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Carotid endarterectomy with primary closure versus patch angioplasty in patients with symptomatic and significant stenosis: PROTOCOL for a systematic review with meta-analyses and Trial Sequential Analysis of randomized clinical trials

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ABSTRACT

Introduction

Use of patch angioplasty in carotid endarterectomy is suggested to reduce the risk of restenosis and recurrent ipsilateral stroke. A systematic review is needed for evaluation of benefits and harms of primary closure versus patch angioplasty in carotid endarterectomy.

Methods and analysis

The review shall be conducted according to this published protocol following the recommendations of the 'Cochrane' and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Randomized clinical trials comparing carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty (regardless of used patch materials) in human adults with a symptomatic and significant carotid stenosis will be included.

Primary outcomes are all-cause mortality at maximal follow-up, health-related quality of life, and serious adverse events. Secondary outcomes are symptomatic or asymptomatic arterial occlusion or restenosis, and non-serious adverse events.

Ethics and dissemination

The objective is to conduct a systematic review with meta-analysis and Trial Sequential Analysis as well as GRADE assessments comparing the benefits and harms of carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty in patients with a symptomatic and significant carotid stenosis. We will primarily base our conclusions on meta-analyses of trials with overall low risk of bias. However, if pooled point-estimates of all trials are similar to pooled point-estimates of trials with overall low risk of bias and there is lack of a statistical significant interaction between estimates from trials with overall high risk of bias and trials with overall low risk of bias we will consider the precision achieved in all trials as the result of our meta-analyses. This protocol will be online available prior to the start of the review process and at the PROSPERO website.

Trial registration number: PROSPERO CRD42014013416

Strengths and limitations of this study

- The review shall be conducted according to this published protocol following the recommendations of the 'Cochrane' and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement).
- Trial Sequential Analysis compared with GRADE assessments of Randomized Clinical Trials are included.
- This review benefits from a comprehensive search strategy, designed to retrieve a broad spectrum of relevant articles for the research question.
- To avoid design error, one technique will be compared to one other technique.

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]. Preventive management of asymptomatic carotid artery stenosis includes antiplatelets, statins, antihypertensives, diabetic control, as well as lifestyle modifications [2-4]. There is still discussion about the severity of the stenosis for surgical treatment and the way the severity of the stenosis should be assessed. Carotid endarterectomy (CEA) is the preferred treatment for patients with a symptomatic and significant (>70%) stenosis of the carotid artery [5], primarily based on the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [6-8]. Restenosis after CEA occurs in 6% to 36% of patients during long-term follow-up of at least 12 months [9-13]. Two operation techniques are well known in literature: the eversion technique and the traditional endarterectomy using a longitudinal arteriotomy. Closure in both techniques can be achieved by either direct suturing of the arterial wall or patch angioplasty in CEA [14]. Use of patch angioplasty in CEA is suggested to reduce both the risks of restenosis and recurrent ipsilateral stroke [15].

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 [8,16,17]. A meta-analysis of ten randomized clinical trials (RCTs) including 2157 operations in 1967 patients compared CEA with primary closure versus CEA with patch angioplasty and concluded that CEA with patch angioplasty may reduce the risks of restenosis, perioperative arterial occlusion, and ipsilateral stroke [15]. However, the observed differences in intervention effects may be explained by several confounding factors and/or differential use of co-interventions, such as the use of perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring, selected use of shunting, regional anesthesia, and variations in materials used for patching [18-25].

To determine which technique, CEA with a primary closure of the arterial wall or CEA with use of patch angioplasty is more effective for a symptomatic and significant (>70%) carotid stenosis, it is important that all available evidence is evaluated according to the risks of errors in a systematic review in line with the Cochrane Handbook for Systematic Reviews of Interventions [26,27]. Therefore, a proper and updated systematic review with meta-analyses and Trial Sequential Analysis (TSA) is needed, including GRADE assessments of the evidence.

Objective

The objective is to conduct a systematic review with meta-analysis and TSA of RCTs, evaluating the benefits and harms of the primary closure versus patch angioplasty in CEA according to a pre-published protocol following the Cochrane Handbook for Systematic Reviews of Interventions [26].

Methods

This review will be conducted according to this protocol which is also registered at PROSPERO (CRD42014013416; https://www.crd.york.ac.uk/prospero/) following the recommendations of the 'Cochrane Handbook for Systematic Reviews of interventions' [26] and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (at: www.prisma-statement.org) [28].

Studies

Only RCTs comparing CEA with primary closure of the arterial wall versus CEA with patch angioplasty (regardless of used patch materials) will be included. Trials will be considered irrespective of language, blinding, outcomes, or publication status. We will also consider quasi-randomized studies, controlled clinical studies, and other observational studies for data on harm if retrieved with our searches for RCTs. This is because adverse events are rarely reported in RCTs [29]. Moreover, such observational studies may provide information on rare or late occurring adverse events [29]. We are aware that the decision not to search for all observational studies may bias our review towards assessment of benefits and may overlook certain harms, such as late or rare harms.

Patients

According to the current guidelines [6-8] patients with a symptomatic and significant stenosis (>70%, measured by computed tomographic angiography or magnetic resonance angiography) of the carotid artery will be considered. Only trials which evaluate CEA in adult patients (≥18 years) will be included [17]. Studies in children and animals will be excluded.

Patient and Public Involvement

Including PPI statements aligns closely with BMJ Open's values of transparency and inclusiveness. We hope that including PPI statements in all articles is the first step of many for BMJ Open in encouraging patient involvement.

Experimental intervention

The experimental intervention is traditional CEA (longitudinal arteriotomy) with primary closure of the arterial wall [14]. RCTs which compare the eversion technique with patch angioplasty will be excluded [30]. Because of comparing two techniques, the eversion technique will be investigated in a separate systematic review, we want to compare one experimental intervention to one control intervention to prevent design error.

Control intervention

The control intervention is CEA with patch angioplasty regardless of the type of patch material used [14].

Co-interventions

Intra-operative monitoring may vary in the trials such as the use of perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring. Other intra-operative cointerventions may also vary in the trials for example the selected use of shunting and the use of variations in materials used for patching.

Outcomes

The outcome measures will be graded from the patient's perspective (GRADE Working Group 2008, Figure 1 appendix 1) [31].

Primary outcomes

- All-cause mortality
- Proportion of participants with one or more serious adverse events; that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect [32]
- Health-related quality of life: any scale used by trialists to assess the participants' reporting of their quality of life

Secondary outcomes

- Symptomatic or asymptomatic (50-99%) arterial occlusion or restenosis.
- Proportion of participants with one or more non-serious adverse events: any untoward medical occurrence in a participant that does not meet the above criteria for a serious adverse event is defined as a non-serious adverse event [32]

Exploratory outcomes

- Separately reported serious adverse events
- Separately reported non-serious adverse events

The numbers of patients with one or more complications will be evaluated rather than the numbers of events, depending on the availability of data.

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 RCTs. The search strategies are provided in appendix 2. Searches will include MeSH descriptors such as "Clinical Trials", "carotid endarterectomy", "thromboendarterectomy", "carotid artery disease". We will also search online trial registries such as ClinicalTrials.gov (https://clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp),

and the Food and Drug Administration (FDA) (www.fda.gov) for ongoing or unpublished trials. In addition, we plan to search Google Scholar (https://scholar.google.nl/) using the term Carotid Endarterectomy in title.

Data collection

Two authors will perform screening and select the trials for inclusion, independently. Excluded trials and studies will be listed with their reasons for exclusion. While disagreements may occur, a third author will be approached to reconcile. The authors will extract the following data: trial characteristics (year and language of publication, country in which the trial was conducted, year of conduction of the trial, single or multicenter trial, number of patients), patient characteristics (inclusion and exclusion criteria, mean age, mean body mass index and gender, smoking, diabetes mellitus, use of statin and platelet inhibitors), intervention characteristics (primary closure, closure by patch, use of shunting), co-interventions (local or general anesthesia, perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring) and the outcome measures evaluated.

If there are any unclear or missing data, the corresponding authors of the individual trials will be contacted at least twice.

Risk of bias assessment

Two authors will assess the risks of bias, without masking for trial names, according to the Cochrane Handbook for Systematic Reviews of Interventions [26], including the domains of generation of the allocation sequence, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other bias risks such as vested interests. Risk of bias components will be scored as low, unclear, or high risk of bias. Trials will be classified as trials at low overall risk of bias if all risk of bias domains are scored as having low risk of bias. If one or more of the bias domains are scored as unclear or at high risk of bias, the trial will be considered at high overall risk of bias [27,33,34].

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

In surgical procedures it is impossible to blind the surgeon who performs the procedure of CEA, while it is possible to blind the caregivers responsible for postoperative care as well as the patients [35]. For this domain we will consider the caregivers and patients and not the surgeon who performs the procedure, although a certain risk of bias will inevitably be present when evaluating surgical procedures.

- 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 judgement 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 judgement 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 the studies 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 studies 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

- 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.

