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[Intervention Review]

Immediate versus delayed treatment for recently symptomatic carotid artery stenosis

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ABSTRACT

Background

The timing of surgery for recently symptomatic carotid artery stenosis remains controversial. Early cerebral revascularization may prevent a disabling or fatal ischemic recurrence, but it may also increase the risk of hemorrhagic transformation, or of dislodging a thrombus. This review examined the randomized controlled evidence that addressed whether the increased risk of recurrent events outweighed the increased benefit of an earlier intervention.

Objectives

To assess the risks and benefits of performing very early cerebral revascularization (within two days) compared with delayed treatment (after two days) for people with recently symptomatic carotid artery stenosis.

Search methods

We searched the Cochrane Stroke Group Trials Register in January 2016, the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2016, Issue 1), MEDLINE (1948 to 26 January 2016), EMBASE (1974 to 26 January 2016), LILACS (1982 to 26 January 2016), and trial registers (from inception to 26 January 2016). We also handsearched conference proceedings and journals, and searched reference lists. There were no language restrictions. We contacted colleagues and pharmaceutical companies to identify further studies and unpublished trials.

Selection criteria

All completed, truly randomized trials (RCT) that compared very early cerebral revascularization (within two days) with delayed treatment (after two days) for people with recently symptomatic carotid artery stenosis.

Data collection and analysis

We independently selected trials for inclusion according to the above criteria, assessed risk of bias for each trial, and performed data extraction. We utilized an intention-to-treat analysis strategy.

Main results

We identified one RCT that involved 40 participants, and addressed the timing of surgery for people with recently symptomatic carotid artery stenosis. It compared very early surgery with surgery performed after 14 days of the last symptomatic event. The overall quality of

the evidence was very low, due to the small number of participants from only one trial, and missing outcome data. We found no statistically significant difference between the effects of very early or delayed surgery in reducing the combined risk of stroke and death within 30 days of surgery (risk ratio (RR) 3.32; confidence interval (CI) 0.38 to 29.23; very low-quality evidence), or the combined risk of perioperative death and stroke (RR 0.47; CI 0.14 to 1.58; very low-quality evidence). To date, no results are available to confirm the optimal timing for surgery.

Authors' conclusions

There is currently no high-quality evidence available to support either very early or delayed cerebral revascularization after a recent ischemic stroke. Hence, further randomized trials to identify which patients should undergo very urgent revascularization are needed. Future studies should stratify participants by age group, sex, grade of ischemia, and degree of stenosis. Currently, there is one ongoing RCT that is examining the timing of cerebral revascularization.

PLAIN LANGUAGE SUMMARY

Timing of treatment for people with recent symptoms from neck artery narrowing

Background

Ischemic stroke occurs when blood flow is blocked from part of the brain. This can be caused by a disease in the neck (carotid) artery that can cause a severe narrowing of the artery, leading to blood clot formation and blockage of a smaller blood vessel downstream. Opening up the carotid artery can reestablish adequate blood flow by surgical removal of the diseased area, or by inserting a tube (stent) to open the artery.

There is uncertainty about whether to perform the treatment immediately, or to wait a few days. Early treatment can improve blood flow, and prevent new strokes. However, early treatment may carry a higher risk of causing a stroke or associated bleeding.

Review question

We reviewed the effectiveness of performing very early treatment (within two days) compared with delayed treatment (after two days) for individuals with recent symptoms from neck (carotid) artery narrowing.

Study characteristics

The searches are up-to-date to 26 January 2016. We found only one randomized trial that assessed the effect of the timing of surgery. It included a total of 40 participants, ranging in age from 47 to 84 years.

Key results

From the limited evidence available, we cannot tell if the timing of surgery is an important factor in determining the outcome for individuals with recent symptoms from carotid artery narrowing.

Quality of the evidence

There is not enough evidence on the best time for surgical treatment for people with recent symptoms from carotid artery narrowing. The overall quality of the evidence was very low, due to the small number of participants from only one trial and missing outcome data. Further studies with a larger number of patients are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Very early cerebral revascularization compared with delayed treatment for recently symptomatic carotid artery stenosis

Very early cerebral revascularization compared with delayed treatment for recently symptomatic carotid artery stenosis

Patient or population: people with recently symptomatic carotid artery stenosis

Settings: hospital

Intervention: very early cerebral revascularization (within two days)

Comparison: delayed treatment (after two days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Very early cerebral revascularization	Delayed Treatment				
Stroke and Death < 30 days	This outcome was poorly reported		RR 3.3 (0.4 to 29.2)	40 (1 study)	⊙⊙⊙ very low 1,2,3	
Perioperative death and strokes	This outcome was poorly reported		RR 0.5 (0.1 to 1.6)	40 (1 study)	⊙⊙⊙ very low 1,2,3	
Length of hospital stay	This outcome was poorly reported: One study reported no difference between groups. No standard deviation was reported.					
Myocardial infarction < 30 days	This outcome was not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded one level: one study with small sample size

- ²Downgraded one level due to risk of bias: incomplete outcome data
³Downgraded one level due to uncertainty in outcome measurement

BACKGROUND

Description of the condition

Annually, approximately 15 million people have a stroke worldwide, and 5.5 million of them die as a result of the event (Mackay 2004). Approximately 88% of all strokes are ischemic (Park 2012), and thromboembolism from an atheromatous plaque in the extracranial carotid artery has been determined to be the sole cause of stroke or a transient ischemic attack (TIA) in about 8% (Flaherty 2013; Park 2012). The risk of developing a future cerebrovascular ischemic event is related to inadequate cerebral blood perfusion as a result of hemodynamic stenosis, or plaque rupture and obstruction of smaller, more distally located blood vessels (Mokin 2013). In people with a recent cerebral or ocular ischemic episode, in whom the relevant (i.e. symptomatic) carotid artery is patent but the atheroma has caused a stenosis, some type of revascularization procedure may be required. According to different guidelines, surgical revascularization is recommended for people with symptomatic 50% to 99% carotid artery stenosis (Brott 2011; Kakisis 2012; Ricotta 2011). Carotid revascularization can be achieved by carotid endarterectomy or carotid artery stenting. The effectiveness of carotid endarterectomy for stroke prevention in people with symptomatic extracranial carotid disease has been established in randomized controlled trials (RCTs; Rothwell 2003). Angioplasty with stenting has emerged as an alternative, less invasive therapeutic method of treating all patients with carotid disease, with the increased risk of periprocedural stroke or death limited to older patients (Bonati 2012).

Description of the intervention

Since the 1950s, when carotid endarterectomy was introduced as an option for treatment and prevention of stroke, the number of procedures has increased (Rerkasem 2011). Carotid revascularization can reestablish adequate blood flow by removal of a critical carotid stenosis; this can be accomplished by surgical or endovascular treatment. Surgical options comprise conventional and eversion carotid endarterectomy. Conventional carotid endarterectomy is achieved by a longitudinal carotid arteriotomy with patch angioplasty, whereas eversion carotid endarterectomy involves a transection of the internal carotid artery and reimplantation into the common carotid artery (Antonopoulos 2011; Ricotta 2011). Clamping of the carotid arteries is required for removal of the plaque in both techniques (Kakisis 2012).

Furthermore, endovascular treatment may be a useful alternative to carotid endarterectomy. Carotid artery stenosis can be treated after a catheter inserted into the femoral artery is advanced, and after the target vessel lesion has been crossed, by deploying a self-expanding stent to cover the entire lesion (Kakisis 2012). Several embolic protection systems, including filters and flow arrest and reversal devices, have been developed in an attempt to reduce the chances of cerebral embolization (Paraskevas 2016). In addition, a transcervical approach carotid artery stenting using flow reversal protection has also been described (EMPIRE 2011).

