For subjects without any stroke before death, we will assign the score 0 (no stroke) for the endpoint any stroke within 90 days.
- For subjects without any recurrent ipsilateral TIA/ischemic stroke before death, we will assign the score 0 (no stroke) for the endpoint recurrent ipsilateral TIA/ischemic stroke within 90 days.
- For subjects without any symptomatic intracranial hemorrhage (according to Heidelberg criteria, see below) before death, we will assign the score 0 (no ICH) for the endpoint Incidence of symptomatic intracranial hemorrhage within 90 days

Note that for the primary efficacy endpoint, death is a part of the score (mRS=6) and does not result in missing data.

A multiple imputation with 10 imputations will be applied. The value 12345 will be used as a seed for all the imputations. In case of computational problems for the large imputation model, primarily 5 times different seed values will be used augmenting the seed number by 1 (12345 to 12349). If computational problems persist, the endpoint with the fewest number of overall events is deleted from the imputation scheme and handled separately later on.

The imputation model will contain the assigned treatment group and the endpoints mRS at 90 days, the NIHSS score at 24 hours and at day 5-7, or at discharge, the TICI score after EVT, final infarct volume on brain CT at 24 hours and arterial occlusive lesion (AOL) score on CTA at 24 hours, carotid artery re-occlusion at 24 hours and 90 days, any stroke within 90 days, symptomatic intracranial hemorrhage (Heidelberg criteria) within 90 days, recurrent ipsilateral TIA/ischemic stroke within 90 days, mortality at 90 days and EQ5D-5L at 90 days. In addition, the covariates used in the primary analysis (age, the pre-stroke mRS score, stroke severity, collateral score and time from symptom onset to randomization) will be added to the imputation model. A full conditional specification method using a regression or logistic regression model, whichever is applicable, will be applied.

Adequate recanalization after EVT will be calculated based on the imputed TICI scores.

In case the efficacy endpoints final infarct volume on brain CT at 24 hours, arterial occlusive lesion (AOL) score on CTA at 24 hours or carotid artery re-occlusion at 24 hours and 90 days is missing due to the fact that the patient died before 24h or 90 days, respectively, the endpoint will be set again to missing. An analysis on only alive patients will be performed for these endpoints.

7 Endpoints

7.1 Primary efficacy endpoint

The primary endpoint is the modified Rankin Scale Score at 90 days after stroke onset. The mRS is a disability scale ranging from 0 (no symptoms at all) to 6 (death) (11). The mRS score is centrally assessed by 2 stroke research nurses by telephone interview, blinded for the treatment allocation.

7.2 Secondary efficacy endpoints

- Excellent functional outcome (mRS score of 0-1) at 90 days
- Good functional outcome (mRS score of 0-2) at 90 days
- Independent ambulation (mRS score of 0-3) at 90 days
- NIHSS score at 24 hours and day 5-7, or at discharge
- Adequate recanalization after EVT (mTICI 2b or higher)
- Final infarct volume on brain CT at 24 hours
- Arterial occlusive lesion (AOL) score on CTA at 24 hours
- Any ischemic stroke within 90 days
- Recurrent ipsilateral TIA/ischemic stroke within 90 days
- Carotid artery re-occlusion at 24 hours and 90 days
- Quality of life (EQ5D-5L) questionnaire at 90 days

For the purpose of health economic evaluation, additional questionnaires will be sent to the study participants at 90 days for measuring loss of productivity (IMTA productivity cost questionnaire (iPCQ)) and medical consumption (IMTA medical consumption questionnaire (iMCQ)).

7.3 Safety endpoints:

- Embolization in new vascular territories during EVT
- Incidence of bradycardia and/or hypotension during CAS
- Incidence of complications at the vascular access site (aneurysm, bleeding, vascular occlusion) within 72 hours after EVT
- Incidence of symptomatic intracranial hemorrhage (sICH) defined as an increase in the NIHSS score of ≥4 points or an increase in the score for an NIHSS subcategory of

≥2 points with presence of parenchymal hemorrhage type 2 according to the Heidelberg criteria[17] within 90 days

- Any intracranial hemorrhage on brain CT at 24 hours, classified according to the Heidelberg criteria[17].
- Any extracranial hemorrhage within 90 days
- Any serious adverse event within 90 days
- Mortality at 90 days

8 Statistical principles and analysis

The statistical analysis will follow the CONSORT guidelines (13). For the primary endpoint, statistical analyses will be performed according to the per-protocol (PP) principle as well as the intention to treat (ITT) principle. Both PP and ITT analyses must demonstrate non-inferiority in order to conclude that immediate CAS during EVT is non-inferior to a deferred treatment strategy.