Statistical methods

Meta-analyses will be performed according to the Cochrane Handbook for Systematic Reviews of Interventions [26]. The software package Review Manager (RevMan) Version 5.3 will be used [36]. Significance levels will be adjusted due to multiplicity of several outcomes. The results of each outcome will be determinative for the use of the intervention and requires an adjusted statistical significance level (threshold). An alfa of (0.05/ ((1+3)/2)=) 0.025 will be used for the primary outcomes to keep the family wise error rate (FWER) below 0.05. For the secondary outcomes this will be 0.033 [37,38]. For exploratory outcomes, we will consider a *p* value less than 0.05 as significant, because we view these outcomes as only hypothesis-generating outcomes. For dichotomous variables, the risk ratio (RR) with TSA-adjusted confidence intervals (CI) will be calculated. For continuous variables, the mean difference (MD) or the standardized mean difference (SMD) with 95% CI will be calculated.

For the outcome of SAE we plan to estimate the proportion of patients with one or more SAE in each group and to analyse this outcome in a binary meta-analysis. However, as we anticipate the reporting of SAEs in trials to vary considerably we plan to do two analyses:
1) Assuming that only one SAE is reported per patient we will add all reported SAE in each trial and calculate the proportion of summed SAE divided with number of randomized patients in the experimental and control intervention group (worst case scenario).
2) To avoid multiple counts of SAE in the same patients (SAE counting is not a statistical independent outcome) we will also analyse the most frequent SAE as if it represents the total number of SAE's in in the experimental and control intervention group (best case scenario). Being aware that none of these intervention effect estimates are exactly correct we will discuss them as possible worst- and best-case scenarios for the effect of the experimental vs the control intervention on the proportion of patients with one or more SAE's.

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. We will conduct both random-effects model and fixed effect model meta-analyses. In case of discrepancies the results of both models will be presented and we will primarily stress the result of the model with the result closet to null effect due to principle of cautiousness [38]. The analyses will be performed on an intention-to-treat basis whenever possible.

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 assess this bias. Begg's and Egger's tests will be used to test for asymmetry in funnel plots [39].

Trial Sequential Analyses (TSA)
Meta-analyses may result in type-I errors and type-II errors due to an increased risk of random error when sparse data are analysed and due to repeated significance testing when a cumulative meta-analysis is updated with new trials [40,41]. To assess the risk of type-I and type-II errors, TSA will be used. The vast majority of meta analyses (nearly 80%) in Cochrane systematic reviews have less than the required information size to conclude on a 30% relative risk reduction (RRR) and less than 2% have sufficient power to conclude on a 10% RRR [42-44].

TSA combines information size estimation for meta-analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance of meta-analysis [40,41,45]. 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 may be insufficient evidence to reach a conclusion [40,41,46,47]. TSA can also be used for the evaluation of type II errors, that is to evaluate whether further randomized trial is futile to show or discard the anticipated intervention effect (RRR or MD). This happens when the cumulative z-curve does cross the TSMBs for futility. TSA will be applied since it controls the risks of type-I and type-II errors 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 (DARIS) [48]. We will do the primary analysis calculating the DARIS based on an a priori anticipated intervention effect of a 10% RRR which is close to a minimal important difference and sensitivity analyses for a 15% RRR as well as a the RRR suggested by the meta-analysis of the included trials [49]. If the estimated Diversity of the meta-analysis is 0%, a sensitivity analysis with 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 [48]. For secondary outcomes the DARIS will be calculated using a power of 80% [48]. As a sensitivity analysis, the DARIS will be calculated using the estimated intervention effect from the trials at low risk of bias in a conventional meta-analysis. If the required information size is surpassed for the TSA using the estimated intervention effect in the conventional meta-analysis or a TSMB is crossed a TSA with an anticipated intervention effect equal to the confidence limit closest to the null effect in the effect estimate from the conventional meta-analysis will be performed. The TSAs will be conducted using the control event proportion calculated from the unweighted control event proportion from the control groups of the actual meta-analyses.

Subgroup analyses

The following subgroup analyses will be performed:

- Trials at overall low risk of bias (all except blinding of surgeons scored as low risk of bias) compared to trials at high overall risk of bias (one or more of the bias domains (excluding blinding of surgeons) scored as unclear or high risk).
- Different patch materials may be used including venous, polytetrafluorethylene (PTFE), Dacron, and bio-patches (bovine/porcine) [25]. Subgroup analyses will be conducted according availability of data on different materials.

GRADE

Summary of findings tables will be produced summarizing the results of the trials with overall low risk of bias and for all trials, separately. Reasons for downgrading the quality of the available evidence are: 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) [50-52]. We will compare the imprecision assessed according to GRADE with that of TSA [53].

Conclusion

The objective is to conduct a systematic review with meta-analysis and Trial Sequential Analysis as well as GRADE assessments comparing the benefits and harms of carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty in patients with a symptomatic and significant carotid stenosis. We will primarily base our conclusions on meta-analyses of trials with overall low risk of bias. However, if pooled point-estimates of all trials are similar to pooled point-estimates of trials with overall low risk of bias and there is lack of a statistical significant interaction between estimates from trials with overall high risk of bias and trials with overall low risk of bias we will consider the precision achieved in all trials as the result of our meta-analyses. This protocol will be online available prior to the start of the review process and at the PROSPERO website.

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Conflicts of interest

None.

Author contributions

MSM is the first author of the protocol. MSM, GGK and AK managed the first draft of this manuscript and coordinated the contributions of coauthors. Contributors JW, AJ, CG, FLM, AK, FK, GGK contributed to the design of the study and revised the paper critically. JW, GC, FK and GGK provided professional and statistical support. All authors read and approved the final version of the manuscript. GGK was initiator and supervisor.

Protocol Timeline

First registration of the protocol at PROSPERO in August 2014. Change of first investigator who updated the protocol August 2018.
Proposed date of starting the search: 10th of September 2018. Proposed date of finishing the review is 31st of December 2018.

Word count:3774

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Appendix 1.

Figure 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy for symptomatic carotid stenosis (GRADE 2008) [31]

(Figure 1 should be inserted here)

*at maximum follow up

Appendix 2.

Proposed search PubMed 20th August 2018

((("Endarterectomy, Carotid"[Mesh] OR "Carotid Stenosis"[Mesh] OR "Stents"[Mesh] OR (Carotid[tiab] AND Endarterectomy[tiab]) OR (eversion[tiab] AND endarterectomy[tiab) OR (eversion[tiab] AND CEA[tiab]) OR eCEA[tiab] OR Carotid Stenos*[tiab] OR (carotid[tiab] AND Stent*[tiab]) OR (carotid[tiab] AND surger*[tiab])) AND ("Blood Vessel Prosthesis"[Mesh] OR "Polyethylene Terephthalates"[Mesh] OR "Polytetrafluoroethylene"[Mesh] OR Polytef[tiab] OR PTFE[tiab] OR TFE[tiab] OR FEP[tiab] OR Tarflen[tiab] OR Fluoroplast[tiab] OR GORE-TEX[tiab] OR Goretex[tiab] OR Teflon[tiab] OR Fluon[tiab] OR Polyethylene Terephthalate[tiab] OR Dacron[tiab] OR Polytetrafluoroethylene[tiab] OR Patch*[tiab] OR Blood Vessel Prosthes*[tiab] OR Vascular Prosthes*[tiab] OR Tissue-Engineered Vascular Graft*[tiab] OR "Angioplasty"[Mesh] OR angioplast*[tiab] OR biopatch*[tiab] OR porcine[tiab] OR bovine[tiab] OR "Endarterectomy, Carotid"[Mesh] OR (carotid[tiab] AND endarterectomy[tiab]) OR cCEA[tiab]))

42462 hits

RCT filter PubMed

(double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR "clinical trial"[tw] OR "pragmatic trial"[tw] OR "real world trial"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square"[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controll*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])

20834 hits (19635 after excluding doubles in systematic reviews)

Proposed search EMBASE 20th of August 2018

(('carotid endarterectomy'/exp OR 'carotid artery obstruction'/exp OR 'carotid artery stenting'/exp OR 'carotid artery stent'/exp or (Carotid:ti,ab AND Endarterectomy:ti,ab) OR (eversion:ti,ab AND endarterectomy:ti,ab) OR (eversion:ti,ab AND CEA:ti,ab) OR 'Carotid Stenos*':ti,ab OR (carotid:ti,ab AND Stent*:ti,ab) OR (carotid:ti,ab AND surger*:ti,ab)) AND ('blood vessel prosthesis'/exp OR 'polyethylene terephthalate'/exp OR 'polytetrafluoroethylene covered stent'/exp OR Polytef:ti,ab OR PTFE:ti,ab OR TFE:ti,ab OR FEP:ti,ab OR Tarflen:ti,ab OR Fluoroplast:ti,ab OR 'GORE-TEX':ti,ab OR Goretex:ti,ab OR Teflon:ti,ab OR Fluon:ti,ab OR 'Polyethylene Terephthalate':ti,ab OR Dacron:ti,ab OR Polytetrafluoroethylene:ti,ab OR Patch*:ti,ab OR 'Blood Vessel Prosthes*':ti,ab OR 'Vascular Prosthes*':ti,ab OR 'Tissue-Engineered Vascular Graft*':ti,ab OR 'angioplasty'/exp OR angioplast*:ti,ab OR biopatch*:ti,ab OR porcine:ti,ab OR bovine:ti,ab OR 'carotid endarterectomy'/exp OR (carotid:ti,ab AND endarterectomy:ti,ab) OR cCEA:ti,ab))

25898 hits

RCT filter EMBASE

('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk

7794 hits (6771 after excluding doubles in systematic reviews)

Proposed search Cochrane 20th of August

Carotid Endarterectomy OR eversion endarterectomy OR eversion CEA OR eCEA OR Carotid Stenos* OR carotid Stent* OR carotid surger*

AND

Polytef OR PTFE OR TFE OR FEP OR Tarflen OR Fluoroplast OR GORE-TEX OR Goretex OR Teflon OR Fluon OR Polyethylene Terephthalate OR Dacron OR Polytetrafluoroethylene OR Patch* OR Blood Vessel Prosthes* OR Vascular Prosthes* OR Tissue-Engineered Vascular Graft* OR angioplast* OR biopatch* OR porcine OR bovine OR carotid endarterectomy OR cCEA

1453 RCTs

Proposed search Google Scholar 20th August 2018

Carotid Endarterectomy in title

1000 hits

The Randomized clinical trial filters (RCT) are used from https://blocks.bmi-online.nl/ configured by the Dutch BioMedical Information specialists [54].

