PROTOCOL

Primary closure versus patch angioplasty in carotid endarterectomy: a systematic review with meta-analyses and trial sequential analyses of randomized clinical trials

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Introduction

Carotid artery stenosis occurs due to atherosclerosis and was described to be a pathologic substrate for ischemic diseases of the ipsilateral brain and eye by C. Miller Fisher in 1951 [1]. Best medical management of asymptomatic carotid artery stenosis includes antiplatelet therapy, statin use, antihypertensive therapy, diabetic control, as well as lifestyle modifications [2-4]. Carotid endarterectomy (CEA) is the preferred treatment for patients with severe (>70%) and symptomatic stenosis of the carotid artery [5]. After CEA restenosis occurs in 6-36% of patients during long-term follow-up [6-10]. There are two alternative CEA techniques: eversion endarterectomy and endarterectomy using a longitudinal arterotomy. Closure can be achieved by either direct suturing or patch angioplasty [11]. Patch angioplasty is suggested to reduce the risk of restenosis and recurrent ipsilateral stroke [12].

Guidelines of both the European Society of Vascular Surgery (ESVS) and the Dutch society for vascular surgery (NVVV) consider CEA with patch angioplasty as the reference technique [13,14]. A meta-analysis of ten randomized clinical trials (RCT's) including 2157 operations in 1967 patients has been performed comparing CEA with primary closure versus CEA with patch angioplasty [12]. The authors concluded that CEA with patch angioplasty may reduce the risk of perioperative arterial occlusion and restenosis, the risk of ipsilateral stroke appears to be reduced [12]. However, there are many confounding factors which may all contribute to heterogeneity in the observed data, such as the use of perioperative monitoring with transcranial doppler, measurement of carotid pressure, electroencephalographic monitoring, selective shunting, regional anesthesia, and different patch materials [15-22].

To determine which technique, CEA with primary closure or CEA with patch angioplasty for severe (>70%) or symptomatic carotid stenosis may have more beneficial or harmful effects, it is important that all available evidence is carefully balanced in a systematic review with an error matrix approach and trial sequential analysis (TSA) [23]. Outcome measures should be graded from the patients' perspective [24], systematic error (bias) of included randomized trials should be assed, and the risk of random error should be evaluated using TSA. Therefore, a systematic review with meta-analyses and trial sequential analysis is needed to evaluate available evidence for both techniques of CEA and to assess whether or not more research is needed,.

Objective

The objective is to conduct a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials, comparing the primary closure versus patch angioplasty in CEA for benefits and harms according to a pre-published protocol following The Cochrane Collaboration methodology [25].

Methods

Studies

Randomized clinical trials comparing CEA with primary closure versus CEA with patch angioplasty (regardless of used patch materials) will be included. All trials irrespective of language, blinding, outcomes, or publication status will be considered for inclusion. Quasi-randomized and observational studies will also be considered, but will be evaluated for serious adverse events only. Studies in animals will be excluded.

Patients

Patients with severe (>70%) stenosis and/or symptomatic stenosis of the carotid artery will be considered. All trials which evaluate CEA in adult patients (≥18 years) will be included [14].

Experimental intervention

The experimental intervention is CEA with primary closure [11].

Control intervention

The control intervention is CEA with patch angioplasty regardless of patch material [11].

Outcomes

The outcome measures will be graded from the patient's perspective (GRADE working group 2008, Fig.1) [24]. Primary outcomes will be all-cause mortality at maximal follow-up, and severe adverse events such as; fatal stroke, ipsilateral stroke, arterial rupture. Secondary outcomes will be any stroke, 90 day mortality, arterial occlusion or restenosis, costs, scar formation, cranial nerve palsy and length of hospital stay according to availability of data. The numbers of patients with one or more complications will be counted rather than the numbers of complications. Severity of complications will be graded using the Clavien-Dindo classification of surgical complications (Table 1) [26].

Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, PubMed/MEDLINE and EMBASE will be searched. References of the identified trials will be searched to identify any further relevant randomized clinical trials. The search strategies are provided in appendix 1 to 3. Searches will include Mesh descriptors such as “Clinical Trials”, “carotid endarterectomy”, “thromboendarterectomy”, “carotid artery disease”.