How the intervention might work

The timing of revascularization of symptomatic internal carotid artery stenosis has changed over the years. Rothwell 2003 showed greater benefit of surgery when performed within 14 days of the last symptomatic event. However, no definite time lag has been observed between occurrence of the neurologic event and surgery.

Early revascularization is beneficial for symptomatic patients because this intervention may prevent a disabling or fatal stroke, but an early intervention may increase perioperative risk of stroke and death from carotid revascularization (Capoccia 2012; Imai 2005; Rantner 2011).

An ischemic stroke recurrence and perioperative risks of revascularization have very different mechanisms (Rerkasem 2011). The presumption is that early revascularization will improve perfusion to a large territory at risk surrounding an infarct core (i.e. the penumbra), will recruit brain areas before cell death occurs, and will prevent new embolic events (Capoccia 2011; Ricotta 2011). Major concerns about early revascularization after TIA or stroke include the following:

- Transformation of the preexisting infarct core into a hemorrhagic lesion as a result of reperfusion or hyperperfusion injury (Ferrero 2014; Tsvigoulis 2014);
- Increased vulnerability of recently infarcted brain tissue to periprocedural cerebral ischemia induced by carotid clamping or profoundly decreased blood pressure (Tsvigoulis 2014);
- Increased vulnerability of carotid plaques in the early phase of cerebral ischemia and thus hazardous removal without distal embolization (Strömberg 2012; Tsvigoulis 2014).

On one hand, the danger of delaying investigation and treatment after a TIA or a non disabling stroke depends on the early risk of ischemic recurrence (Lovett 2003; Rantner 2011). Early risk of stroke after a TIA or a non-disabling stroke is around 3.1% to 5.2% within 48 hours; this increases to 8.3% to 11.2% at 14 days (Giles 2007; Johansson 2013; Marnane 2011). On the other hand, the risk of hemorrhagic transformation or of dislodging a thrombus is a matter of major concern during the early intervention. All major adverse events and vascular complications that occur within 30 days of the procedure are attributed to the procedure. Within 30 days of endarterectomy, the risk of death or stroke is 2.4% to 7.6% within 48 hours, and 0.8% to 6.9% at 14 days (Halm 2009; Johansson 2013; Rantner 2013; Sharpe 2013).

In addition, carotid artery stenting has a periprocedural stroke and death risk of 7.1% within 48 hours of a neurologic event, and 2.8% to 8.1% at 14 days (Rantner 2013; Wach 2014). The theoretical benefit of early carotid artery stenting is that it provides the possibility of reopening a critical stenosis with rare reduction in cerebral blood flow (Imai 2005). However, carotid artery stenting within the first few days of a neurologic event may carry excessive risk of mobilization of a thrombus (Rantner 2013).

Why it is important to do this review

The inability to predict which patients may have neurologic worsening during the first 24 to 48 hours after stroke may explain the variation in management of acute stroke among physicians and institutions (Battocchio 2012; Ferrero 2014).

In the UK, current guidelines recommend that carotid intervention should ideally be performed within two days for symptomatic severe carotid stenosis in stable patients (as cited in Capoccia 2011; Strömberg 2012). In the USA, it is recommended that carotid endarterectomy should be performed within two weeks of the neurologic event, and urgent revascularization may be considered for stable patients who have limited areas of infarct with a large penumbra (Ricotta 2011).

Analysis of RCTs is necessary to determine whether increased risk of recurrent events outweighs the increased risk of an earlier intervention. Reliable data on risk of surgery or carotid artery stenting in relation to timing of the intervention are necessary if clinicians are to plan surgery or carotid artery stenting most effectively, to adjust risks for case-mix, and to understand the mechanisms of operative stroke.

OBJECTIVES

To assess the risks and benefits of performing very early cerebral revascularization (within two days) compared with delayed treatment (after two days) for people with recently symptomatic carotid artery stenosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs that compared early intervention versus delayed revascularization in people with recently symptomatic carotid artery stenosis (up to 14 days from onset of symptoms). We included studies only if data on clinically significant endpoints, such as ischemic stroke, hemorrhagic stroke, or death, were available.

Types of participants

We included people who had suffered a recent neurologic (TIA or stroke) event ipsilateral to stenosis of 50% to 99% in the carotid artery. We defined a stroke as any cerebrovascular or retinal event with symptoms lasting longer than 24 hours ([Rerkasem 2011](#); [Rothwell 2003](#)), and a TIA as a focal neurologic deficit lasting 24 hours ([Ferrero 2014](#); [Giles 2007](#)). We defined a nondisabling stroke as a stroke that resulted in no disability of functional significance (modified Rankin score < 3; [Brott 2011](#); [Rerkasem 2011](#); [Rothwell 2003](#)).

Brain imaging that demonstrated a new lesion involving a different anatomic site or vascular territory from the index event could be used to support the diagnosis of perioperative stroke. We classified strokes as disabling or nondisabling (as defined by trial authors), fatal or nonfatal, or contralateral, ipsilateral, hemorrhagic, or ischemic.

Types of interventions

All techniques aimed at revascularization in symptomatic carotid artery stenosis, including but not confined to:

- percutaneous transluminal balloon angioplasty and stenting;
- carotid endarterectomy; and
- carotid eversion.

We included randomized studies comparing early intervention (within two days) versus delayed treatment (after two days).

Types of outcome measures

Primary outcomes

- The combined outcome of any stroke or death occurring within 30 days of surgery or endovascular treatment (postoperative).

Secondary outcomes

- Myocardial infarction within 30 days of surgery.
- Myocardial infarction within 30 days of endovascular treatment.
- Strokes or deaths, or both, during the perioperative period. For the purposes of this review the term perioperative refers to the three phases of surgery: preoperative, intraoperative, and postoperative, and commonly includes ward admission, anesthesia, surgery, and recovery.
- Duration of procedures, length of hospital stay, and procedure-related costs (if data are available).
- Significant local complications related to revascularization, such as access site hematoma, infection, cranial nerve palsy, or pseudoaneurysm formation.

Myocardial infarction is defined by the presence of two of the following criteria:

- Specific cardiac enzymes more than twice the upper limit of normal;
- History of chest discomfort lasting at least 30 minutes;
- Development of specific abnormalities on a standard 12-lead electrocardiogram (ECG).

Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module. We searched for relevant trials published in all languages and arranged translation of trial reports if required.

Electronic searches

We searched the Cochrane Stroke Group's Trials Register (strokecenter.org/trials) and the following electronic databases and trials registers:

- The Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2016, Issue 1; [Appendix 1](#));
- MEDLINE (Ovid; 1948 to 26 January 2016; [Appendix 2](#));
- EMBASE (Ovid; 1948 to 26 January 2016; [Appendix 3](#));
- Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS; 1948 to 26 January 2016; [Appendix 4](#));
- ClinicalTrials.gov (clinicaltrials.gov)
- Current Controlled Trials (controlled-trials.com)
- European Union (EU) Clinical Trials Register (clinicaltrialsregister.eu)
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch)

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist and modified it for use with the other databases.

Searching other resources

In an effort to identify further published, unpublished, and ongoing trials, we:

- searched the reference lists of identified studies and reviews;
- contacted study authors and experts in the field;
- contacted relevant pharmaceutical companies; and

- used Science Citation Index Cited Reference Search for forward tracking of important articles.

