Statistical analysis plan of the STROKE-CARD outcome paper

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1. Purpose of this document

This document pre-specifies the statistical analyses that will be conducted in the outcome paper of the STROKE-CARD trial to minimise misleading inferences that could arise from post-hoc analyses. It has been written in advance of looking at the 1-year outcome data from the trial and is based on what was specified in the STROKE-CARD design paper.[1] The final version of this plan will be published online in advance of undertaking the principal trial analyses and will be included as an appendix to a relevant paper.[2]

2. Trial design

We conducted this pragmatic randomised, controlled, open interventional phase III trial [ClinicalTrials.gov NCT02156778] at two centres, namely the Departments of Neurology at the Innsbruck University Hospital and the Hospital St. John of God in Vienna. The first patient underwent randomization on 3 January 2014 and the last on 31 December 2017. Details on rationale, design details and eligibility criteria have been previously published.[1] There were no changes to the trial design methods (such as eligibility criteria) after trial commencement. Trial results will be reported according to CONSORT guidelines.

3. Timelines and scope of the trial analysis

Follow-up of patients was completed in December 2018 and adjudication of endpoints is scheduled to be completed by February 2019. Dummy statistical analyses (blinded to the randomised group) will be run from January 2019, according to the plan outlined here, in order to develop analysis code and streamline the final analyses. The main trial data will be analysed from March 2019, with the intention of submitting a paper for publication before May 2019. Presentations at relevant conferences are also planned.

4. Participants

Patients were eligible for enrolment if they were ≥18 years of age and had had an acute ischaemic stroke or a transient ischaemic attack (TIA) of an ABCD2 score ≥3. Ischaemic stroke is ascertained using the American Heart Association criteria based on clinical and imaging features.[3] Patients were excluded if they lived outside the catchment area, reported malignancies or other severe disease with life-expectancy less than one year, reported drug addiction or severe alcohol abuse, or were suffering from permanent severe disability with low probability of successful rehabilitation indicated by a modified Rankin scale (mRS) of 5 at hospital discharge. Written informed consent was obtained from all patients.

5. Interventions

Patients were randomly assigned in a 2:1 ratio in blocks of 4-8 weeks to receive STROKE-CARD care or standard care for 12 months. Standard care has been described previously[4] in detail and involved (i) detailed patient counselling and education about stroke pathophysiology, risk factor management, life style improvement and medication compliance by a stroke specialist, (ii) provision of the complimentary book “After a stroke”, (iii) individual in-hospital advice by a dietitian for patients with diabetes, severe dyslipidaemia, and obesity, and smoking cessation support for heavy smokers, (iv) provision of standardised information materials (e.g. for oral anticoagulation therapy), and (v) provision at discharge of detailed medical reports for the general practitioner as well as the patient containing target levels for risk factor management. On top of standard care measures, STROKE-CARD care involved (i) a three-month outpatient appointment with re-assessment of risk factors and re-evaluation of stroke aetiology, screening for post-stroke complications, other health problems and residual deficits, demand for nursing services and medication intake, and (ii) access to a web-based patient portal for risk factor monitoring, ascertainment of post-stroke complications, and patient empowerment and education.

6. Pre-specified outcomes

All outcomes were pre-specified and are being adjudicated based on pre-specified diagnostic criteria by a committee in which the members are unaware of study-group assignments. The effect of STROKE-CARD care compared to usual care on primary, secondary and safety outcomes will be assessed from the time of hospital discharge until the 12-month visit. The font colours below indicate whether outcomes will be analysed as time-to-event data (**orange**), continuous data (**blue**), or categorical data (**green**).

Co-primary outcomes will be:

1. **the composite cardiovascular outcome** defined as nonfatal ischaemic stroke, nonfatal haemorrhagic stroke, nonfatal myocardial infarction, or vascular death (i.e. sudden cardiac death and death from acute myocardial infarction, ischaemic or haemorrhagic stroke, heart failure, cardiovascular procedures, pulmonary embolism, or peripheral artery disease), and
2. **health-related quality of life** at the 12-month visit (quantified with the EQ-5D-3L overall health utility score calculated from individual 3-level components using rescaled European visual analogue scale weights[5,6]).