Data collection

Two authors will independently identify trials and studies for inclusion. Excluded trials and studies will be listed with their reasons for exclusion. The authors will extract the following data: year and language of publication, country in which the trial was conducted, year of conduction of the trial, single or multicenter trial, inclusion and exclusion criteria, patient demographics (e.g. number of patients, mean age, mean body mass index and gender, smoking, diabetes mellitus, use of statins, use of platelet inhibitors), local or general anesthesia, use of shunting, outcome measures.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and PRISMA flow diagram for systematic reviews will be used [27]. If there is any unclear or missing data the corresponding authors of the individual trials will be contacted.

Assessment of bias risk

Two authors will assess the risk of bias, without masking for trial names, according to the Cochrane Handbook for Systematic Reviews of Interventions [25].

Sequence generation

- Low risk of bias: the method used (e.g. central allocation) is unlikely to induce bias on the final observed effect, such as:
    - referring to a random number table
    - using a computer random number generator
    - coin tossing
    - shuffling cards or envelopes
    - throwing dice
    - drawing of lots
- Unclear risk of bias: insufficient information to assess whether the method used is likely to introduce confounders.
- High risk of bias: the method is improper and likely of introduce confounding, e.g. based on date of admission, or record number, or by odd or even date of birth.

Allocation concealment

- Low risk of bias: participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:
    - central allocation (including telephone)
    - web-based and pharmacy-controlled randomization
    - sequentially numbered drug containers of identical appearance
    - Sequentially numbered, opaque, sealed envelopes
- Unclear risk of bias: insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
- High risk of bias: participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:
    - an open random allocation schedule
    - assignment envelopes were used without appropriate safeguards
    - alternation or rotation
    - date of birth
    - case record number
    - any other explicitly unconcealed procedure

Blinding of participants and personnel

- Low risk of bias: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding or blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgment of 'Low risk' or 'High risk', or the study did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment

- Low risk of bias: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding or blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgment of 'Low risk', or 'High risk' or the study did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding, or blinding of outcome assessment, but likely that the

blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias:
    - no missing outcome data
    - reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)
    - missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
    - for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate
    - for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not enough to have a clinically relevant impact on observed effect size
    - missing data have been imputed using appropriate methods
- Unclear risk of bias: insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided) or the study did not address this outcome.
- High risk of bias:
    - reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups
    - for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
    - for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size
    - 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization
    - potentially inappropriate application of simple imputation

Selective outcome reporting

- Low risk of bias: the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way, or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.

- Unclear risk of bias: insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. It is likely that the majority of studies will fall into this category.
- High risk of bias:
    - not all of the study’s pre-specified primary outcomes have been reported
    - one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified
    - one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect)
    - one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis
    - the study report fails to include results for a key outcome that would be expected to have been reported for such a study

Other bias (e.g. financial bias)

- Low risk of bias: the study appears to be free of other sources of bias.
- Unclear risk of bias: there may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias.
- High risk of bias: there is at least one important risk of bias.

Trials classified as low risk of bias in all domains of sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, source of funding and other potential risks of bias will be considered trials with a low risk of bias. Trials with one or more of these domains scored as unclear or high risk of bias will be considered trials with high risk of bias [25]. If there are no trials with a low risk of bias a group of trials with lower risk bias will be defined based on the domains of sequence generation, allocation concealment, and blinding of patients, personnel and outcome assessors. The authors are aware that even such trials may still possess a considerable risk of bias due to the other bias components. The results from the analyses of the trials with low(er) risk of bias will be considered as the main results of the review unless there are no bias effects or unexpectedly that trials with unclear or high risk of bias show less beneficial and more harmful effects.

Error matrix approach

All the extracted data will be assessed for the risk of bias measured by the level of evidence, the risk of random error measured by standard error (SE), and the design error measured by grading the outcomes [23]. To facilitate an overview of the available data a three dimensional ‘Manhattan Error Matrix’ will be constructed [23].