Data collection and analysis

Selection of studies

Two review authors (VV and NC) independently screened titles and abstracts of the references obtained as a result of our searching activities and excluded obviously irrelevant reports. We retrieved full-text articles for the remaining references, and two review

authors (VV and NC) independently screened the full-text articles, identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion; if required, we consulted a third review author (JCCBS) for resolution. We collated multiple reports on the same study, so that each study, not each reference, was the unit of interest in the review. We recorded the selection process and completed a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

Data extraction and management

Two review authors (VV and NC) independently extracted the following data from eligible studies and recorded this information on standard data extraction forms:

- Participants: sample size, age, sex, number of participants originally allocated to each treatment group, diagnostic criteria used for carotid stenosis, number of participants in each group with early or delayed intervention.
- Intervention: time interval from onset of symptoms of TIA or stroke to randomization, and from randomization to surgery, type of anesthesia, technique of carotid endarterectomy, technique of carotid artery stenting, any other major vascular surgery.
- Outcomes: number of participants in each group with outcome events, including stroke, myocardial infarction, and death.
- Withdrawals and adverse effects.
- Length of follow-up.
- Additional important information.

We resolved disagreements between review authors by discussion.

Assessment of risk of bias in included studies

Two review authors (VV and NC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by involving another review author (JCCBS). We assessed the following domains as 'Yes' (low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (high risk of bias):

- Random sequence generation: was the sequence generation adequate?
- Allocation concealment: was allocation adequately concealed?
- Blinding of participants and personnel: were participants and personnel blinded to the allocated interventions?
- Blinding of outcome assessment: were the outcome assessors blinded to the allocated interventions?
- Incomplete outcome data: were incomplete outcome data adequately addressed and similar across intervention groups?
- Selective outcome reporting: are reports of the study free of the suggestion of selective outcome reporting?
- Other bias: was the study apparently free of other problems that could put it at a risk of bias?

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report together with a justification for our judgment in the 'Risk of bias' tables.

Measures of treatment effect

For dichotomous variables, we calculated risk ratios (RRs) and 95% confidence intervals (CIs). For continuous data, we would have calculated mean differences (MDs) and 95% CIs between treatment groups if studies reported exactly the same outcomes. If similar outcomes were reported on different scales, we would have calculated the standardized mean difference (SMD) and the 95% CI. The most appropriate way of summarizing time-to-event data would have been to use methods of survival analysis while expressing the intervention effect as a hazard ratio; we extracted these data directly from the results of studies (Higgins 2011).

Unit of analysis issues

We based the unit of analysis on the individual participant (unit randomized for interventions to be compared; i.e. the number of observations in the analysis should have matched the number of individuals randomly assigned).

Dealing with missing data

For missing or unavailable data, we contacted study authors to request additional information. If we received no response, regardless of the type of data, we had planned to report dropout rates in the 'Characteristics of included studies' tables of the review, and use intention-to-treat analysis (Higgins 2011). Therefore, we included all randomized participants in the groups to which they were allocated.

Assessment of heterogeneity

We would have assessed clinical and methodological diversity in terms of participants, interventions, outcomes, and study characteristics for the included studies in order to determine whether a meta-analysis was appropriate. We would have conducted this by observing these data from the data extraction tables. We would have assessed statistical heterogeneity by visual inspection of the forest plot for obvious differences in results between the studies, and by using the I^2 and Chi^2 statistical tests.

We would have qualified inconsistency among pooled estimates by using the I^2 statistic: $((Q - df)/Q) \times 100\%$ test, where Q was the Chi^2 statistic and df represented the degree of freedom). This would have examined the percentage of total variation across studies due to heterogeneity rather than to chance (Higgins 2003; Higgins 2011).

We would have used these thresholds for interpretation of I^2 :

- 0% to 25%: low heterogeneity.
- 25% to 75%: moderate heterogeneity.
- Greater than 75%: significant heterogeneity (Higgins 2003).

Assessment of reporting biases

Given the limited number of eligible trials available, we did not create funnel plots to assess reporting biases. In future updates of this review, we will interpret any funnel plot asymmetry with caution.

Data synthesis

Methods of synthesizing studies depend on quality, design, and heterogeneity. We would have explored both clinical and statistical heterogeneity. Where we considered studies to be sufficiently similar, we would have conducted a meta-analysis by pooling appropriate data using RevMan (RevMan 2014).

We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE 2015) approach and constructed 'Summary of findings for the main comparison' for the outcomes.

Subgroup analysis and investigation of heterogeneity

If we had found sources of heterogeneity, and when data were sufficient, we had planned to conduct meta-analyses by subgroups. If we had identified an adequate number of studies, we had planned to performed subgroup analyses according to participant age,

participant sex, type of revascularization, degree of stenosis, and initial neurologic severity.

If we had identified no significant heterogeneity, we had planned to compute pooled estimates of the treatment effect for each outcome using a fixed-effect model. When we detected significant heterogeneity despite subgroup analyses, we would have calculated the pooled estimate of treatment effects using random-effects models.

Sensitivity analysis

If an adequate number of studies had been identified, we had planned to perform sensitivity analyses based on separation of studies according to risk of bias. We would have done this by excluding trials that were most susceptible to bias, based on our risk of bias assessment: those with inadequate allocation concealment, high levels of post-randomization losses or exclusions, and uncertain or unblinded outcome assessment (Deeks 2011).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

We identified a total of 4255 articles, and after removing duplicates, we manually screened 3151 records. We identified six articles from the search of the Cochrane Stroke Group's Trials Register; two reports of one study fulfilled the entry criteria (McCollum 2004). There were no randomized clinical trials involving carotid percutaneous transluminal balloon angioplasty and stenting. [Figure 1](#) depicts the process of study identification and selection.

Included studies

To date we have identified one completed randomized controlled trial comparing very early cerebral revascularization with delayed treatment for individuals with recently symptomatic carotid artery

stenosis (McCollum 2004). However, it compared very early surgery with surgery performed after 14 days of the last symptomatic event. Forty participants fit for surgery with partial anterior circulation infarction and a Barthel score greater than 18 within the preceding seven days and with 70% ipsilateral internal carotid stenosis were randomized into two surgical treatment groups:

- very early surgery (within 24 hours); and
- late surgery (six to eight weeks).

Participants in the late surgery group received the best medical care at the time, which consisted of antiplatelet therapy and rigorous attention to the control of risk factors. Outcomes were assessed at seven days, and two, six and 12 months following the surgery.

Excluded studies

Excluded studies were those that did not meet the inclusion criteria after we had reviewed the full text. We excluded three studies because they were:

- confounded with no control group (Keunen 2012); or
- non-acute study (Ballota 2002, Sbatigia 2003); or
- not randomized (Keunen 2012, Sbatigia 2003).

Ongoing studies

There is one ongoing randomized trial that involves the timing of cerebral revascularization (SPREAD-STACI). Correspondence with the principal investigator indicated that a full publication is planned in a few years.

Risk of bias in included studies

The included study was of very low methodological quality (McCollum 2004). This study was classified as having a low risk of bias for randomization, performance and reporting. It was also classified as having an unclear risk of bias for detection and allocation concealment because the study did not provide any information on this. We judged that the included study was at high risk for attrition and small sample size biases ([Figure 2](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Randomization of 40 participants with recently symptomatic carotid artery stenosis was undertaken by computer. Although the participants in the early group underwent surgery soon after randomization, the time between the neurological event and the operation was not clear. According to the author, most of the participants in the trial were operated on within a day or two of

cerebral infarction. However, there were no available data on the proportion who underwent surgery within 48 hours of the onset of symptoms (personal communication).