Secondary outcomes will be:

1. the **composite outcome of ischaemic stroke, haemorrhagic stroke, or transient ischaemic attack** (defined as transient neurological deficit <24h and absence of DWI positive lesions on MRI),
2. **all-cause mortality**,
3. **individual 3-level components of the EQ-5D-3L questionnaire** (i.e. mobility, self-care, usual activities, no pain or discomfort, no anxiety or depression) comparing people reporting no problems (level 1) with those reporting problems (level 2 and 3) in the respective component at the 12-month visit, and
4. **achievement of target levels of risk factors**, including:
    a. achieving a systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg[7] at the 12-month visit or a systolic blood pressure <130 mmHg and a diastolic blood pressure <85 mmHg at the 12-month visit in patients with diabetes mellitus,[8] renal impairment (defined as estimated glomerular filtration rate <30 mL/min/1.73m^2), or small-vessel disease at baseline,
    b. achieving a HbA_{1c} concentration <7.5% at the 12-month visit in patients with diabetes mellitus at baseline,
    c. having quit smoking by the 12-month visit in patients that had been smokers at baseline,
    d. a reduction in the number of components of the metabolic syndrome from hospital discharge to the 12-month visit as defined by the AHA/NHLBI guidelines,[9] i.e. (i) waist circumference ≥102 cm in men or ≥88 cm in women, (ii) triglyceride concentration ≥150 mg/dL or drug treatment for elevated triglycerides, (iii) HDL cholesterol <40 mg/dL in men or <50 mg/dL in women or drug treatment for low HDL cholesterol, (iv) systolic blood pressure ≥130 mmHg

or drug treatment for elevated blood pressure, and (v) fasting plasma glucose ≥100 mg/dL or drug treatment for elevated blood glucose,

e. being physically active for an average of >90 minutes per week assessed with the Baecke questionnaire[10] based on the questions on the (i) number of hours playing sports per week, (ii) months practicing this sport in a year, (iii) minutes spent walking during leisure time, and (iv) minutes spent cycling during leisure time,
f. taking lipid-lowering medication in all patients except those with an ischaemic stroke or transient ischaemic attack of other determined aetiology (e.g. index event due to vasculitis or carotid artery, vertebral artery or aortic dissection),
g. achieving a LDL cholesterol concentration <100 mg/dL or achieving a LDL cholesterol concentration <70 mg/dL in patients with ischaemic stroke or transient ischaemic attack due to large-artery atherosclerosis or small-vessel occlusion, with other evidence of atherosclerotic vascular disease (i.e. history of coronary heart disease, peripheral arterial disease, or revascularisation procedures) or with baseline diabetes,[11,12]
h. taking anticoagulation or antiplatelet therapy in patients that had been prescribed such medication at hospital discharge,
i. taking anticoagulation in patients with baseline atrial fibrillation, and
j. having spent >70% of follow-up time in the therapeutic range of INR 2-3 in patients with baseline atrial fibrillation that had been taking a vitamin K antagonist during follow-up, estimated from repeat INR measurements during follow-up with the Rosendaal method[13],

5. good functional outcome at 12-month visit defined as **mRS≤2**, and
6. **distribution across mRS categories at 12-month visit** (“shift analysis”).

Adherence to medication (i.e the proportion of days covered ≥ 90%) and the overall number of out-of-schedule consultations of physicians and out-patient hospital services will not be reported as a secondary outcome as planned at initiation of the trial, since these data will not be available.