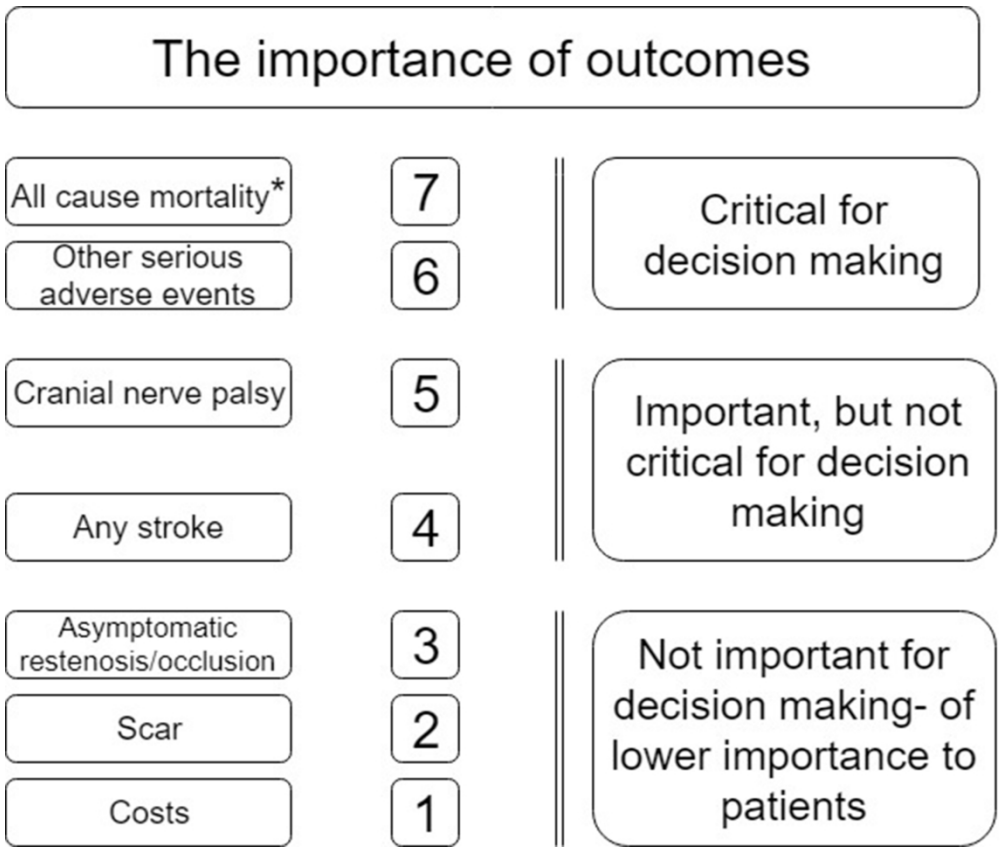

Figure 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy for symptomatic carotid stenosis (GRADE 2008) [31] Legenda:*at maximum follow up

210x176mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	none
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	none
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Carotid endarterectomy with primary closure versus patch angioplasty in patients with symptomatic and significant stenosis: PROTOCOL for a systematic review with meta-analyses and Trial Sequential Analysis of randomized clinical trials

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Carotid endarterectomy with primary closure versus patch angioplasty in patients with symptomatic and significant stenosis: PROTOCOL for a systematic review with meta-analyses and Trial Sequential Analysis of randomized clinical trials

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September 2018

ABSTRACT

Introduction

Use of patch angioplasty in carotid endarterectomy is suggested to reduce the risk of restenosis and recurrent ipsilateral stroke. A systematic review is needed for evaluation of benefits and harms of primary closure versus patch angioplasty in carotid endarterectomy.

Methods and analysis

The review shall be conducted according to this published protocol following the recommendations of the 'Cochrane' and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Randomized clinical trials comparing carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty (regardless of used patch materials) in human adults with a symptomatic and significant carotid stenosis will be included.

Primary outcomes are all-cause mortality at maximal follow-up, health-related quality of life, and serious adverse events. Secondary outcomes are symptomatic or asymptomatic arterial occlusion or restenosis, and non-serious adverse events.

Ethics and dissemination

The objective is to conduct a systematic review with meta-analysis and Trial Sequential Analysis as well as GRADE assessments comparing the benefits and harms of carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty in patients with a symptomatic and significant carotid stenosis. We will primarily base our conclusions on meta-analyses of trials with overall low risk of bias. However, if pooled point-estimates of all trials are similar to pooled point-estimates of trials with overall low risk of bias and there is lack of a statistical significant interaction between estimates from trials with overall high risk of bias and trials with overall low risk of bias we will consider the precision achieved in all trials as the result of our meta-analyses. This protocol will be online available prior to the start of the review process and at the PROSPERO website.

Review protocol registration number: PROSPERO CRD42014013416

Strengths and limitations of this study

- The review shall be conducted according to this published protocol following the recommendations of the 'Cochrane' and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement).
- Trial Sequential Analysis compared with GRADE assessments of Randomized Clinical Trials are included.
- This review benefits from a comprehensive search strategy, designed to retrieve a broad spectrum of relevant articles for the research question.
- To avoid design error, one technique will be compared to one other technique.

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]. Preventive management of asymptomatic carotid artery stenosis includes antiplatelets, statins, antihypertensives, diabetic control, as well as lifestyle modifications [2-4]. There is still discussion about the severity of the stenosis for surgical treatment and the way the severity of the stenosis should be assessed. Carotid endarterectomy (CEA) is the preferred treatment for patients with a symptomatic and significant (>70%) stenosis of the carotid artery [5], primarily based on the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [6-8]. Restenosis after CEA occurs in 6% to 36% of patients during long-term follow-up of at least 12 months [9-13]. Two operation techniques are well known in literature: the eversion technique and the traditional endarterectomy using a longitudinal arteriotomy. Closure in both techniques can be achieved by either direct suturing of the arterial wall or patch angioplasty in CEA [14]. Use of patch angioplasty in CEA is suggested to reduce both the risks of restenosis and recurrent ipsilateral stroke [15].

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 [8,16,17]. A meta-analysis of ten randomized clinical trials (RCTs) including 2157 operations in 1967 patients compared CEA with primary closure versus CEA with patch angioplasty and concluded that CEA with patch angioplasty may reduce the risks of restenosis, perioperative arterial occlusion, and ipsilateral stroke [15]. However, the observed differences in intervention effects may be explained by several confounding factors and/or differential use of co-interventions, such as the use of perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring, selected use of shunting, regional anesthesia, and variations in materials used for patching [18-25].

To determine which technique, CEA with a primary closure of the arterial wall or CEA with use of patch angioplasty is more effective for a symptomatic and significant (>70%) carotid stenosis, it is important that all available evidence is evaluated according to the risks of errors in a systematic review in line with the Cochrane Handbook for Systematic Reviews of Interventions [26,27]. Therefore, a proper and updated systematic review with meta-analyses and Trial Sequential Analysis (TSA) is needed, including GRADE assessments of the evidence.

Objective

The objective is to conduct a systematic review with meta-analysis and TSA of RCTs, evaluating the benefits and harms of the primary closure versus patch angioplasty in CEA according to a pre-published protocol following the Cochrane Handbook for Systematic Reviews of Interventions [26].

Methods

This review will be conducted according to this protocol which is also registered at PROSPERO (CRD42014013416; https://www.crd.york.ac.uk/prospero/) following the recommendations of the 'Cochrane Handbook for Systematic Reviews of interventions' [26] and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (at: www.prisma-statement.org) [28].

Studies

Only RCTs comparing CEA with primary closure of the arterial wall versus CEA with patch angioplasty (regardless of used patch materials) will be included. Trials will be considered irrespective of language, blinding, outcomes, or publication status. We will also consider quasi-randomized studies, controlled clinical studies, and other observational studies for data on harm if retrieved with our searches for RCTs. This is because adverse events are rarely reported in RCTs [29]. Moreover, such observational studies may provide information on rare or late occurring adverse events [29]. We are aware that the decision not to search for all observational studies may bias our review towards assessment of benefits and may overlook certain harms, such as late or rare harms.