Blinding

Due to the study design and the nature of the intervention and outcomes, health workers and participants were not blinded to treatment or outcome.

All the carotid endarterectomies were performed by the same vascular surgeon, using a standard surgical technique. Participants were followed up by the trial coordinator seven days after treatment and then again at two, six, and 12 months following randomization. No reference was made as to whether the outcome assessor was blinded to the timing of surgery.

Incomplete outcome data

Of the 21 participants randomized to 'delayed' surgery, nine participants did not undergo carotid endarterectomy at two months. Data were analyzed on an intention-to-treat basis. The included study reported losses, and therefore, was classified as having a high risk of attrition bias

Selective reporting

Outcome measures were recorded using the Barthel Activities of Daily Living score for disability and the Modified Rankin Scale for independence. All of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported

Other potential sources of bias

We assessed possible bias by small size of the included study, as small studies have been shown to overestimate treatment effects, allowing critical criteria to be compromised. We considered studies to be at low risk of bias if they had 200 participants or more per arm, at unclear risk if they had 50 to 200 participants, and at high risk if they had fewer than 50 participants ([Dechartres 2013](#)). Therefore, we considered the included study was at high risk.

Effects of interventions

See: [Summary of findings for the main comparison Very early cerebral revascularization compared with delayed treatment for recently symptomatic carotid artery stenosis](#)

In the one included study, both study groups achieved an adequate distribution of patient characteristics such as age, sex, and the severity of carotid disease or stroke ([McCollum 2004](#)).

Nineteen participants were allocated to early surgery (usually within two to six hours) and 21 to late surgery (six to eight weeks). Outcome was determined 12 months after the stroke in this study. Nine of the 21 participants randomized to the delayed group did not undergo surgery due to occlusion of internal carotid following randomization (three participants), participants refusal of surgery (three participants), considered to be medically unfit for surgery after stroke progression (two participants), and regression of carotid stenosis to less than 70% (one participant).

We used a random-effects model because, after inclusion of future studies, it is possible that the interventions themselves will differ from one study to the next. The timing of the intervention, or the 'best medical therapy' can be very different across time, as seen in other studies ([Ballota 2002](#); [McCollum 2004](#)).

Relative risks between early and late surgery did not attain statistical significance for any of the outcomes assessed (see [Data](#)

and analyses). When we considered the cumulative unweighted risk of stroke or death, or both, within 30 days of surgery, the risks for late and early surgery were 5% (1/21) and 16% (3/19), respectively. Three post-operative strokes were recorded in the early group and none in the delayed group. Late surgery was favored, although confidence intervals were wide (RR 3.32; 95% CI 0.38 to 29.23; [Analysis 1.1](#)). However, when we considered the combined outcome of perioperative death and strokes, the risks for the early and delayed groups were 16% (3/19) and 33% (7/21), respectively. Perioperative death rate was 5% in the delayed surgical group and 0% in the early group. In addition, six neurologic events were recorded before surgery in the late group and none in the early group. The relative risk between early and late surgery showed a trend for better outcome in participants undergoing early surgery. The benefits or hazards of early surgery in perioperative death and stroke risks from these data remains unclear (RR 0.47; CI 0.14 to 1.58; [Analysis 1.2](#)).

The average length of hospital stay was 11 days for the early group and 28 days for the delayed group. However, we were unable to estimate 95% CIs of the difference due to the lack of standard deviations.

DISCUSSION

Summary of main results

Most studies that examine the influence of timing of cerebral revascularization on outcomes after a neurological event are not randomized. We identified only one completed, randomized study that compared timing of surgery after a stroke, and there were not enough data to draw any reliable conclusions about the preferred timing of surgery ([McCollum 2004](#)). Hence there is a need for further randomized trials.

There is one ongoing RCT that compares the timing of surgery after an acute neurological event ([SPREAD-STACI](#)). The data should be available within the next two years.

Although the study compared very early surgery with surgery performed after 14 days of the onset of symptoms, there is already evidence that carotid endarterectomy performed within 14 days of the symptoms produces better long-term results than if it is delayed ([Rothwell 2003](#)). Therefore, it is unclear whether the risk of stroke, death, or both in the delayed group was related to the carotid surgery or to the conditions of the participants.

Overall completeness and applicability of evidence

The primary outcome of this review, the combined outcome of stroke, death, or both occurring within 30 days of intervention, was poorly reported by the study, and the relative risks between early and late surgery did not attain statistical significance. Therefore, it was difficult to analyze and draw reliable conclusions.

Quality of the evidence

Overall, the included study was at a very high risk of bias. The reasons for downgrading the quality of the evidence related to the uncertainty in outcome measurement, the incompleteness of outcome data available in the study, and a very small sample size. The quality of all outcomes included in [Summary of findings for the main comparison](#) was downgraded three levels, resulting in a very low-quality of the evidence for all outcomes ([GRADE 2015](#)).

Another issue is that medical management has changed over the study period, as more advanced pharmacological agents and more stringent management of various risk factors of atherosclerosis have led to an overall decline in the incidence of stroke.

Potential biases in the review process

We strived to prevent bias in the review process by involving two independent review authors at each step of the review, and by performing a comprehensive search with no language restrictions.

Agreements and disagreements with other studies or reviews

We identified other systematic reviews that examined the timing of interventions for recently symptomatic patients, which included non-randomized clinical trials. They found no substantially elevated risk with early surgery in stable patients (Rerkasem 2009), but found an elevated risk in people with unstable neurological symptoms (Naylor 2009; Rerkasem 2009).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence to determine the relative risks and benefits of very early cerebral revascularization. Optimal periods of cerebral revascularization for recently symptomatic patients should be clarified. Until better evidence is available, the choice of timing for surgery should depend on other sources of information.

Implications for research

General

Little is known about the natural history of very recently symptomatic carotid artery stenosis and what constitutes the best timing for treatment. Calculation of the sample size to verify the difference in efficacy of early and delayed surgery is difficult, due

to the lack of data. From observational studies, we can assume a cumulative unweighted risk of perioperative stroke, death, or both of 7.2% for carotid endarterectomy performed within 48 hours of the onset of the initial ischemic symptom, and 18.1% for carotid endarterectomy performed after 48 hours (Halm 2009; Johansson 2013; Sharpe 2013). Therefore, we would need around 145 participants in each arm for 80% power and 5% two-sided significance. Considering possible dropouts of 10% over the whole study, the required sample size in each study arm would be 160 participants. Further studies, probably multicenter to obtain a larger sample, are needed to consolidate this evidence.

Design

There is a need for further well conducted, prospective, randomized controlled trials (i.e. adequate randomization, allocation concealment, blinding, etc), that assess the effects of timing of surgery on participants with recently symptomatic carotid artery stenosis. Aggressive treatment of vascular risk factors and antiplatelet therapy must be promptly initiated because it is crucial to the prevention of recurrent strokes. Future studies should standardize the observation time and stratify participants by age group, sex, grade of ischemia, and degree of stenosis.

Measurement

The most important outcomes are the cumulative risk of strokes and/or death before and within 30 days of surgery, and cumulative risk of perioperative death and strokes. Other important issues that require examination include patient age (do the elderly fare worse?), grade of ischemia (major stroke), sex (male versus female), and duration of hospitalizations.