Statistical methods

Meta-analyses will be performed according to the Cochrane Handbook for Systematic Reviews of Interventions [25]. The software package Review Manager 5.2.11 will be used [28].

For dichotomous variables, the risk ratio (RR) with 95% confidence interval (CI) will be calculated. The amount of patients with complications in each group and the difference (and 95% confidence interval) in proportions of patients with complications between the groups will be reported. A *p*-value of less than 0.05 will be considered statistically significant.

The impact of attrition bias will be explored using best/worst and worst/best case scenarios: a best /worst case scenario is one where all patients lost to follow-up in the intervention group are supposed to have survived while all patients lost to follow-up in the control intervention group have died. A worst/best case scenario is the reverse.

Heterogeneity will be explored by chi-squared test with significance set at *p*-value of 0.10, and the quantity of heterogeneity will be measured by I^2. A random-effects model will be used, unless heterogeneity is 0% then a fixed-effect model will be used. In case of discrepancies the results of both models will be presented. The analyses will be performed on an intention-to-treat basis whenever possible.

Subgroup analyses

The following subgroup analyses will be performed:

- Trials with low(er) risk of bias (all, or all but blinding of caregivers, bias components scored as low risk) will be compared to trials with unclear or high risk of bias (one or more of the bias components (except blinding of caregivers) scored as unclear or high risk). If there are no trials with low risk of bias a subgroup analysis comparing our previous defined group of trials with lower risk of bias versus trials with high risk of bias will be conducted.
- Different patch materials will be compared. Use of venous, polytetrafluorethylene (PTFE), Dacron, and bovine patches have been described [23]. Subgroup analyses will be conducted according availability of data on different materials.

Bias exploration

A funnel plot will be used to explore small trial bias and to use asymmetry in funnel plot of trial size against treatment effect to asses this bias. Begg's and Egger's tests will be used to test for asymmetry in funnel plots [29].

Trial sequential analyses (TSA)

Meta-analyses may result in type-I errors due to an increased risk of random error when sparse data are collected and due to repeated significance testing when a cumulative meta-analysis is updated with new trials [30,31]. To assess the risk of type-I errors, TSA will be used.

TSA combines information size estimation for meta-analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance of meta-analysis [30-32]. The latter, called trial sequential monitoring boundaries (TSMB), reduce type-I errors. In TSA the addition of each trial in a cumulative meta-analysis is regarded as an interim analysis and helps to clarify whether additional trials are needed or not. The idea in TSA is that when the cumulative z-curve crosses the TSMB, a sufficient level of evidence has been reached and no further trials may be needed. If the z-curve does not cross the boundary of benefit and the required information size has not been reached, there is insufficient evidence to reach a conclusion [30,31,33,34]. TSA may also be used for the evaluation of type II errors, that is to evaluate whether any further randomized trial is futile. TSA will be applied since it reduces the risk of type-I error in a cumulative meta-analysis and may provide important information on how many more patients need to be included in further trials. The information size will be calculated as diversity adjusted required information size (DIS), suggested by the relative risk reduction (RRR) of the intervention in the included trials [35]. If the estimated diversity of the meta-analysis is 0%, a TSA using a diversity of 25% will be conducted. TSA will be performed on all outcomes. The required information size for primary outcomes will be calculated based on an *a priori* RRR of 10% and appropriately adjusted for diversity according to an overall type-I error of 5% and a power of 90% considering early and repetitive testing [35]. For secondary outcomes the required information size will be calculated using a power of 80% [35]. As a sensitivity analysis the diversity adjusted required information size will be calculated using the estimated intervention effect from the trials with lower risk of bias in a conventional meta-analysis. If the required information size is surpassed for the TSA using the estimated information size in the conventional meta-analysis or a trial sequential monitoring boundary is crossed a TSA with an anticipated intervention effect equal to the lower confidence limit in the effect estimate from the conventional meta-analysis will be performed. If heterogeneity is zero in the actual meta-analysis the impact of e.g. diversity rising to 25% will be explored. The TSA will be conducted using the control event proportion calculated from the actual meta-analyses.