Patients

According to the current guidelines [6-8] patients with a symptomatic and significant stenosis (>70%, measured by computed tomographic angiography or magnetic resonance angiography) of the carotid artery will be considered. Repeated Doppler ultrasound or digital subtraction angiography is possible as an imaging modality to measure the degree of the carotid stenosis, but the threshold of stenosis should be at least 70%. Only trials which evaluate CEA in adult patients (≥18 years) will be included [17]. Studies in children and animals will be excluded.

Patient and Public Involvement

Including PPI statements aligns closely with BMJ Open's values of transparency and inclusiveness. We hope that including PPI statements in all articles is the first step of many for BMJ Open in encouraging patient involvement.

Experimental intervention

The experimental intervention is traditional CEA (longitudinal arteriotomy) with primary closure of the arterial wall [14]. RCTs which compare the eversion technique with patch angioplasty will be excluded [30]. Because of comparing two techniques, the eversion technique will be investigated in a separate systematic review, we want to compare one experimental intervention to one control intervention to prevent design error.

Control intervention

The control intervention is CEA with patch angioplasty regardless of the type of patch material used [14].

Co-interventions

Intra-operative monitoring may vary in the trials such as the use of perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring. Other intra-operative cointerventions may also vary in the trials for example the selected use of shunting and the use of variations in materials used for patching.

Outcomes

The outcome measures will be graded from the patient's perspective (GRADE Working Group 2008, Figure 1 appendix 1) [31].

Primary outcomes

- All-cause mortality
- Proportion of participants with one or more serious adverse events; that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity [32]
- Health-related quality of life: any scale used by trialists to assess the participants' reporting of their quality of life

Secondary outcomes

- Symptomatic or asymptomatic (50-99%) arterial occlusion or restenosis.
- Proportion of participants with one or more non-serious adverse events: any untoward medical occurrence in a participant that does not meet the above criteria for a serious adverse event is defined as a non-serious adverse event [32]

Exploratory outcomes

- Separately reported serious adverse events
- Separately reported non-serious adverse events

The numbers of patients with one or more complications will be evaluated rather than the numbers of events, depending on the availability of data.

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 RCTs. The search strategies are provided in appendix 2. Searches will include MeSH descriptors such as "Clinical Trials", "carotid endarterectomy", "thromboendarterectomy", "carotid artery disease". We will also search online trial registries such as ClinicalTrials.gov (https://clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp),

and the Food and Drug Administration (FDA) (www.fda.gov) for ongoing or unpublished trials. In addition, we plan to search Google Scholar (https://scholar.google.nl/) using the term Carotid Endarterectomy in title.

Data collection

Two authors will perform screening and select the trials for inclusion, independently. Excluded trials and studies will be listed with their reasons for exclusion. While disagreements may occur, a third author will be approached to reconcile. The authors will extract the following data: trial characteristics (year and language of publication, country in which the trial was conducted, year of conduction of the trial, single or multicenter trial, number of patients), patient characteristics (inclusion and exclusion criteria, mean age, mean body mass index and gender, smoking, diabetes mellitus, use of statin and platelet inhibitors), intervention characteristics (primary closure, closure by patch, use of shunting), co-interventions (local or general anesthesia, perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring) and the outcome measures evaluated.

If there are any unclear or missing data, the corresponding authors of the individual trials will be contacted at least twice.

Risk of bias assessment

Two authors will assess the risks of bias, without masking for trial names, according to the Cochrane Handbook for Systematic Reviews of Interventions [26], including the domains of generation of the allocation sequence, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other bias risks such as vested interests. Risk of bias components will be scored as low, unclear, or high risk of bias. Trials will be classified as trials at low overall risk of bias if all risk of bias domains are scored as having low risk of bias. If one or more of the bias domains are scored as unclear or at high risk of bias, the trial will be considered at high overall risk of bias [27,33,34].

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

In surgical procedures it is impossible to blind the surgeon who performs the procedure of CEA, while it is possible to blind the caregivers responsible for postoperative care as well as the patients [35]. For this domain we will consider the caregivers and patients and not the surgeon who performs the procedure, although a certain risk of bias will inevitably be present when evaluating surgical procedures. The statistician who performs the analyses can be blinded.

- 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 judgement 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 judgement 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 the studies 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 studies 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

- 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.

Statistical methods

Meta-analyses will be performed according to the Cochrane Handbook for Systematic Reviews of Interventions [26]. The software package Review Manager (RevMan) Version 5.3 will be used [36]. Significance levels will be adjusted due to multiplicity of several outcomes. The results of each outcome will be determinative for the use of the intervention and requires an adjusted statistical significance level (threshold). An alfa of (0.05/ ((1+3)/2)=) 0.025 will be used for the primary outcomes to keep the family wise error rate (FWER) below 0.05. For the secondary outcomes this will be 0.033 [37,38]. For exploratory outcomes, we will consider a *p* value less than 0.05 as significant, because we view these outcomes as only hypothesis-generating outcomes. For dichotomous variables, the risk ratio (RR) with TSA-adjusted confidence intervals (CI) will be calculated. For continuous variables, the mean difference (MD) or the standardized mean difference (SMD) with 95% CI will be calculated.

For the outcome of SAE we plan to estimate the proportion of patients with one or more SAE in each group and to analyse this outcome in a binary meta-analysis. However, as we anticipate the reporting of SAEs in trials to vary considerably we plan to do two analyses:
1) Assuming that only one SAE is reported per patient we will add all reported SAE in each trial and calculate the proportion of summed SAE divided with number of randomized patients in the experimental and control intervention group (worst case scenario).
2) To avoid multiple counts of SAE in the same patients (SAE counting is not a statistical independent outcome) we will also analyse the most frequent SAE as if it represents the total number of SAE's in the experimental and control intervention group (best case scenario). Being aware that none of these intervention effect estimates are exactly correct we will discuss them as possible worst- and best-case scenarios for the effect of the experimental vs the control intervention on the proportion of patients with one or more SAE's.

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. We will conduct both random-effects model and fixed effect model meta-analyses. In case of discrepancies the results of both models will be presented and we will primarily stress the result of the model with the result closet to null effect due to principle of cautiousness [38]. The analyses will be performed on an intention-to-treat basis whenever possible.

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 assess this bias. Begg's and Egger's tests will be used to test for asymmetry in funnel plots [39].

Trial Sequential Analyses (TSA)
Meta-analyses may result in type-I errors and type-II errors due to an increased risk of random error when sparse data are analysed and due to repeated significance testing when a cumulative meta-analysis is updated with new trials [40,41]. To assess the risk of type-I and type-II errors, TSA will be used. The vast majority of meta analyses (nearly 80%) in Cochrane systematic reviews have less than the required information size to conclude on a 30% relative risk reduction (RRR) and less than 2% have sufficient power to conclude on a 10% RRR [42-44].

TSA combines information size estimation for meta-analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance of meta-analysis [40,41,45]. 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 may be insufficient evidence to reach a conclusion [40,41,46,47]. TSA can also be used for the evaluation of type II errors, that is to evaluate whether further randomized trial is futile to show or discard the anticipated intervention effect (RRR or MD). This happens when the cumulative z-curve does cross the TSMBs for futility. TSA will be applied since it controls the risks of type-I and type-II errors 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 (DARIS) [48]. We will do the primary analysis calculating the DARIS based on an a priori anticipated intervention effect of a 10% RRR which is close to a minimal important difference and sensitivity analyses for a 15% RRR as well as a the RRR suggested by the meta-analysis of the included trials [49]. If the estimated Diversity of the meta-analysis is 0%, a sensitivity analysis with 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 [48]. For secondary outcomes the DARIS will be calculated using a power of 80% [48]. As a sensitivity analysis, the DARIS will be calculated using the estimated intervention effect from the trials at low risk of bias in a conventional meta-analysis. If the required information size is surpassed for the TSA using the estimated intervention effect in the conventional meta-analysis or a TSMB is crossed a TSA with an anticipated intervention effect equal to the confidence limit closest to the null effect in the effect estimate from the conventional meta-analysis will be performed. The TSAs will be conducted using the control event proportion calculated from the unweighted control event proportion from the control groups of the actual meta-analyses.

Subgroup analyses

The following subgroup analyses will be performed:

- Trials at overall low risk of bias (all except blinding of surgeons scored as low risk of bias) compared to trials at high overall risk of bias (one or more of the bias domains (excluding blinding of surgeons) scored as unclear or high risk).
- Different patch materials may be used including venous, polytetrafluorethylene (PTFE), Dacron, and bio-patches (bovine/porcine) [25]. Subgroup analyses will be conducted according availability of data on different materials.

GRADE

Summary of findings tables will be produced summarizing the results of the trials with overall low risk of bias and for all trials, separately. Reasons for downgrading the quality of the available evidence are: 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) [50-52]. We will compare the imprecision assessed according to GRADE with that of TSA [53].