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REFERENCES

References to studies included in this review

McCollum 2004 {published data only}

Mead GE, Murray H, Farrell A, O'Neill PA, McCollum CN. Pilot study of carotid surgery for acute stroke. *British Journal of Surgery* 1997;**84**:990-2.

* Welsh S, Mead G, Chant H, Picton A, O'Neill PAA, McCollum CN. Early carotid surgery in acute stroke: a multicentre randomised pilot study. *Cerebrovascular Diseases* 2004;**18**:200-5. [DOI: [10.1159/000079942](https://doi.org/10.1159/000079942)]

References to studies excluded from this review

Ballota 2002 {published data only}

Ballota E, Giau G, Baracchini C, Abbruzzese E, Saladini M, Meneghetti G. Early versus delayed endarterectomy after a nondisabling ischemic stroke: a prospective randomized study. *Surgery* 2002;**131**:287-92. [DOI: [10.1067/msy.2002.119987](https://doi.org/10.1067/msy.2002.119987)]

Keunen 2012 {published data only}

Keunen RWM, van Sonderen A, Hunfeld M, Remmers M, Tavy DL, de Bruijn, et al. Exploration of a zero-tolerance regime on cerebral embolism in symptomatic carotid artery disease. *Prospectives In Medicine* 2012;**1**:218-23. [DOI: [10.1016/j.permed.2012.02.064](https://doi.org/10.1016/j.permed.2012.02.064)]

Sbatigia 2003 {published data only}

Sbatigia E, Toni D, Speziale F, Falcou A, Sachetti ML, Panico MA, et al. Emergency and early carotid endarterectomy in patients with acute ischemic stroke selected with a predefined protocol: a prospective pilot study. *International Angiology* 2003;**22**:426-30.

References to ongoing studies

SPREAD-STACI {unpublished data only}

Lanza G, Ricci S, Speziale F, Toni D, Sbarigia E, Setacci C, et al. SPREAD-STACI study: a protocol for a randomized multicenter clinical trial comparing urgent with delayed endarterectomy in symptomatic carotid artery stenosis. *International Journal of Stroke* 2012;**7**(1):81-5.

Additional references

Antonopoulos 2011

Antonopoulos CN, Kakisis JD, Sergentanis TN, Liapis CD. Eversion versus conventional carotid endarterectomy: a meta-analysis of randomised and non-randomised studies. *European Journal of Vascular and Endovascular Surgery* 2011;**42**(6):751-65. [DOI: [10.1016/j.ejvs.2011.08.012](https://doi.org/10.1016/j.ejvs.2011.08.012)]

Battocchio 2012

Battocchio C, Fantozzi C, Rizzo L, Persiani F, Raffa S, Taurino M. Urgent carotid surgery: is it still out of debate?. *International Journal of Vascular Medicine* 2012;**2012**:536392. [DOI: [10.1155/2012/536392](https://doi.org/10.1155/2012/536392)]

Bonati 2012

Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: [10.1002/14651858.CD000515.pub3](https://doi.org/10.1002/14651858.CD000515.pub3)]

Brott 2011

Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. *Catheterization and Cardiovascular Interventions* 2013;**81**(1):E76-123. [DOI: [10.1002/ccd.22983](https://doi.org/10.1002/ccd.22983)]

Capoccia 2011

Capoccia L, Sbarigia E, Speziale F, Toni D, Fiorani P. Urgent carotid endarterectomy to prevent recurrence and improve neurologic outcome in mild-to-moderate acute neurologic events. *Journal of Vascular Surgery* 2011;**53**(3):622-8. [DOI: [10.1016/j.jvs.2010.09.016](https://doi.org/10.1016/j.jvs.2010.09.016)]

Capoccia 2012

Capoccia L, Sbarigia E, Speziale F, Toni D, Biello A, Montelione N, et al. The need for emergency surgical treatment in carotid-related stroke in evolution and crescendo transient ischemic attack. *Journal of Vascular Surgery* 2012;**55**(6):1611-7. [DOI: [10.1016/j.jvs.2011.11.144](https://doi.org/10.1016/j.jvs.2011.11.144)]

Dechartres 2013

Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;**346**:f2304.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org/.

EMPIRE 2011

Clair DG, Hopkins LN, Mehta M, Kasirajan K, Schermerhorn M, Schönholz C, et al. Neuroprotection during carotid artery stenting using the GORE flow reversal system: 30-day outcomes in the EMPIRE Clinical Study. *Catheterization and Cardiovascular Interventions* 2011;**77**(3):420-9. [DOI: [10.1002/ccd.22789](https://doi.org/10.1002/ccd.22789)]

Ferrero 2014

Ferrero E, Ferri M, Viazzo A, Labate C, Berardi G, Pecchio A, et al. A retrospective study on early carotid endarterectomy within 48 hours after transient ischemic attack and stroke in evolution. *Annals of Vascular Surgery* 2014;**28**:227-38. [DOI: [10.1016/j.avsg.2013.02.015](https://doi.org/10.1016/j.avsg.2013.02.015)]

Flaherty 2013

Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, et al. Carotid artery stenosis as a cause of stroke. *Neuroepidemiology* 2013;**40**(1):36-41.

Giles 2007

Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurology* 2007;**6**(12):1063-72.

GRADE 2015 [Computer program]

GRADE Working Group, McMaster University (developed by Evidence Prime, Inc.). Available from gradepro.org. GRADEpro GDT 2015: GRADEpro Guideline Development Tool [Software]. Hamilton (ON): GRADE Working Group, McMaster University (developed by Evidence Prime, Inc.). Available from gradepro.org, 2015.

Halm 2009

Halm EA, Tuhim S, Wang JJ, Rockman C, Riles TS, Chassin MR. Risk factors for perioperative death and stroke after carotid endarterectomy: results of the New York carotid artery surgery study. *Stroke* 2009;**40**(1):221-9. [DOI: [10.1161/STROKEAHA](https://doi.org/10.1161/STROKEAHA)]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**(7414):557-60. [PUBMED: 12958120]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org/.

Imai 2005

Imai K, Mori T, Izumoto H, Watanabe M, Majima K. Emergency carotid artery stent placement in patients with acute ischemic stroke. *American Journal of Neuroradiology* 2005;**26**:1249-58.

Johansson 2013

Johansson EP, Arnerlöv C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. *International Journal of Stroke* 2013;**8**(4):220-7. [DOI: [10.1111/j.1747-4949.2012.00790.x](https://doi.org/10.1111/j.1747-4949.2012.00790.x)]

Kakisis 2012

Kakisis JD, Avgerinos ED, Antonopoulos CN, Giannakopoulos TG, Moulakakis K, Liapis CD. The European Society for Vascular Surgery guidelines for carotid intervention: an updated independent assessment and literature review. *European Journal of Vascular and Endovascular Surgery* 2012;**44**(3):238-43. [DOI: [10.1016/j.ejvs.2012.04.015](https://doi.org/10.1016/j.ejvs.2012.04.015)]

Lovett 2003

Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. *Stroke* 2003;**34**(8):138-40.

Mackay 2004

Mackay J, Mensah G. The Atlas of Heart Disease and Stroke. Geneva: World Health Organization (WHO), 2004.

Marnane 2011

Marnane M, Ni Chroinin D, Callaly E, Sheehan OC, Merwick A, Hannon N, et al. Stroke recurrence within the time window recommended for carotid endarterectomy. *Neurology* 2011;**77**(8):738-43. [DOI: [10.1212/WNL.0b013e31822b00cf](https://doi.org/10.1212/WNL.0b013e31822b00cf)]

Mokin 2013

Mokin M, Dumont TM, Kass-Hout T, Levy EI. Carotid and vertebral artery disease. *Primary Care* 2013;**40**(1):135-51.