GRADE

Summary of findings tables will be produced summarizing the results of the trials with low(er) risk of bias and for all trials. Reasons for downgrading the quality of the available evidence are: overall risk of bias evaluation of the included bias domains, publication bias, heterogeneity, imprecision, and indirectness (e.g. length of stay is a surrogate outcome measure) [36-38].

Conclusion

The objective is to perform a systematic review using the Cochrane Collaboration methodology with meta-analysis and trial sequential analysis comparing the benefits and harms of CEA with primary

closure versus CEA with patch angioplasty. This protocol will be online available prior to the start of the review process at the PROSPERO website.

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Conflicts of interest

None.

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Fig. 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy (GRADE 2008) [24]

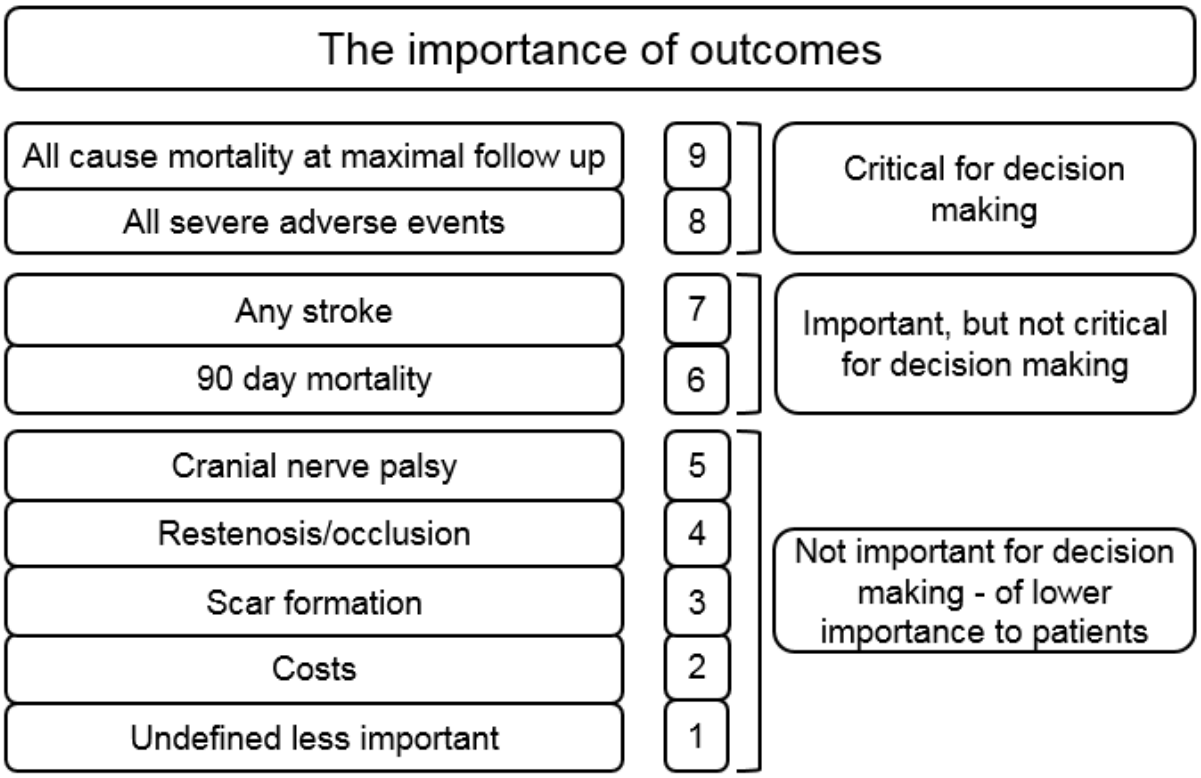

Table 1. Clavien-Dindo classification of surgical complications [26]

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antypiretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III Grade IIIa Grade IIIb	Requiring surgical, endoscopic, or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
Grade IV Grade IVa Grade IVb	Life threatening complication (including CNS complications)* requiring IC/ICU management Single organ dysfunction Multiorgan dysfunction
Grade V	Death of a patient.
Suffix "d"	If the patient suffers from a complication at the time of discharge. The suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

* brain hemorrhage, ischemic stroke; IC: Intermediate care; ICU: Intensive care unit