Conclusion

The objective is to conduct a systematic review with meta-analysis and Trial Sequential Analysis as well as GRADE assessments comparing the benefits and harms of carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty in patients with a symptomatic and significant carotid stenosis. We will primarily base our conclusions on meta-analyses of trials with overall low risk of bias. However, if pooled point-estimates of all trials are similar to pooled point-estimates of trials with overall low risk of bias and there is lack of a statistical significant interaction between estimates from trials with overall high risk of bias and trials with overall low risk of bias we will consider the precision achieved in all trials as the result of our meta-analyses. This protocol will be online available prior to the start of the review process and at the PROSPERO website.

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Conflicts of interest

None.

Author contributions

MSM is the first author of the protocol. MSM, GGK and AK managed the first draft of this manuscript and coordinated the contributions of coauthors. Contributors JW, AJ, CG, FLM, AK, FK, GGK contributed to the design of the study and revised the paper critically. JW, GC, FK and GGK provided professional and statistical support. All authors read and approved the final version of the manuscript. GGK was initiator and supervisor.

Protocol Timeline

First registration of the protocol at PROSPERO in August 2014. Change of first author who updated the protocol August 2018.

Proposed date of starting the search: 10th of September 2018. Proposed date of finishing the review is 31st of December 2018.

Word count:3845

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Appendix 1.

Figure 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy for symptomatic carotid stenosis (GRADE 2008) [31]

(Figure 1 should be inserted here)

*at maximum follow up

Appendix 2.

Proposed search PubMed 20th August 2018

(("Endarterectomy, Carotid"[Mesh] OR "Carotid Stenosis"[Mesh] OR "Stents"[Mesh] OR (Carotid[tiab] AND Endarterectomy[tiab]) OR (eversion[tiab] AND endarterectomy[tiab) OR (eversion[tiab] AND CEA[tiab]) OR eCEA[tiab] OR Carotid Stenos*[tiab] OR (carotid[tiab] AND Stent*[tiab]) OR (carotid[tiab] AND surger*[tiab])) AND ("Blood Vessel Prosthesis"[Mesh] OR "Polyethylene Terephthalates"[Mesh] OR "Polytetrafluoroethylene"[Mesh] OR Polytef[tiab] OR PTFE[tiab] OR TFE[tiab] OR FEP[tiab] OR Tarflen[tiab] OR Fluoroplast[tiab] OR GORE-TEX[tiab] OR Goretex[tiab] OR Teflon[tiab] OR Fluon[tiab] OR Polyethylene Terephthalate[tiab] OR Dacron[tiab] OR Polytetrafluoroethylene[tiab] OR Patch*[tiab] OR Blood Vessel Prosthes*[tiab] OR Vascular Prosthes*[tiab] OR Tissue-Engineered Vascular Graft*[tiab] OR "Angioplasty"[Mesh] OR angioplast*[tiab] OR biopatch*[tiab] OR porcine[tiab] OR bovine[tiab] OR "Endarterectomy, Carotid"[Mesh] OR (carotid[tiab] AND endarterectomy[tiab]) OR cCEA[tiab]))

42462 hits

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(('carotid endarterectomy'/exp OR 'carotid artery obstruction'/exp OR 'carotid artery stenting'/exp OR 'carotid artery stent'/exp or (Carotid:ti,ab AND Endarterectomy:ti,ab) OR (eversion:ti,ab AND endarterectomy:ti,ab) OR (eversion:ti,ab AND CEA:ti,ab) OR 'Carotid Stenos*':ti,ab OR (carotid:ti,ab AND Stent*:ti,ab) OR (carotid:ti,ab AND surger*:ti,ab)) AND ('blood vessel prosthesis'/exp OR 'polyethylene terephthalate'/exp OR 'polytetrafluoroethylene covered stent'/exp OR Polytef:ti,ab OR PTFE:ti,ab OR TFE:ti,ab OR FEP:ti,ab OR Tarflen:ti,ab OR Fluoroplast:ti,ab OR 'GORE-TEX':ti,ab OR Goretex:ti,ab OR Teflon:ti,ab OR Fluon:ti,ab OR 'Polyethylene Terephthalate':ti,ab OR Dacron:ti,ab OR Polytetrafluoroethylene:ti,ab OR Patch*:ti,ab OR 'Blood Vessel Prosthes*':ti,ab OR 'Vascular Prosthes*':ti,ab OR 'Tissue-Engineered Vascular Graft*':ti,ab OR 'angioplasty'/exp OR angioplast*:ti,ab OR biopatch*:ti,ab OR porcine:ti,ab OR bovine:ti,ab OR 'carotid endarterectomy'/exp OR (carotid:ti,ab AND endarterectomy:ti,ab) OR cCEA:ti,ab))

25898 hits

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Carotid Endarterectomy OR eversion endarterectomy OR eversion CEA OR eCEA OR Carotid Stenos* OR carotid Stent* OR carotid surger*

AND

Polytef OR PTFE OR TFE OR FEP OR Tarflen OR Fluoroplast OR GORE-TEX OR Goretex OR Teflon OR Fluon OR Polyethylene Terephthalate OR Dacron OR Polytetrafluoroethylene OR Patch* OR Blood Vessel Prosthes* OR Vascular Prosthes* OR Tissue-Engineered Vascular Graft* OR angioplast* OR biopatch* OR porcine OR bovine OR carotid endarterectomy OR cCEA

1453 hits

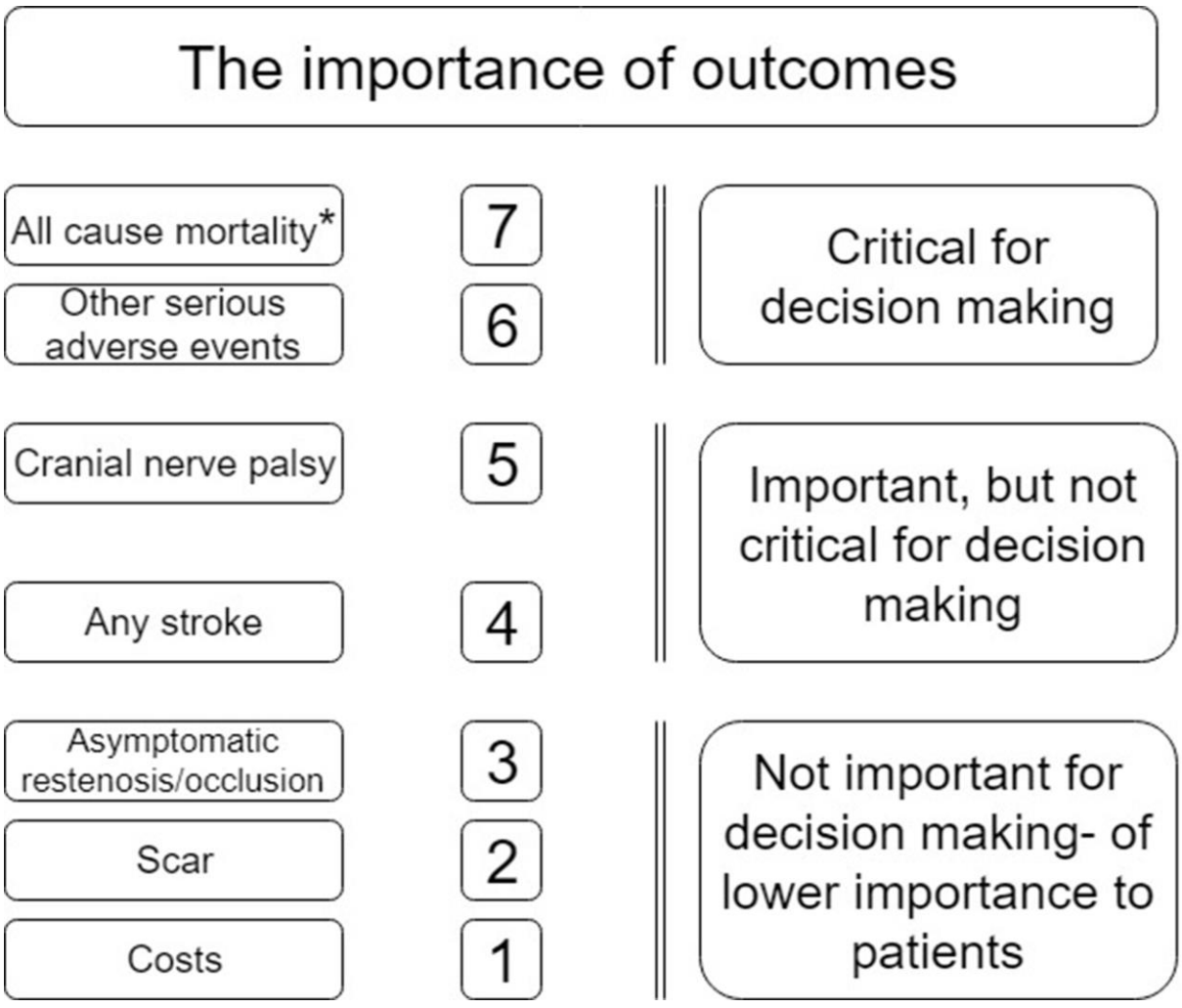
Proposed search Google Scholar 20th August 2018

Carotid Endarterectomy in title

1000 hits

Appendix 1.