Safety outcomes will be:

1. **major bleeding** defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 units of whole blood or red cells,[14]

2. **syncopes** (ascertained with self-report and/or review of medical records),
3. **fractures** (validated by review of X-ray imaging),
4. **alanine aminotransferase concentration >150 U/L** (i.e. three times the upper limit of the reference range) at any time point during follow-up,
5. **creatin kinase concentration >570 U/L** (i.e. three times the upper limit of the reference range) at any time point during follow-up,
6. **glomerular filtration rate <30 mL/min/1.73m^2** (i.e chronic kidney disease stages 4 and 5) at the 12-month visit estimated with the CKD-EPI formula[15], and
7. **rhabdomyolysis** defined as increase of creatin kinase concentration >950 U/L (i.e. five times the upper limit of the reference range) under statin therapy without alternative explanations (e.g. acute myocardial infarction, chronic kidney disease, recent fall) and leading to a halt of the prescription of the statin.

7. Sample size

It was estimated that a trial with 2400 patients would be required to detect an absolute risk reduction for the primary composite CVD endpoint from 15% in the control arm to 10% in the intervention arm with 90% power ($\alpha = 0.05$), assuming an attrition rate of 15% (7.5% dropout rate [withdrawal of consent] and a loss-to-follow-up of 7.5%). Since the data monitoring board observed a lower-than-expected attrition rate between January 2014 and June 2017 (<5%), it recommended revising the sample size to 2160 patients. Such a sample size would allow detection a difference of 0.03 points on the EQ-5D-3L overall health utility score (co-primary efficacy endpoint) with 90% power, assuming a standard deviation of 0.2.

No interim analyses have been or will be performed.

8. Overall analysis strategy

The principal analyses will include all patients randomised and will consider them in the groups as randomised (i.e. intention to treat). Recruitment of patients at two different centres will be taken into account by stratifying Cox models regression by centre (allowing for separate baseline hazard functions) or adjusting other types of regression models for centre. Sensitivity analyses will be presented adjusted for baseline covariates (see Section 0). Continuous variables with a distribution incompatible with a normal distribution will be log-transformed for further analysis.

9. Controlling false positive rates

In the analysis of co-primary endpoints, nominal two-sided P values ≤0.05 will be considered to indicate statistical significance, with successful outcome of the trial only being claimed if clinical objectives for both co-primary endpoints are met.[16] We will use the Hochberg procedure[16] to correct for multiple testing in the descriptive analysis (34 tests), analysis of secondary outcomes (19 tests), and analysis of pre-specified subgroups (4 tests). Analysis of the seven safety outcomes will not be corrected for multiple testing.

10. Descriptive analyses

The flow of patients through the trial after randomisation will be reported as a CONSORT diagram[2], including numbers who were randomly assigned, received intended treatment, were lost or excluded after randomisation (with reasons), and were analysed for the co-primary outcomes.

Patients assigned to the STROKE-CARD care will be classified as adherent to the assignment if they had used the web-based patient portal during follow-up and/or had attended the 3-month visits in person (i.e. excluding patients deceased by the time of the 3-month visit and patients who participated in the visit via phone call).

Baseline characteristics for each of the two trial arms will be described as mean (SD), median (IQR) or numbers (%), as appropriate. Logistic regression adjusted for centre will be used to test for differences by trial arm. The following characteristics will be reported:

- Age – years
- Female sex – no. (%)
- Ischaemic stroke as index event – no. (%)
    - Median NIHSS score at hospital admission (IQR)
    - Recurrent stroke – no. (%)
    - Intravenous thrombolysis – no. (%)
    - Mechanical thrombectomy – no. (%)
    - Discharged to rehabilitation centre – no. (%)
- Transient ischaemic attack as index event – no. (%)
    - Median $ABCD_2$ score (IQR)
    - Recurrent TIA – no. (%)
- TOAST classification – no. (%) for each category
- Median duration of hospital stay in days (IQR)