Naylor 2009

Karkos CD, Hernandez-Lahoz I, Naylor AR. Urgent carotid surgery in patients with crescendo transient ischaemic attacks and stroke-in-evolution: a systematic review. *European Journal of Vascular and Endovascular Surgery* 2009;**37**(3):279-88.

Paraskevas 2016

Paraskevas KI, Veith FJ, Parodi JC. Commentary: Transcervical carotid artery stenting (CAS) with flow reversal: a promising technique for the reduction of strokes associated With CAS. *Journal of Endovascular Therapy* 2016;**23**(2):255-7. [DOI: [10.1177/1526602816633830](https://doi.org/10.1177/1526602816633830)]

Park 2012

Park JH, Razuk A, Saad PF, Telles GJ, Karakhanian WK, Fioranelli A, et al. Carotid stenosis: what is the high-risk population?. *Clinics (São Paulo)* 2012;**67**(10):1233.

Rantner 2011

Rantner B, Kollerits B, Schmidauer C, Willeit J, Thauerer M, Rieger M, et al. Carotid endarterectomy within seven days after the neurological index event is safe and effective in stroke prevention. *European Journal of Vascular and Endovascular Surgery* 2011;**42**(6):732-9. [DOI: [10.1016/j.ejvs.2011.08.004](https://doi.org/10.1016/j.ejvs.2011.08.004)]

Rantner 2013

Rantner B, Goebel G, Bonati LH, Ringleb PA, Mas JL, Fraedrich G, Carotid Stenting Trialists' Collaboration. The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms. *Journal of Vascular Surgery* 2013;**57**(3):619-26.

Rerkasem 2009

Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke* 2009;**40**(10):e564-72.

Rerkasem 2011

Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: [10.1002/14651858.CD001081.pub2](https://doi.org/10.1002/14651858.CD001081.pub2)]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ricotta 2011

Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK, Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. *Journal of Vascular Surgery* 2011;**54**:832-6. [DOI: [10.1016/j.jvs.2011.07.004](https://doi.org/10.1016/j.jvs.2011.07.004)]

Rothwell 2003

Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**(9352):107-16. [12531577]

Sharpe 2013

Sharpe R, Sayers RD, London NJ, Bown MJ, McCarthy MJ, Nasim A, et al. Procedural risk following carotid endarterectomy in the hyperacute period after onset of symptoms. *European Journal of Vascular and Endovascular Surgery* 2013;**46**(5):519-24.

Strömberg 2012

Strömberg S, Gelin J, Osterberg T, Bergström GML, Karlström L, Osterberg K, Swedish Vascular Registry (Swedvasc) Steering Committee. Very urgent carotid endarterectomy confers increased procedural risk. *Stroke* 2012;**43**(5):1331-5. [DOI: [10.1161/STROKEAHA.111.639344](https://doi.org/10.1161/STROKEAHA.111.639344)]

Tsivgoulis 2014

Tsivgoulis G, Krogias C, Georgiadis GS, Mikulik R, Safouris A, Meves SH, et al. Safety of early endarterectomy in patients with symptomatic carotid artery stenosis: an international multicenter study. *European Journal of Neurology* 2014;**21**(10):1251-e76. [DOI: [10.1111/ene.12461](https://doi.org/10.1111/ene.12461)]

Wach 2014

Wach MM, Dumont TM, Mokin M, Kass-Hout T, Snyder KV, Hopkins LN, et al. Early carotid angioplasty and stenting may offer non-inferior treatment for symptomatic cases of carotid artery stenosis. *Journal of Neurointerventional Surgery* 2014;**6**(4):276-80. [DOI: [10.1136/neurintsurg-2013-010744](https://doi.org/10.1136/neurintsurg-2013-010744)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

McCollum 2004

Methods	Randomized Multicenter 12 months follow-up Intention-to-treat analysis
Participants	40 participants within 7 days of the onset of symptoms Partial anterior circulation infarction More than 70% ipsilateral carotid stenosis Barthel score > 18
Interventions	Early surgery (usually within 2 to 6 hours) Late surgery (6 to 8 weeks)
Outcomes	Outcome measures were recorded using Barthel Activities of Daily Living score for disability and Modified Rankin scale for independence
Notes	Study dates not reported Nine of the 21 participants randomized to the late surgery group did not undergo surgery
Risk of bias	
Bias	Authors' judgement Support for judgement

McCollum 2004 (Continued)

Random sequence generation (selection bias)	Low risk	Participants were randomized by computer
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of study participants and personnel could not be done as 1 treatment group had surgery arranged as soon as possible while the other group did not
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Allocation to the delayed surgical group was retained in accordance with the 'intention-to-treat' principle
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary outcomes were presented
Other bias	High risk	Size: sample size less than 50 per treatment arm

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ballota 2002	Non-acute study (participants in the early group received carotid endarterectomy between 15 and 30 days)
Keunen 2012	Confounded with no control group; not randomized
Sbatigia 2003	Not randomized

Characteristics of ongoing studies [ordered by study ID]

SPREAD-STACI

Trial name or title	SPREAD-STACI study
Methods	Randomized Multicenter Blind follow-up at 90 days
Participants	People presenting with TIA, amaurosis fugax or minor stroke within only a few hours of their first symptom Stenosis ranging between 51% and 99% of the carotid artery
Interventions	CEA within 48 hours or between 48 hours and 15 days from their initial ischemic symptom

SPREAD-STACI (Continued)

Outcomes	Primary outcome: any type of stroke, myocardial infarction, and death due to the procedures Secondary outcome: ipsilateral stroke, identification of predictive risk factors, confirmation of the safety of urgent CEA
Starting date	2010
Contact information	Dr Gaetano Lanza – U.O. Chirurgia Vascolare, Ospedale MultiMedica, V.le Piemonte, 70, 21053 Castellanza (Va)
Notes	Size: 456 participants

CEA: carotid endarterectomy

TIA: transient ischemic attack

DATA AND ANALYSES

Comparison 1. Stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke and death < 30days	1	40	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.38, 29.23]
2 Perioperative death and all strokes	1	40	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.14, 1.58]

Analysis 1.1. Comparison 1 Stroke, Outcome 1 Stroke and death < 30days.

Analysis 1.2. Comparison 1 Stroke, Outcome 2 Perioperative death and all strokes.