Figure 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy for symptomatic carotid stenosis (GRADE 2008) [31]



*at maximum follow up

Appendix 2.

Proposed search PubMed 20th August 2018

(("Endarterectomy, Carotid"[Mesh] OR "Carotid Stenosis"[Mesh] OR "Stents"[Mesh] OR (Carotid[tiab] AND Endarterectomy[tiab]) OR (eversion[tiab] AND endarterectomy[tiab) OR (eversion[tiab] AND CEA[tiab]) OR eCEA[tiab] OR Carotid Stenos*[tiab] OR (carotid[tiab] AND Stent*[tiab]) OR (carotid[tiab] AND surger*[tiab])) AND ("Blood Vessel Prosthesis"[Mesh] OR "Polyethylene Terephthalates"[Mesh] OR "Polytetrafluoroethylene"[Mesh] OR Polytef[tiab] OR PTFE[tiab] OR TFE[tiab] OR FEP[tiab] OR Tarflen[tiab] OR Fluoroplast[tiab] OR GORE-TEX[tiab] OR Goretex[tiab] OR Teflon[tiab] OR Fluon[tiab] OR Polyethylene Terephthalate[tiab] OR Dacron[tiab] OR Polytetrafluoroethylene[tiab] OR Patch*[tiab] OR Blood Vessel Prosthes*[tiab] OR Vascular Prosthes*[tiab] OR Tissue-Engineered Vascular Graft*[tiab] OR "Angioplasty"[Mesh] OR angioplast*[tiab] OR biopatch*[tiab] OR porcine[tiab] OR bovine[tiab] OR "Endarterectomy, Carotid"[Mesh] OR (carotid[tiab] AND endarterectomy[tiab]) OR cCEA[tiab]))

42462 hits

Proposed search EMBASE 20th of August 2018

(('carotid endarterectomy'/exp OR 'carotid artery obstruction'/exp OR 'carotid artery stenting'/exp OR 'carotid artery stent'/exp or (Carotid:ti,ab AND Endarterectomy:ti,ab) OR (eversion:ti,ab AND endarterectomy:ti,ab) OR (eversion:ti,ab AND CEA:ti,ab) OR 'Carotid Stenos*':ti,ab OR (carotid:ti,ab AND Stent*:ti,ab) OR (carotid:ti,ab AND surger*:ti,ab)) AND ('blood vessel prosthesis'/exp OR 'polyethylene terephthalate'/exp OR 'polytetrafluoroethylene covered stent'/exp OR Polytef:ti,ab OR PTFE:ti,ab OR TFE:ti,ab OR FEP:ti,ab OR Tarflen:ti,ab OR Fluoroplast:ti,ab OR 'GORE-TEX':ti,ab OR Goretex:ti,ab OR Teflon:ti,ab OR Fluon:ti,ab OR 'Polyethylene Terephthalate':ti,ab OR Dacron:ti,ab OR Polytetrafluoroethylene:ti,ab OR Patch*:ti,ab OR 'Blood Vessel Prosthes*':ti,ab OR 'Vascular Prosthes*':ti,ab OR 'Tissue-Engineered Vascular Graft*':ti,ab OR 'angioplasty'/exp OR angioplast*:ti,ab OR biopatch*:ti,ab OR porcine:ti,ab OR bovine:ti,ab OR 'carotid endarterectomy'/exp OR (carotid:ti,ab AND endarterectomy:ti,ab) OR cCEA:ti,ab))

25898 hits

Proposed search Cochrane 20th of August

Carotid Endarterectomy OR eversion endarterectomy OR eversion CEA OR eCEA OR Carotid Stenos* OR carotid Stent* OR carotid surger*

AND

Polytef OR PTFE OR TFE OR FEP OR Tarflen OR Fluoroplast OR GORE-TEX OR Goretex OR Teflon OR Fluon OR Polyethylene Terephthalate OR Dacron OR Polytetrafluoroethylene OR Patch* OR Blood Vessel Prosthes* OR Vascular Prosthes* OR Tissue-Engineered Vascular Graft* OR angioplast* OR biopatch* OR porcine OR bovine OR carotid endarterectomy OR cCEA

1453 hits

Proposed search Google Scholar 20th August 2018

Carotid Endarterectomy in title

1000 hits

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	none
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	none
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Carotid endarterectomy with primary closure versus patch angioplasty in patients with symptomatic and significant stenosis: PROTOCOL for a systematic review with meta-analyses and Trial Sequential Analysis of randomized clinical trials

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Carotid endarterectomy with primary closure versus patch angioplasty in patients with symptomatic and significant stenosis: PROTOCOL for a systematic review with meta-analyses and Trial Sequential Analysis of randomized clinical trials

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September 2018

ABSTRACT

Introduction

Use of patch angioplasty in carotid endarterectomy is suggested to reduce the risk of restenosis and recurrent ipsilateral stroke. The objective is to conduct a systematic review with meta-analysis and Trial Sequential Analysis as well as GRADE assessments comparing the benefits and harms of carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty in patients with a symptomatic and significant carotid stenosis.

Methods and analysis

The review shall be conducted according to this published protocol following the recommendations of the 'Cochrane' and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Randomized clinical trials comparing carotid endarterectomy with primary closure of the arterial wall versus carotid endarterectomy with patch angioplasty (regardless of used patch materials) in human adults with a symptomatic and significant carotid stenosis will be included.

Primary outcomes are all-cause mortality at maximal follow-up, health-related quality of life, and serious adverse events. Secondary outcomes are symptomatic or asymptomatic arterial occlusion or restenosis, and non-serious adverse events.

We will primarily base our conclusions on meta-analyses of trials with overall low risk of bias. However, if pooled point-estimates of all trials are similar to pooled point-estimates of trials with overall low risk of bias and there is lack of a statistical significant interaction between estimates from trials with overall high risk of bias and trials with overall low risk of bias we will consider the precision achieved in all trials as the result of our meta-analyses.

Ethics and dissemination

The proposed systematic review will collect and analyse secondary data from published studies therefor ethical approval is not required. The results of the systematic review will be disseminated by publication in a peer-review journal and submitted for presentation at relevant conferences.

Review protocol registration number: PROSPERO CRD42014013416

Strengths and limitations of this study

- The review shall be conducted according to this published protocol following the recommendations of the 'Cochrane' and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement).

- Trial Sequential Analysis compared with GRADE assessments of Randomized Clinical Trials are included.

- This review benefits from a comprehensive search strategy, designed to retrieve a broad spectrum of relevant articles for the research question.

- To avoid design error, one technique will be compared to one other technique.

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]. Preventive management of asymptomatic carotid artery stenosis includes antiplatelets, statins, antihypertensives, diabetic control, as well as lifestyle modifications [2-4]. There is still discussion about the severity of the stenosis for surgical treatment and the way the severity of the stenosis should be assessed. Carotid endarterectomy (CEA) is the preferred treatment for patients with a symptomatic and significant (>70%) stenosis of the carotid artery [5], primarily based on the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [6-8]. Restenosis after CEA occurs in 6% to 36% of patients during long-term follow-up of at least 12 months [9-13]. Two operation techniques are well known in literature: the eversion technique and the traditional endarterectomy using a longitudinal arteriotomy. Closure in both techniques can be achieved by either direct suturing of the arterial wall or patch angioplasty in CEA [14]. Use of patch angioplasty in CEA is suggested to reduce both the risks of restenosis and recurrent ipsilateral stroke [15].

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 [8,16,17]. A meta-analysis of ten randomized clinical trials (RCTs) including 2157 operations in 1967 patients compared CEA with primary closure versus CEA with patch angioplasty and concluded that CEA with patch angioplasty may reduce the risks of restenosis, perioperative arterial occlusion, and ipsilateral stroke [15]. However, the observed differences in intervention effects may be explained by several confounding factors and/or differential use of co-interventions, such as the use of perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring, selected use of shunting, regional anesthesia, and variations in materials used for patching [18-25].

To determine which technique, CEA with a primary closure of the arterial wall or CEA with use of patch angioplasty is more effective for a symptomatic and significant (>70%) carotid stenosis, it is important that all available evidence is evaluated according to the risks of errors in a systematic review in line with the Cochrane Handbook for Systematic Reviews of Interventions [26,27]. Therefore, a proper and updated systematic review with meta-analyses and Trial Sequential Analysis (TSA) is needed, including GRADE assessments of the evidence.

Objective

The objective is to conduct a systematic review with meta-analysis and TSA of RCTs, evaluating the benefits and harms of the primary closure versus patch angioplasty in CEA according to a pre-published protocol following the Cochrane Handbook for Systematic Reviews of Interventions [26].

Methods

This review will be conducted according to this protocol which is also registered at PROSPERO (CRD42014013416; https://www.crd.york.ac.uk/prospero/) following the recommendations of the 'Cochrane Handbook for Systematic Reviews of interventions' [26] and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (at: www.prisma-statement.org) [28].

Studies

Only RCTs comparing CEA with primary closure of the arterial wall versus CEA with patch angioplasty (regardless of used patch materials) will be included. Trials will be considered irrespective of language, blinding, outcomes, or publication status. We will also consider quasi-randomized studies, controlled clinical studies, and other observational studies for data on harm if retrieved with our searches for RCTs. This is because adverse events are rarely reported in RCTs [29]. Moreover, such observational studies may provide information on rare or late occurring adverse events [29]. We are aware that the decision not to search for all observational studies may bias our review towards assessment of benefits and may overlook certain harms, such as late or rare harms.