- Median modified Rankin scale prior to index event (IQR)
- Median modified Rankin scale at hospital discharge (IQR)
- Median EQ-5D-3L overall utility score at hospital discharge (IQR)
- Disease history at baseline
    - Coronary heart disease – no. (%)
    - Peripheral vascular disease – no. (%)
    - Revascularisation procedures – no. (%)
    - Hypertension – no. (%)
    - Diabetes mellitus – no. (%)
        - HbA_{1c} at hospital discharge in patients with diabetes – %
    - Atrial fibrillation – no. (%)
- Medication at hospital discharge
    - Lipid-lowering medication – no. (%)
    - Anticoagulation or antiplatelet therapy – no. (%)
    - Anticoagulation in patients with atrial fibrillation – no. (%)
- Systolic blood pressure at hospital discharge – mmHg
- Diastolic blood pressure at hospital discharge – mmHg
- Median time physically active before index event in min/week (IQR)
- Smoking status at baseline – no. (%) for current, ex- and never-smokers
- Median number of metabolic syndrome components at baseline (IQR)
- LDL cholesterol at hospital discharge – mmol/L
- Body mass index – kg/m^2
- Estimated glomerular filtration rate – $mL/min/1.73m^2$

It is planned to provide a supplementary table that compares baseline characteristics of patients recruited at the Innsbruck centre and patients recruited at the Vienna centre.

11. Analysis of time-to-event data

Analysis of time-to-event data will be based on the time from hospital discharge to the occurrence of the event of interest, death, or end of follow-up, whichever will have been first. For patients who will have attended the 12-month examination later than planned (>13 months after hospital discharge), analysis of time-to-event data will be censored at 13 months of follow-up. For patients that will have died by the time of the 12-month examination, any incident non-fatal events before the fatal event will be ascertained by scanning patient hospital records and calling the patient's relatives and general practitioner. Incident outcomes will be summarised – for each trial arm separately – as the number of events, 12-month cumulative incidence, and

Kaplan Meier-Plots with number-at-risk tables. Hazard ratios and 95% confidence intervals will be estimated using Cox regression models stratified by trial centre (Innsbruck, Vienna). The proportional hazards assumption will be checked using Schoenfeld residuals.

12. Analysis of categorical outcomes

Because we expect the dichotomous outcomes analysed to occur frequently (i.e. >10%), thereby complicating the interpretation of odds ratios as a measure of relative risk, the effect of the STROKE-CARD programme on these outcomes will be quantified as incidence rate ratios using Poisson regression with robust error variance.[17] In addition, differences in the distribution of patients across mRS categories at the 12-month visit between the two trial arms will be quantified using ordinal logistic regression ("shift analysis") and presented together with a stacked bar graph. Both types of regression models will be adjusted for trial centre (Innsbruck, Vienna).

13. Analysis of continuous outcomes

For each trial arm, the health-related quality of life score will be summarised as medians interquartile ranges; its distribution will be depicted in a histogram. Given the expected non-normal distribution, the Mann Whitney U-test will be used to test for a difference in the score between the two arms. The difference in the medians will be provided, together with 95% confidence intervals estimated using bootstrapping.

14. Sensitivity analysis

Four sets of sensitivity analyses will be performed for the composite cardiovascular outcome. First, effect sizes will be adjusted for age at hospital discharge, sex, type of index event (stroke vs. transient ischaemic attack), in addition to trial centre (Innsbruck, Vienna). Further adjusted analyses will be reported in case the two trial arms differed according to any other baseline characteristics. Second, a per-protocol analysis will be performed. Third, formal tests of interaction will be performed to investigate any differences in effect sizes across three pre-specified subgroups (men vs. women; age at hospital discharge <70 vs. ≥70 years; stroke vs. transient ischaemic attack as index event; Innsbruck vs. Vienna centre). Fourth, a sensitivity analysis will be conducted which excluding patients had a transient ischaemic attack with $ABCD_2$-score of 3 as index event as a validation study classified such patients as having a low 7-day risk of stroke.[18] For the co-primary outcome of health-related quality of life, sensitivity

analyses will be limited to those that do not require a normal distribution (i.e. per-protocol analysis and analysis excluding patients with an $ABCD_2$-score of 3).

It is also planned to present a supplementary figure that compares mRS at discharge, at the 3-month visit (for the STROKE-CARD arm), and at the 12-month visit for each trial arm.

15. Bibliography

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