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh ^"brain ischemia"] or [mh "brain infarction"] or [mh ^"hypoxia-ischemia, brain"] or [mh ^"ischemic attack, transient"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"carotid stenosis"] or [mh "carotid artery injuries"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh stroke] or [mh ^"vertebral artery dissection"]

#2 (isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)):ti,ab

#3 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or anterior next circulation) near/5 (isch*emi* or infarct* or thrombo* or emboli*)):ti,ab

#4 (transient next isch* or TIA or TIAs):ti,ab

#5 (carotid near/5 (stenosis or thrombo* or disease* or arter* or atherosclero* or atheroma* or narrow* or plaque* or occlus* or occlud* or constrict* or emboli* or block*)):ti,ab

#6 #1 or #2 or #3 or #4 or #5

#7 [mh ^"carotid artery diseases"/SU] or [mh ^"carotid artery thrombosis"/SU] or [mh ^"carotid artery, internal, dissection"/SU] or [mh ^"carotid stenosis"/SU] or [mh "carotid artery injuries"/SU] or [mh "Carotid Arteries"/SU]

#8 [mh ^"Endarterectomy, Carotid"]

#9 (carotid near/5 (endarterectomy or thromboendarterectomy or surgery or revasculari* or eversion)):ti,ab

#10 CEA:ti,ab

#11 [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"carotid stenosis"] or [mh "carotid artery injuries"] or [mh "Carotid Arteries"]

#12 carotid:ti,ab

#13 #11 or #12

#14 [mh ^"Endarterectomy"] or [mh ^"Vascular Surgical Procedures"]

#15 #13 and #14

#16 [mh ^angioplasty] or [mh ^"angioplasty, balloon"] or [mh ^"angioplasty, balloon, laser-assisted"] or [mh ^"angioplasty, laser"]

#17 [mh ^stents]

#18 (angioplasty or stent* or endovascular):ti,ab

#19 (balloon near/5 (dilat* or catheter*)):ti,ab

#20 ((endoluminal or transluminal) near/5 repair*):ti,ab

#21 [mh ^"cerebral revascularization"]

#22 [mh "cerebral arteries"/SU]

#23 [mh ^"arterial occlusive diseases"/SU]

#24 [mh "cerebral arteries"]

#25 [mh ^"vascular surgical procedures"] or [mh ^"anastomosis, surgical"]

#26 #24 and #25

#27 (extra*cranial near/5 intra*cranial):ti,ab

#28 ((cerebral or brain or arterial or surgical or microsurgical) near/5 (anastomosis or revascular* or bypass or graft)):ti,ab

#29 (EC-IC or ECIC or EC?IC or "extra-intracranial" or STA-MCA):ti,ab

#30 #7 or #8 or #9 or #10 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #26 or #27 or #28 or #29

#31 [mh ^"early medical intervention"] or [mh ^"time factors"] or [mh ^emergencies] or [mh ^"emergency medical services"] or [mh ^"emergency treatment"]

#32 ((urgent or emergenc* or early or immediate* or delay or delayed or defer or deferred or late or timing or time) near/5 (intervention or surg* or treat* or revasculari* or angioplasty or stent* or endarterectomy or CEA)):ti,ab

#33 #31 or #32

#34 #6 and #30 and #33

Appendix 2. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or ischemic attack, transient/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or carotid stenosis/ or exp carotid artery injuries/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$)).tw.
4. (transient isch\$ or TIA or TIAs).tw.
5. (carotid adj5 (stenosis or thrombo\$ or disease\$ or arter\$ or atherosclero\$ or atheroma\$ or narrow\$ or plaque\$ or occlus\$ or occlud\$ or constrict\$ or emboli* or block\$)).tw.
6. 1 or 2 or 3 or 4 or 5
7. carotid artery diseases/su or carotid artery thrombosis/su or carotid artery, internal, dissection/su or carotid stenosis/su or exp carotid artery injuries/su or exp Carotid Arteries/su
8. Endarterectomy, Carotid/
9. (carotid adj5 (endarterectomy or thromboendarterectomy or surgery or revasculari\$ or eversion)).tw.
10. CEA.tw.
11. carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or carotid stenosis/ or exp carotid artery injuries/ or exp Carotid Arteries/
12. carotid.tw.
13. 11 or 12
14. Endarterectomy/ or Vascular Surgical Procedures/
15. 13 and 14
16. angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/
17. Stents/
18. (angioplasty or stent\$ or endovascular).tw.
19. (balloon adj5 (dilat\$ or catheter\$)).tw.
20. ((endoluminal or transluminal) adj5 repair\$).tw.
21. cerebral revascularization/
22. exp cerebral arteries/su
23. arterial occlusive diseases/su

24. exp cerebral arteries/
25. vascular surgical procedures/ or anastomosis, surgical/
26. 24 and 25
27. (extra?cranial adj5 intra?cranial).tw.
28. ((cerebral or brain or arterial or surgical or microsurgical) adj5 (anastomosis or revascular\$ or bypass or graft)).tw.
29. (EC-IC or ECIC or EC#IC or extra-intracranial or STA-MCA).tw.
30. 7 or 8 or 9 or 10 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 26 or 27 or 28 or 29
31. early medical intervention/ or time factors/ or emergencies/ or emergency medical services/ or emergency treatment/
32. ((urgent or emergenc\$ or early or immediate\$ or delay or delayed or defer or deferred or timing or time) adj5 (intervention or surg\$ or treat\$ or revasculari\$ or angioplasty or stent\$ or endarterectomy or CEA)).tw.
33. 31 or 32
34. 6 and 30 and 33
35. Randomized Controlled Trials as Topic/
36. random allocation/
37. Controlled Clinical Trials as Topic/
38. control groups/
39. clinical trials as topic/
40. Therapies, Investigational/
41. Research Design/
42. randomized controlled trial.pt.
43. controlled clinical trial.pt.
44. clinical trial.pt.
45. (random\$ or RCT or RCTs).tw.
46. (controlled adj5 (trial\$ or stud\$)).tw.
47. (clinical\$ adj5 trial\$).tw.
48. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
49. (surgical adj5 (group\$ or subject\$ or patient\$)).tw.
50. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
51. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
52. trial.ti.
53. (assign\$ or allocat\$).tw.
54. controls.tw.
55. or/35-54
56. 34 and 55
57. exp animals/ not humans.sh.
58. 56 not 57

59. (coronary or myocardial).ti

60. 58 not 59

Appendix 3. EMBASE (Ovid) search strategy

1. cerebrovascular disease/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or carotid artery injury/ or carotid atherosclerosis/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$)).tw.
4. (transient isch\$ or TIA or TIAs).tw.
5. (carotid adj5 (stenosis or thrombo\$ or disease\$ or arter\$ or atherosclero\$ or atheroma\$ or narrow\$ or plaque\$ or occlus\$ or occlud\$ or constrict\$ or emboli* or block\$)).tw.
6. 1 or 2 or 3 or 4 or 5
7. carotid artery disease/su or exp carotid artery obstruction/su or carotid artery injury/su or carotid atherosclerosis/su or exp carotid artery/su
8. carotid endarterectomy/ or carotid artery surgery/

9. (carotid adj5 (endarterectomy or thromboendarterectomy or surgery or revasculari\$ or eversion)).tw.
10. CEA.tw.
11. carotid artery disease/ or exp carotid artery obstruction/ or carotid artery injury/ or carotid atherosclerosis/ or exp carotid artery/
12. carotid.tw.
13. 11 or 12
14. Endarterectomy/ or vascular surgery/ or artery surgery/ or cerebrovascular surgery/
15. 13 and 14
16. carotid angioplasty/ or carotid artery stenting/ or carotid artery stent/ or angioplasty/ or laser angioplasty/ or patch angioplasty/ or percutaneous transluminal angioplasty/
17. Stent/ or exp cardiovascular stent/
18. (angioplasty or stent\$ or endovascular).tw.
19. (balloon adj5 (dilat\$ or catheter\$)).tw.
20. ((endoluminal or transluminal) adj5 repair\$).tw.
21. brain artery bypass/ or cerebral revascularization/
22. extracranial anastomosis/
23. exp brain artery/su
24. exp brain artery/
25. vascular surgery/ or exp anastomosis/ or bypass surgery/
26. 24 and 25
27. (extra?cranial adj5 intra?cranial).tw.
28. ((cerebral or brain or arterial or surgical or microsurgical) adj5 (anastomosis or revascular\$ or bypass or graft)).tw.
29. (EC-IC or ECIC or EC#IC or extra-intracranial or STA-MCA).tw.
30. 7 or 8 or 9 or 10 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 26 or 27 or 28 or 29
31. early intervention/ or time/ or time to treatment/ or emergency/ or emergency care/ or emergency treatment/ or emergency surgery/
32. ((urgent or emergenc\$ or early or immediate\$ or delay or delayed or defer or deferred or late or timing or time) adj5 (intervention or surg\$ or treat\$ or revasculari\$ or angioplasty or stent\$ or endarterectomy or CEA)).tw.
33. 31 or 32
34. 6 and 30 and 33
35. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
36. Randomization/
37. Controlled clinical trial/ or "controlled clinical trial (topic)"/
38. control group/ or controlled study/
39. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
40. (random\$ or RCT or RCTs).tw.
41. (controlled adj5 (trial\$ or stud\$)).tw.
42. (clinical\$ adj5 trial\$).tw.

43. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
44. (surgical adj5 (group\$ or subject\$ or patient\$)).tw.
45. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
46. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
47. trial.ti.
48. (assign\$ or allocat\$).tw.
49. controls.tw.
50. or/35-49
51. 34 and 50
52. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
53. 51 not 52
54. (coronary or myocardial).ti
55. 53 not 54

Appendix 4. LILACS search strategy

#1 MH:"Transtornos Cerebrovasculares" OR (Transtornos Cerebrovasculares) OR (Cerebrovascular Disorders) OR (Transtornos Vasculares do Cerebro) OR (Transtornos Vasculares Intracranianos) OR (Doenças Vasculares Intracranianas) OR MH:C10.228.140.300\$ OR MH:C14.907.253\$ OR MH:"Isquemia" OR (Ischemia) OR (Isquemia) OR MH:23.550.513\$ OR MH:"Isquemia Encefálica" OR (Brain Ischemia) OR (Isquemia Encefálica) OR (Isquemia Cerebral) OR (Encefalopatia Isquêmica) OR MH:10.228.140.300.150\$ OR C14.907.253.092\$ OR MH:"Ataque Isquêmico Transitório" OR (Ischemic Attack, Transient) OR (Ataque Isquêmico Transitório) OR (TIA) OR (Isquemia Cerebral Transitória) OR (Isquemia Transitória do Tronco Encefálico) OR (Isquemia do Tronco Encefálico Transitória) OR (Ataque Isquêmico Transitório em Crescendo) OR MH:10.228.140.300.150.836\$ OR C14.907.253.092.836\$ [Palavras] or MH:"Doenças das Artérias Carótidas" OR (Carotid Artery Diseases) OR (Enfermedades de las Arterias Carótidas) OR (Aterosclerose Carotídea) OR (Aterosclerose da Carótida) OR MH:10.228.140.300.200\$ OR C14.907.253.123\$ OR MH:"Arteriopatias Oclusivas" OR (Arteriopatías Oclusivas) OR (Arterial Occlusive Diseases) OR (Arteriopatias Obstrutivas) OR MH:C14.907.137\$ [Palavras]

#2 MH:"Endarterectomia das Carótidas" OR (Endarterectomía Carotídea) OR (Endarterectomy, Carotid) OR MH:04.100.814.456.250\$ OR MH:"Procedimientos Cirúrgicos Vasculares" OR (Procedimientos Quirúrgicos Vasculares) OR (Vascular Surgical Procedures) OR MH:E04.100.814\$ OR MH:"Anastomose Cirúrgica" OR (Anastomosis, Surgical) OR (Anastomosis Quirúrgica) OR MH:E04.035\$ OR MH:"Angioplastia" OR (Angioplasty) OR (Angioplastia) OR MH:E04.148.050 OR MH:E04.100.814.529.124 OR E:04.800.382.124\$ OR MH:"Angioplastia com Balão" OR (Angioplasty, Ballon) OR (Angioplastia de Balón) OR MH:E02.148.050.060\$ OR MH:E04.100.814.529.124.060\$ OR E:04.800.382.124.060\$ OR MH:"Stents" OR (Stents) OR (Stents) OR MH:E07.695.750\$ OR MH:"Procedimientos Endovasculares" OR (Endovascular Procedures) OR (Procedimientos Endovasculares) OR MH:E04.100.814.529\$ OR MH:"Revascularização Cerebral" OR (Revascularización Cerebral) OR (Cerebral Revascularization) OR (Derivação Arterial Extracraniana-Intracraniana) OR (Derivação STA-MCA) OR (Derivação EC-IC) OR (Revascularização Cerebral Microcirúrgica) OR MH:E04.100.814.868.625\$ OR MH:04.494.150\$ [Palavras]

#3 MH:"Intervenção Médica Precoce" OR (Early Medical Intervention) OR (Intervención Médica Temprana) OR MH:N02.421.143.827.363\$ OR MH:"Fatores de Tempo" OR (Time Factors) OR (Factores de Tiempo) OR MH:G01.910.857\$ OR MH:"Emergências" OR (Emergencies) OR (Urgencias Médicas) OR (Urgências) OR MH:C23.550.291.781\$ OR MH:HP2.029.300.067.074\$ OR MH:HP3.007.053\$ OR MH:N06.230.100.083\$ OR MH:N06.850.376\$ OR MH:"Serviços Médicos de Emergência" OR (Emergency Medical Services) OR (Servicios Médicos de Urgencia) OR (Pronto-Socorro) OR (Atendimento de Emergência) OR (Serviços de Saúde de Emergência) OR (Centros de Emergência) OR Atendimento de Emergência Pré-Hospitalar OR MH:N02.421.297 OR MH:SP8.946.117.190.187\$ OR MH:VS3.002.001.001.009\$ OR MH:"Tratamento de Emergência" OR (Emergency Treatment) OR (Tratamiento de Urgencia) OR MH:E02.365\$ OR MH:VS3.003.001.006.001\$

#4 (pt ensaio controlado aleatorio) OR (pt ensaio clinico controlado) OR (mh ensaios controlados aleatorios) OR (mh distribuicao aleatoria) OR (mh método duplo-cego) OR (mh método simples-cego) OR (pt estudo multicentrico) OR (tw ensaio) OR (tw ensayo) OR (tw trial) (tw azar) OR (tw acaso) OR (tw placebo) OR (tw control\$) OR (tw aleat\$) OR (tw random\$) OR (tw duplo) OR (tw doble) OR (tw double) AND (tw cego) OR (tw ciego) OR (tw blind) OR (tw clinic\$)

CONTRIBUTIONS OF AUTHORS

Protocol stage: draft the protocol	EMKS, VV, NC, and JCCBS
Review stage: select which trials to include	VV, NC, and EMKS
Review stage: extract data from trials	VV and NC
Review stage: enter data into RevMan	VV and NC
Review stage: carry out the analysis	VV and EMKS
Review stage: interpret the analysis	VV and EMKS
Review stage: draft the final review	VV, EMKS, and JCCBS
Update stage: update the review	VV, EMKS, and JCCBS

DECLARATIONS OF INTEREST

Vladimir Vasconcelos: none known.

Nicolle Cassola: none known.

Edina MK da Silva: none known.

Jose CC Baptista-Silva: none known.

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Internal sources

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- Department of emergency Medicine of Universidade Federal de São Paulo, UNIFESP, Brazil.
- Brazilian Cochrane Center, Brazil.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Secondary outcomes in the protocol included "All strokes during the follow-up period and perioperative deaths". In the review, we defined 'perioperative'. In addition, we included "neurological events before surgery" in order to make a distinction between pre and postoperative strokes.