Patients

According to the current guidelines [6-8] patients with a symptomatic and significant stenosis (>70%, measured by computed tomographic angiography or magnetic resonance angiography) of the carotid artery will be considered. Repeated Doppler ultrasound or digital subtraction angiography is possible as an imaging modality to measure the degree of the carotid stenosis, but the threshold of stenosis should be at least 70%. Only trials which evaluate CEA in adult patients (≥18 years) will be included [17]. Studies in children and animals will be excluded.

Experimental intervention

The experimental intervention is traditional CEA (longitudinal arteriotomy) with primary closure of the arterial wall [14]. RCTs which compare the eversion technique with patch angioplasty will be excluded [30]. Because of comparing two techniques, the eversion technique will be investigated in a separate systematic review, we want to compare one experimental intervention to one control intervention to prevent design error.

Control intervention

The control intervention is CEA with patch angioplasty regardless of the type of patch material used [14].

Co-interventions

Intra-operative monitoring may vary in the trials such as the use of perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring. Other intra-operative cointerventions may also vary in the trials for example the selected use of shunting and the use of variations in materials used for patching.

Outcomes

The outcome measures will be graded from the patient's perspective (GRADE Working Group 2008, Figure 1 appendix 1) [31].

Primary outcomes

- All-cause mortality
- Proportion of participants with one or more serious adverse events; that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity [32]
- Health-related quality of life: any scale used by trialists to assess the participants' reporting of their quality of life

Secondary outcomes

- Symptomatic or asymptomatic (50-99%) arterial occlusion or restenosis.
- Proportion of participants with one or more non-serious adverse events: any untoward medical occurrence in a participant that does not meet the above criteria for a serious adverse event is defined as a non-serious adverse event [32]

Exploratory outcomes

- Separately reported serious adverse events
- Separately reported non-serious adverse events

The numbers of patients with one or more complications will be evaluated rather than the numbers of events, depending on the availability of data.

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 RCTs. The search strategies are provided in appendix 2. Searches will include MeSH descriptors such as “Clinical Trials”, “carotid endarterectomy”, “thromboendarterectomy”, “carotid artery disease”. We will also search online trial registries such as ClinicalTrials.gov (https://clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA) (www.fda.gov) for ongoing or unpublished trials. In addition, we plan to search Google Scholar (https://scholar.google.nl/) using the term Carotid Endarterectomy in title.

Data collection

Two authors will perform screening and select the trials for inclusion, independently. Excluded trials and studies will be listed with their reasons for exclusion. While disagreements may occur, a third author will be approached to reconcile. The authors will extract the following data: trial characteristics (year and language of publication, country in which the trial was conducted, year of conduction of the trial, single or multicenter trial, number of patients), patient characteristics (inclusion and exclusion criteria, mean age, mean body mass index and gender, smoking, diabetes mellitus, use of statin and platelet inhibitors), intervention characteristics (primary closure, closure by patch, use of shunting), co-interventions (local or general anesthesia, perioperative transcranial doppler monitoring, perioperative carotid pressure measurement, electroencephalographic monitoring) and the outcome measures evaluated.

If there are any unclear or missing data, the corresponding authors of the individual trials will be contacted at least twice.

Risk of bias assessment

Two authors will assess the risks of bias, without masking for trial names, according to the Cochrane Handbook for Systematic Reviews of Interventions [26], including the domains of generation of the allocation sequence, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other bias risks such as vested interests. Risk of bias components will be scored as low, unclear, or high risk of bias. Trials will be classified as trials at low overall risk of bias if all risk of bias domains are scored as having low risk of bias. If one or more of the bias domains are scored as unclear or at high risk of bias, the trial will be considered at high overall risk of bias [27,33,34].

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

In surgical procedures it is impossible to blind the surgeon who performs the procedure of CEA, while it is possible to blind the caregivers responsible for postoperative care as well as the patients [35]. For this domain we will consider the caregivers and patients and not the surgeon who performs the procedure, although a certain risk of bias will inevitably be present when evaluating surgical procedures. The statistician who performs the analyses can be blinded.

- 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 judgement 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 judgement 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 the studies 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 studies 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

- 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.

Statistical methods

Meta-analyses will be performed according to the Cochrane Handbook for Systematic Reviews of Interventions [26]. The software package Review Manager (RevMan) Version 5.3 will be used [36]. Significance levels will be adjusted due to multiplicity of several outcomes. The results of each outcome will be determinative for the use of the intervention and requires an adjusted statistical significance level (threshold). An alfa of (0.05/ ((1+3)/2)=) 0.025 will be used for the primary outcomes to keep the family wise error rate (FWER) below 0.05. For the secondary outcomes this will be 0.033 [37,38]. For exploratory outcomes, we will consider a *p* value less than 0.05 as significant, because we view these outcomes as only hypothesis-generating outcomes. For dichotomous variables, the risk ratio (RR) with TSA-adjusted confidence intervals (CI) will be calculated. For continuous variables, the mean difference (MD) or the standardized mean difference (SMD) with 95% CI will be calculated.

For the outcome of SAE we plan to estimate the proportion of patients with one or more SAE in each group and to analyse this outcome in a binary meta-analysis. However, as we anticipate the reporting of SAEs in trials to vary considerably we plan to do two analyses:
1) Assuming that only one SAE is reported per patient we will add all reported SAE in each trial and calculate the proportion of summed SAE divided with number of randomized patients in the experimental and control intervention group (worst case scenario).
2) To avoid multiple counts of SAE in the same patients (SAE counting is not a statistical independent outcome) we will also analyse the most frequent SAE as if it represents the total number of SAE's in the experimental and control intervention group (best case scenario). Being aware that none of these intervention effect estimates are exactly correct we will discuss them as possible worst- and best-case scenarios for the effect of the experimental vs the control intervention on the proportion of patients with one or more SAE's.

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. We will conduct both random-effects model and fixed effect model meta-analyses. In case of discrepancies the results of both models will be presented and we will primarily stress the result of the model with the result closet to null effect due to principle of cautiousness [38]. The analyses will be performed on an intention-to-treat basis whenever possible.

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 assess this bias. Begg's and Egger's tests will be used to test for asymmetry in funnel plots [39].

Trial Sequential Analyses (TSA)

Meta-analyses may result in type-I errors and type-II errors due to an increased risk of random error when sparse data are analysed and due to repeated significance testing when a cumulative meta-analysis is updated with new trials [40,41]. To assess the risk of type-I and type-II errors, TSA will be used. The vast majority of meta analyses (nearly 80%) in Cochrane systematic reviews have less than the required information size to conclude on a 30% relative risk reduction (RRR) and less than 2% have sufficient power to conclude on a 10% RRR [42-44].

TSA combines information size estimation for meta-analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance of meta-analysis [40,41,45]. 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 may be insufficient evidence to reach a conclusion [40,41,46,47]. TSA can also be used for the evaluation of type II errors, that is to evaluate whether further randomized trial is futile to show or discard the anticipated intervention effect (RRR or MD). This happens when the cumulative z-curve does cross the TSMBs for futility. TSA will be applied since it controls the risks of type-I and type-II errors 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 (DARIS) [48]. We will do the primary analysis calculating the DARIS based on an a priori anticipated intervention effect of a 10% RRR which is close to a minimal important difference and sensitivity analyses for a 15% RRR as well as a the RRR suggested by the meta-analysis of the included trials [49]. If the estimated Diversity of the meta-analysis is 0%, a sensitivity analysis with 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 [48]. For secondary outcomes the DARIS will be calculated using a power of 80% [48].

As a sensitivity analysis, the DARIS will be calculated using the estimated intervention effect from the trials at low risk of bias in a conventional meta-analysis. If the required information size is surpassed for the TSA using the estimated intervention effect in the conventional meta-analysis or a TSMB is crossed a TSA with an anticipated intervention effect equal to the confidence limit closest to the null effect in the effect estimate from the conventional meta-analysis will be performed. The TSAs will be conducted using the control event proportion calculated from the unweighted control event proportion from the control groups of the actual meta-analyses.

Subgroup analyses

The following subgroup analyses will be performed:

- Trials at overall low risk of bias (all except blinding of surgeons scored as low risk of bias) compared to trials at high overall risk of bias (one or more of the bias domains (excluding blinding of surgeons) scored as unclear or high risk).
- Different patch materials may be used including venous, polytetrafluorethylene (PTFE), Dacron, and bio-patches (bovine/porcine) [25]. Subgroup analyses will be conducted according availability of data on different materials.

GRADE

Summary of findings tables will be produced summarizing the results of the trials with overall low risk of bias and for all trials, separately. Reasons for downgrading the quality of the available evidence are: 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) [50-52]. We will compare the imprecision assessed according to GRADE with that of TSA [53].

Patient and public involvement

Patients and/ or public were not involved in this study.

Ethics and dissemination

The proposed systematic review will collect and analyse secondary data from published studies therefor ethical approval is not required. The results of the systematic review will be disseminated by publication in a peer-review journal and submitted for presentation at relevant conferences.