In our analyses, we will handle the NIHSS score, ASPECTS and EQ5D-5L score as continuous variables.

When multiple imputations have been performed, Rubin's rule will be used for combining the results.

Statistical significance is defined as $p < 0.05$.

8.1 Baseline Characteristics

For the continuous variables, the mean, standard deviation (SD), median, and range will be reported in each treatment group, whichever is appropriate. For the discrete variables, the number of subjects in each category and the percentage with respect to the number of subjects with non-missing information for that item will be reported in each treatment group.

8.2 Protocol deviations

Protocol deviations will be classified as major if they affect the scientific integrity of the trial, are major errors in inclusion criteria, or are likely to have a significant impact on patient safety. Examples include recruitment of patients with non-atherosclerotic carotid artery stenosis (e.g. dissection, pseudo-occlusion) and patients not treated according to treatment allocation (unjustified crossovers). Only major protocol deviations will be reported. Major deviations expressed as numbers or percentages of patients will be reported by randomized arm.

8.3 Efficacy endpoints

8.3.1 Primary endpoint analysis

The primary analysis of the primary efficacy endpoint will be fitted using an ordinal logistic regression model adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time. The primary effect parameter will be expressed by an adjusted common odds ratio (acOR) for a shift in a favorable direction on the full mRS for the treatment group (immediate CAS vs deferred treatment) with a two-sided 95% confidence interval. In case the lower limit of the 95% confidence interval of the acOR is larger than 0.8, the immediate CAS treatment will be considered to be non-inferior to the deferred treatment group. A corresponding p-value for the non-inferiority test will also be reported. Non-inferiority of immediate CAS will only be claimed if both the PP and FAS analysis support the non-inferiority claim. If non-inferiority is shown, a test for superiority will be applied.

As supplementary analyses, also unadjusted estimates will be reported with 95% confidence intervals.

8.3.2 Secondary endpoints analyses

Given the explorative nature of the secondary endpoints, no formal p-values will be reported but only confidence intervals on the effect parameter will be provided.

The endpoints mRS score of 0-1 at 90 days, mRS score of 0-2 at 90 days, mRS score of 0-3 at 90 days, adequate recanalization after EVT (TICI 2b or higher), AOL score on CTA at 24 hours and carotid re-occlusion at 24 hours and 90 days, will be fitted using a logistic regression model adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time. The treatment effect will be expressed by the odds ratio for a shift in a favorable direction on the full mRS for the treatment group (immediate CAS vs deferred treatment) with a 95% confidence interval. Both adjusted and unadjusted analyses will be performed. Note that arterial occlusive lesion (AOL) score on CTA at 24 hours and carotid re-occlusion at 24 hours and 90 days be analyzed on the patients still alive at the particular time points.

The endpoints NIHSS score at 24 hours and at day 5-7, or discharge, final infarct volume on brain CT at 24 hours, and quality of life (EQ5D-5L score) will be analyzed using a linear regression model adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time. The treatment effect will be expressed by the mean difference in the NIHSS scores between the two treatment groups with a 95% confidence interval. Both adjusted and unadjusted analyses will be performed. Final infarct volume on brain CT at 24 hours will be analyzed on the patients still alive at 24h.

The EQ5D-5L health index will be calculated using Boekaert et al, for Belgian patients and Versteegh et al, for Dutch patients (14, 15).

The endpoint arterial occlusive lesion (AOL) score on CTA at 24 hours will be fitted using an ordinal logistic regression model adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time. The effect parameter will be expressed by a common odds ratio for a shift in a favorable direction on the AOL score for the treatment group (immediate CAS vs deferred treatment) with a 95% confidence interval.

