Statistical analysis plan (SAP)

Sahlgrenska Carotid Cohort.

The main aims of this study had prespecified SAP. Minor issues have a brief summary of what data is to be assessed. All are presented in the main protocol. Excerpts from that protocol:

Conservative treatment of near-occlusion

Planned analyses

The main statistical analysis is survival analysis by intention-to-treat approach when the last participants has been followed for 5 years. Death, lost-to-follow up and last follow-up are censors except when death is within 30 days of trial surgery (then it is an outcome). Events between index-date and censoring will be assessed. Secondary analyses will include comparison with historical controls from previous studies and for all secondary outcomes. Secondary analyses will also include assessments where index date is changed to presenting event.

Pre-specified subgroup analyses for main outcome (and presented for both with and without operative risk) are age (<65, 65-74, ≥75 years), sex, type of presenting event (stroke, TIA, retinal), time between last event and index date (quartiles), >1 event within 30 days of index date (yes/no), free-floating thrombus on CTA (yes/no) and severity of the collapse in 3 ways: 1) CTA-based distal ICA diameter ratio (quartiles, not available with contralateral occlusion), 2) ICA-CBF-flow rate ratio (quartiles, not available for many historical controls), 3) full collapse per exclusion criteria definition.

Sample size

Main analysis is descriptive, why it is difficult to assess power, largest studies have to-date included 100-150 near-occlusions in the medical arm [1, 18]. For secondary analyses, an expected sample of 100-200 participants will be required, based on two power calculations (below). Assuming that 20% of annual carotid cases can be included in this trial, 100 participants will take approximately 5 years to include. Therefore, 100 participants is the target if this study is conducted as single-center (current application). However, if additional centers can be recruited (with separate ethics approval), the target will be 200 participants.

Power analyses for secondary analyses with historical controls were done with 80% power, α=0.05 and a 1-sided approach (non-inferiority). The expected outcome could be 6.2% risk at 5 years, being double that of asymptomatic stenosis [19], or it could be 8.5% at 5 years, given risks seen in a smaller 2-year study of symptomatic CNO with modern medical treatment [18]. The 5-year surgical risk (11.8%) assumption is based on the outcome 5-year surgical risk for near-occlusions in the NASCET and ECST trials (148 patients, 16.9%) [1] and assuming a 30% relative risk reduction by improvements in medical treatments since then. To this 11.8% we added 20% as the non-inferiority margin (14.2%). Comparing 6.2% and 8.5% with 14.2% results in 95 and 202 participants, that is approximately 100-200.

Interim analyses

Interim analyses are conducted after 50, 100 and every 100 patient-years thereafter.

The trial will be terminated if the medical group (current cases) has an excessive risk – unless the subgroup of particular importance issue is the cause (see below). Excessive risk is defined by a Kaplan-Meier curve analysis at the day of current mean follow-up time (not at the end to avoid statistical anomalies with small samples). Excessive risk is defined as the lower border of 2-sided 95%CI is above a threshold. The threshold is based on current mean follow-up time:

1. Day 0-365, 0.01973% risk per day. This is a linear description of 7.2% risk during the first year, from the medical arm of symptomatic near-occlusions in NASCET+ECST [1]. This does not account for improvements in medical treatment as it is not clearly relevant the first year.
2. Day 366 and beyond: 7.2% + 0.00315% risk per day. This is a linear description for reaching 11.8% at 5 years (1.15% risk/year) after reaching 7.2% the first year.

Cases bordering conventional stenosis is an interim analysis of a subgroup of particular importance. As presented elsewhere [10], it is particularly relevant to assess the medical risk of cases close to the border of conventional stenosis. If the risk is too high, the inclusion criteria will be changed. Therefore, in every interim analysis, the ICA-CBF flow rate ratio values of the medical treatment (current study) cases will be divided into quartiles. If the highest quartile (closest to conventional) has higher risk than the three other quartiles combined, the inclusion criteria will be modified accordingly (lowering the inclusion criteria to the 75^{th} percentile of the interim analysis, i.e. excluding the highest quartile from further inclusion). This is assessed by Kaplan-Meier truncated at current mean follow-up, log rank $p<0.05$ is positive. If this happens, all trial termination assessments will exclude the cases in the excessive risk subgroup, including if trial termination was triggered at the same interim analysis. I.e. if the study show high risk because of a subgroup that will no longer be included, the trial will continue for remaining cases.

Management of near-occlusion – non-prognostic aspects

We will make comparisons between various ways to assess near-occlusion with CT-angiography, phase-contrast MRI and carotid ultrasound. The main emphasis will be on validation of diagnostic criteria that are being developed from a previous material when the study starts. The diagnostic criteria are aimed reproducing the findings with PC-MRI (such as the 99% specificity required for trial inclusion as an alternative to PC-MRI). All exams are done as part of clinical routine. In cases where conventional angiography or CT-perfusion is available, additional analyses for diagnostics and pathophysiology are possible – but few participants are expected to be examined with these modalities.