Acknowledgement

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Conflicts of interest

None.

Author contributions

MSM is the first author of the protocol. MSM, GGK and AK managed the first draft of this manuscript and coordinated the contributions of coauthors. Contributors JW, AJ, CG, FLM, AK, FK, GGK contributed to the design of the study and revised the paper critically. JW, GC, FK and GGK provided professional and statistical support. All authors read and approved the final version of the manuscript. GGK was initiator and supervisor.

Protocol Timeline

First registration of the protocol at PROSPERO in August 2014. Change of first author who updated the protocol August 2018.

Proposed date of starting the search: 10th of September 2018. Proposed date of finishing the review is 31st of December 2018.

Word count:3790

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Appendix 1.

Figure 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy for symptomatic carotid stenosis (GRADE 2008) [31]

(Figure 1 should be inserted here)

*at maximum follow up

Appendix 2.

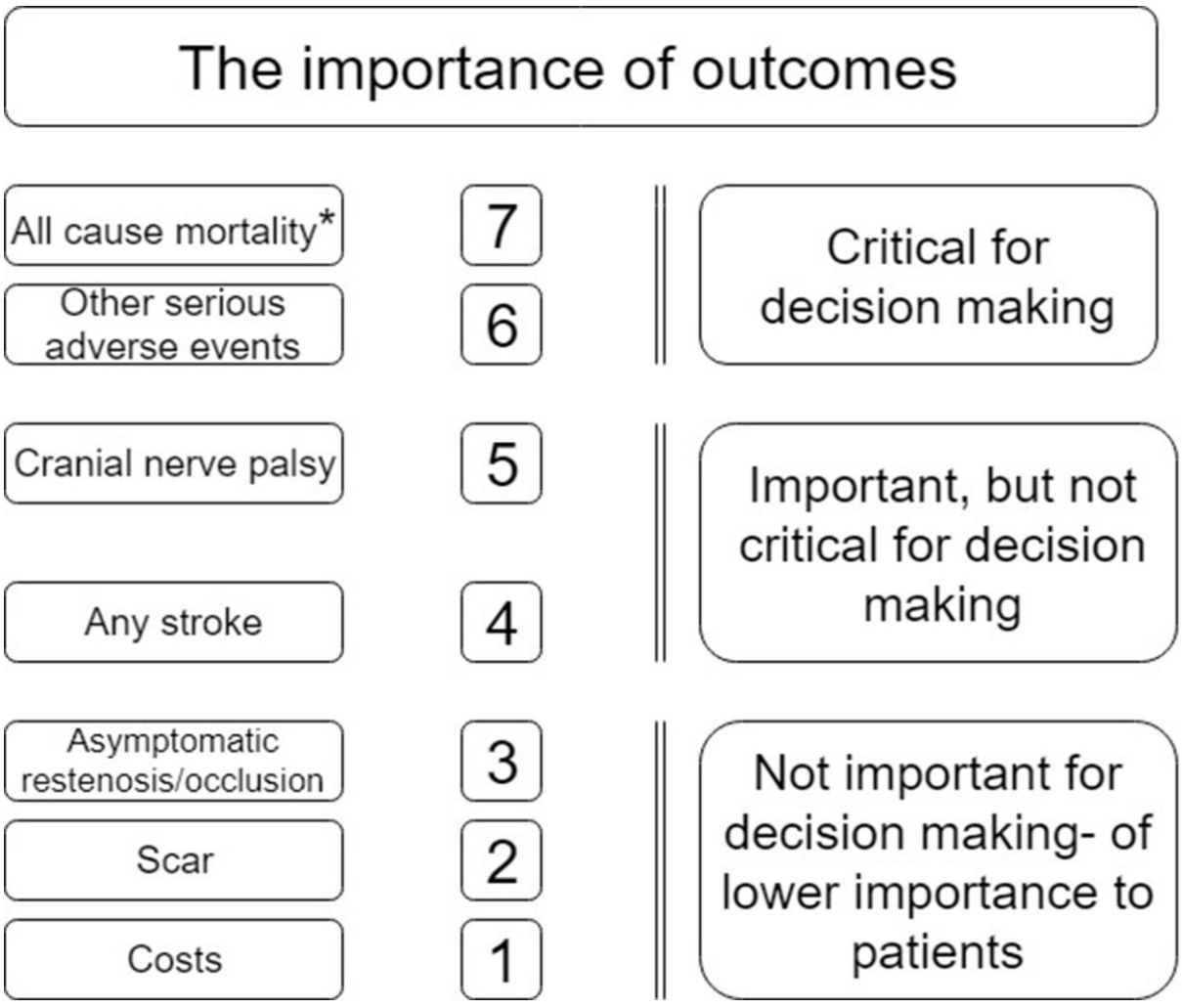
Proposed search PubMed 20th August 2018

Proposed search EMBASE 20th of August 2018

Proposed search Cochrane 20th of August

Appendix 1.

Figure 1: Outcomes prioritized according to importance to patients undergoing carotid endarterectomy for symptomatic carotid stenosis (GRADE 2008) [31]



*at maximum follow up

Appendix 2.

Proposed search PubMed 20th August 2018

(("Endarterectomy, Carotid"[Mesh] OR "Carotid Stenosis"[Mesh] OR "Stents"[Mesh] OR (Carotid[tiab] AND Endarterectomy[tiab]) OR (eversion[tiab] AND endarterectomy[tiab) OR (eversion[tiab] AND CEA[tiab]) OR eCEA[tiab] OR Carotid Stenos*[tiab] OR (carotid[tiab] AND Stent*[tiab]) OR (carotid[tiab] AND surger*[tiab])) AND ("Blood Vessel Prosthesis"[Mesh] OR "Polyethylene Terephthalates"[Mesh] OR "Polytetrafluoroethylene"[Mesh] OR Polytef[tiab] OR PTFE[tiab] OR TFE[tiab] OR FEP[tiab] OR Tarflen[tiab] OR Fluoroplast[tiab] OR GORE-TEX[tiab] OR Goretex[tiab] OR Teflon[tiab] OR Fluon[tiab] OR Polyethylene Terephthalate[tiab] OR Dacron[tiab] OR Polytetrafluoroethylene[tiab] OR Patch*[tiab] OR Blood Vessel Prosthes*[tiab] OR Vascular Prosthes*[tiab] OR Tissue-Engineered Vascular Graft*[tiab] OR "Angioplasty"[Mesh] OR angioplast*[tiab] OR biopatch*[tiab] OR porcine[tiab] OR bovine[tiab] OR "Endarterectomy, Carotid"[Mesh] OR (carotid[tiab] AND endarterectomy[tiab]) OR cCEA[tiab]))

42462 hits

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(('carotid endarterectomy'/exp OR 'carotid artery obstruction'/exp OR 'carotid artery stenting'/exp OR 'carotid artery stent'/exp or (Carotid:ti,ab AND Endarterectomy:ti,ab) OR (eversion:ti,ab AND endarterectomy:ti,ab) OR (eversion:ti,ab AND CEA:ti,ab) OR 'Carotid Stenos*':ti,ab OR (carotid:ti,ab AND Stent*:ti,ab) OR (carotid:ti,ab AND surger*:ti,ab)) AND ('blood vessel prosthesis'/exp OR 'polyethylene terephthalate'/exp OR 'polytetrafluoroethylene covered stent'/exp OR Polytef:ti,ab OR PTFE:ti,ab OR TFE:ti,ab OR FEP:ti,ab OR Tarflen:ti,ab OR Fluoroplast:ti,ab OR 'GORE-TEX':ti,ab OR Goretex:ti,ab OR Teflon:ti,ab OR Fluon:ti,ab OR 'Polyethylene Terephthalate':ti,ab OR Dacron:ti,ab OR Polytetrafluoroethylene:ti,ab OR Patch*:ti,ab OR 'Blood Vessel Prosthes*':ti,ab OR 'Vascular Prosthes*':ti,ab OR 'Tissue-Engineered Vascular Graft*':ti,ab OR 'angioplasty'/exp OR angioplast*:ti,ab OR biopatch*:ti,ab OR porcine:ti,ab OR bovine:ti,ab OR 'carotid endarterectomy'/exp OR (carotid:ti,ab AND endarterectomy:ti,ab) OR cCEA:ti,ab))

25898 hits

Proposed search Cochrane 20th of August

Carotid Endarterectomy OR eversion endarterectomy OR eversion CEA OR eCEA OR Carotid Stenos* OR carotid Stent* OR carotid surger*

AND

Polytef OR PTFE OR TFE OR FEP OR Tarflen OR Fluoroplast OR GORE-TEX OR Goretex OR Teflon OR Fluon OR Polyethylene Terephthalate OR Dacron OR Polytetrafluoroethylene OR Patch* OR Blood Vessel Prosthes* OR Vascular Prosthes* OR Tissue-Engineered Vascular Graft* OR angioplast* OR biopatch* OR porcine OR bovine OR carotid endarterectomy OR cCEA

1453 hits

Proposed search Google Scholar 20th August 2018

Carotid Endarterectomy in title

1000 hits

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	none
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	none
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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