8.4 Safety endpoints analyses

The following safety outcomes will be described in the SS by reporting numbers and proportions in each treatment arm:

1. Embolization in new vascular territories during EVT
2. Incidence of bradycardia and/or hypotension during CAS
3. Incidence of complications at the vascular access site (aneurysm, bleeding, vascular occlusion) within 72 hours after the intervention
4. Incidence of symptomatic intracranial hemorrhage (sICH) defined as an increase in the NIHSS score of ≥4 points or an increase in the score for an NIHSS subcategory of ≥2 points with presence of parenchymal hemorrhage type 2 according to the Heidelberg criteria[17] within 90 days
5. Any intracranial hemorrhage on brain CT at 24 hours, classified according to the Heidelberg criteria[17].
6. Any extracranial hemorrhage within 90 days
7. Any serious adverse event within 90 days
8. Mortality within 90 days

In addition, for endpoints 1, 4 to 6 and 8, a logistic regression analysis will be performed and the odds ratio for treatment group with a 95% CI will be reported. In case the overall event rate of any of these endpoints is larger than 10%, also an adjusted analysis will be performed.

There will be corrected for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to randomization time. Note that endpoints 1 to 3, 5, and 7 will not be imputed and an analysis on observed data will be performed.

The data from the Safety Set will be used for a sensitivity analysis of the treatment effect estimates of EVT and CAS vs no CAS on symptomatic intracranial hemorrhage and death.

8.5 Subgroup analyses

Predefined subgroup analyses will be performed to test for interaction between a specific variable and the treatment.

The following subgroups will be investigated:

- Birth sex (Male vs Female)
- Intermediate grade stenosis (50-70%), high-grade stenosis (>70%) versus occlusion of the ICA
- Occlusion location (ICA, M1, M2)
- Collateral score on baseline CTA (0,1,2 and 3)
- Performance of PTA during EVT(yes or no)
- NIHSS stroke scale severity (NIHSS > median versus NIHSS ≤ median)
- Age (>80 years versus ≤ 80 years)
- Onset to groin puncture time (tertiles)
- ASPECT score (>6 versus ≤ 6)
- prior IVT (yes/no)

In the interest of statistical power, for subgroups that are based on a continuous variable, the continuous variable will be used in the statistical analysis of the interaction with treatment (i.e. the whole range of age instead of the categorized variable).

The planned subgroup analyses will focus on the primary endpoint. Analyses of other potential endpoints may be conducted with prior approval from the Data Access and Writing Committee (DAWC) of the Collaboration for New Treatments of Acute Stroke (CONTRAST 2.0) consortium.

8.6 Cost-utility analysis

A cost-utility analysis will be performed to assess the cost-effectiveness of the intervention under study. A separate detailed analysis plan will be available for this analysis.

9 Timing of the analyses

9.1 Interim safety analyses

The trial will be monitored by a data safety monitoring board (DSMB), that will include a vascular neurologist, neuro-interventionist and an independent methodologist/statistician. The role of the DSMB is to monitor the safety of the trial and to provide the steering committee with recommendations on the continuation or termination of the trial. The DSMB will meet once before the first inclusion and thereafter based on the occurrence of mortality and symptomatic intracranial hemorrhages.

For safety interim analyses, the DSMB will evaluate mortality, the incidence of symptomatic intracranial hemorrhage and other endpoints concerning severe adverse events (SAE's). Safety assessments are required after every 5 symptomatic intracranial hemorrhages and after every 10 deaths or otherwise if deemed necessary by the DSMB. In the light of these analyses,

the DSMB will advise the chairman of the Steering committee if, in their view, the randomized comparisons in the trial have provided both (i) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a safety endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

9.2 Interim efficacy analysis

An efficacy interim analysis will be performed after 300 included patients (who gave consent or died before consent could be obtained) have reached their 90-day follow-up. For the efficacy interim analysis, the DSMB will analyze the distribution of mRS scores at 90 days in both arms. The Haybittle-Peto boundary rule for premature termination of the trial will be applied, with a p-value threshold of less than 0.001 (16). Full details of the efficacy interim analysis are described in a separate interim analysis plan.

9.3 Timing of final analysis

After the 90-day follow-up of the final patient, we aim to complete data collection and cleaning within two months, after which the database will be locked. After locking the database, the treatment allocation will be revealed and the primary and secondary analyses will be performed by the study coordinators and principal investigators of the trial, in collaboration with the independent trial statistician. The final results confirmed by the trial statistician will then be shared for consideration with the Executive Committee, the DSMB and then with the Steering Committee of the trial. Within 3 months after obtaining the final results, a manuscript describing the main results of the trial will be submitted for publication.

10 References

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