What is the best medical therapy before surgery?

This is a short-term observational cluster group comparison. All participants are given best medical therapy, which at Sahlgrenska is defined as DAPT except for cases with indication for anticoagulant (such as atrial fibrillation). However, in a previous study performed in Umeå, best medical therapy was defined as SAPT. Outcomes are assessed in the same way in both studies. By combining the studies, a comparative analysis can be performed. Inclusion criteria in the analysis is symptomatic ≥50% stenosis.

Main analysis will be a cluster comparison by intention to treat, i.e. the groups are Umeå participants Vs Sahlgrenska participants. Primary outcome is the combination of preoperative recurrence and post-operative complications: Here, preoperative recurrence is ipsilateral ischemic stroke or retinal artery occlusion (retinal stroke) after presenting event until surgery/stenting or until 90 days if no surgery/stenting was performed. Post-operative complications are stroke or death within 30 days of surgery/stenting. Secondary outcomes are both parts of primary outcome separately, recurrent pre- or postoperative TIA/Afx, surgery length and reoperation for wound hematoma. Relevant subgroups are degree of stenosis, type of presenting event, number of preoperative events and timing between preoperative events and surgery [5, 12]. Genetic Clopidogrel resistance will be assessed by stored blood samples unless done in routine practice (which might start in the near future). The medications actually taken/administered during the management period will be registered for descriptive purposes.

With 80% power, $\alpha=0.05$, a 33% relative risk reduction (15% to 10%) of preoperative stroke, 686 participants are required in each group. This is available from the Umeå studies. 686 DAPT-treated participants will take approximately 7 years to gather at Sahlgrenska. As this is the longest duration of all relevant analyses, it defines overall study size. During the study period, approximately 850 patients with final diagnosis will be assessed (approximately 160 patients not treated with DAPT, such as those treated with anticoagulation for atrial fibrillation). During the same time, approximately 150 additional patients that also fulfill the inclusion criteria are estimated to be enrolled (such as those not having symptomatic stenosis). Thus, 1000 participants are expected in the entire study.

Why does the prognosis with and without treatment differ between patients with cerebral and retinal events? Is there a pathophysiological difference?

Thus far, detailed assessments of patient history and neurological examination (nervstatus) are lacking for visual symptoms in the carotid stenosis field. To systematically gather and categorize symptoms might lead to new insights. This includes comparing onset placement, spread pattern, nadir (worst) pattern, regression pattern and color description of the visual symptoms between transient (amaurosis fugax) and permanent (retinal artery occlusion) symptoms. This is relevant as the former has no proven mechanism, but the latter has an identified embolus. Example, it is our anecdotal experience that few with amaurosis fugax present with a quadrant pattern at nadir, but many with retinal artery occlusion do so. Comparing with TIA and stroke (often embolic mechanism and have higher risk of stroke) will be assessed. Are there differences in previous vascular disease burden? Can imaging or blood biomarker findings explain differences? Collateral flow patterns of phase contrast MRI? Is retinal claudication associated with symptom types or prognosis? What are the risk factors for stroke recurrence among patients with retinal events?

What is the impact of novel stroke definitions on the carotid field?
When analyzing baseline events and prognostic data, will assess the participants with both the traditional and the novel stroke definition and compare the differences.

Do two recent events increase the risk of perioperative stroke?
All preoperative events are cataloged. The association between repeated preoperative events and risk of perioperative stroke will be assessed.

How is carotid web diagnosed and managed in routine practice?
Descriptive approach. How carotid web should be managed in routine practice is unclear. In the study we observe what is done in routine practice and describe outcomes during follow-up.

Can blood biomarker analyses improve prognostic or pathophysiological understanding?
This is a broad comparison between the blood samples stored in the study and the prognostic/pathophysiological data we gather in the study. One planned analysis is validation of a hypothesis generating study examined with Olink by using the same platform again or targeted analyses of specific proteins. We will also assess genetic Clopidogrel resistance. There will be joint analyses with other studies – but these are then legally/technically performed in each study separately (by separate ethics approvals – our approval cover only our samples). There are no known relevant biomarkers in carotid stenosis, but the intention is to validate those that might appear. See below for ethical considerations, especially what will not be studied.

Can assessment of effective reserve improve prognostic understanding in patients with carotid stenosis?
The MRI brain scans done as part of clinical routine will be assessed for effective reserve capacity and compared with the prognostic data we collet, to predict outcome in patients with carotid stenosis.

What affects long-term prognosis for patients with carotid stenosis?
Long-term prognosis is compared with various baseline data including imaging markers and blood biomarkers are particularly relevant. Here, we expect improvements in how the exams we do as part of clinical routine can be analyzed, such as how to categorize calcifications, how to define free-floating thrombus and advanced software to assess plaque content. We will not only study stroke outcomes but all vascular endpoints as the carotid stenosis is not only a risk factor for stroke but also a marker for how advanced a person's atherosclerotic burden is. We will take the medical treatment taken during follow-up into account.

References:

See main protocol