Carotid Artery Stenting Versus Carotid Endarterectomy
A Comprehensive Meta-Analysis of Short-Term and Long-Term Outcomes

Konstantinos P. Economopoulos, MD; Theodoros N. Sergentanis, MS; Georgios Tsivgoulis, MD; Anargiros D. Mariolis, MD, PhD; Christodoulos Stefanadis, MD, PhD

Background and Purpose—The comparison between carotid endarterectomy and carotid artery stenting (CAS) remains a debated field, especially in the context of long-term outcomes.

Methods—Concerning the short-term (30-day) analysis, the numbers of outcomes per arm were abstracted, whereas outcomes per arm and hazard ratios were abstracted for long-term (≥1-year) results.

Results—Thirteen randomized trials (3723 carotid endarterectomy and 3754 CAS patients) were eligible. Regarding short-term outcomes, CAS was associated with elevated risk for stroke and “death or stroke.” CAS also exhibited a marginal trend toward higher death and “death or disabling stroke” rates. Carotid endarterectomy presented with higher rates of myocardial infarction and cranial nerve injury. Concerning long-term outcomes, CAS was associated with higher rates of stroke (pooled OR, 1.37; 95% CI, 1.13 to 1.65) and “death or stroke” (pooled OR, 1.25; 95% CI, 1.06 to 1.48). These findings were replicated at the level of pooled hazard ratios and marginally regarding secondary preventive efficacy. The difference in long-term stroke rates was particularly sizeable in patients >68 years, but little difference in rates was observed in those <68 years. No statistically significant heterogeneity became evident. Metaregression did not reveal any significant modifying effect mediated by symptomatic/asymptomatic status, distal protection, early termination of trials, area of study origin, or CAS learning curve.

Conclusions—This meta-analysis points to the significantly less frequent stroke events after carotid endarterectomy at the long-term context. The outcomes of carotid endarterectomy seem superior to CAS, but there may be subgroups, particularly younger patients, in whom the results seem equivalent. (Stroke. 2011;42:00-00.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ meta-analysis ■ stenting

Carotid endarterectomy (CEA) is the gold standard for treating severe carotid artery stenosis; carotid artery stenting (CAS) represents a therapeutic option for patients in whom CEA is contraindicated.1 This timely topic has drawn attention at the meta-analytic level; several publication-based meta-analyses have appeared in the literature. A recent meta-analysis by Meier et al has examined short-term (periprocedural, 30-day outcomes) and intermediate-term (long-term) discrepancies between CEA and CAS.2 At the short-term, Meier et al2 pointed to lower periprocedural risk of death or stroke for CEA mainly due to a borderline decrease in the risk of stroke but not death; on the other hand, CEA was accompanied by a higher risk of periprocedural myocardial infarction and cranial nerve injury. Importantly, no long-term differences were demonstrated in the meta-analysis by Meier et al2 concerning the outcome of stroke or death.

After the recent meta-analysis by Meier et al,2 the appearance of the results by the Carotid Revascularization Endarterectomy versus Stent Trial (CREST)3 has marked a turning point in the continuum of studies examining CEA versus CAS because the inclusion of 2502 patients has shed light on both short-term and long-term outcomes. In addition, the publication of long-term results by Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)4 and Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy (SPACE)5 studies has created a new context concerning long-term effects. In view of the former considerations, this meta-analysis aims to provide a comprehensive approach to short-term and long-term comparison between CEA and CAS synthesizing all available data coming from published randomized studies.

Methods

Trial Identification
This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for

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The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.606079.
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.606079
systematic reviews and meta-analyses. Details of the search strategy are provided in the Supplemental Methods (Methods I, available at http://stroke.ahajournals.org).

Data Abstraction
The following data were collected: journal name, year of publication, country, single center/multicenter status, early termination of the trial, source of funding, reporting of short-term (30-days) or long-term (≥1-year) data, definitions adopted, inclusion criteria, duration of follow-up, number of patients, proportion of patients being asymptomatic, having hypertension, diabetes, hyperlipidemia/dyslipidemia, cardiovascular disease, distal protection rate, type of stent, antiplatelet therapy, surgical technique, and the number of outcome events per arm. Short-term outcomes were the following: death, stroke, myocardial infarction, death or stroke, death or ipsilateral stroke, death or disabling stroke, death or stroke or myocardial infarction, and cranial nerve injury. Data (number of patients and, where available, hazard ratio [HR]) were abstracted for the following long-term outcomes: death, stroke, myocardial infarction, death or stroke, death or disabling stroke, death or disabling stroke, death or stroke, or myocardial infarction.

Statistical Analysis
Statistical analysis comprised calculation of pooled ORs and HRs, evaluation of between-study heterogeneity and publication bias, metaregression, and sensitivity analysis. Details of statistical analysis are provided in the Supplemental Methods (Methods II).

Results
Among the 1206 articles in MEDLINE that were retrieved, the relevant conference abstracts, 13 randomized trials (whose results are presented in 20 abstracts/articles) were eligible; this corresponds to 3723 CEA and 3754 CAS patients. Characteristics of eligible trials are provided in Supplemental Table III. The definitions adopted and the outcomes examined are presented in Supplemental Tables IV and V. The number of events and patients is provided in Supplemental Table VI.

Pooled ORs and HRs for all outcomes are provided in the Table. Concerning short-term outcomes, CAS was associated with elevated risk for stroke and “death or stroke.” CAS also exhibited a trend of borderline significance toward higher death and death or disabling stroke rates. On the other hand, CEA presented with higher rates of myocardial infarction and cranial nerve injury. Figure 1 depicts the relevant forest plots.

Regarding long-term outcomes, CAS was associated with higher rates of stroke and “death or stroke.” These findings were replicated at the level of pooled HRs. No significant associations implicated death or the combined outcome of death or disabling stroke. Figure 2 depicts the respective forest plots.

A post hoc analysis focusing especially on the postprocedural phase (ie, later than 30 days after the intervention) replicated the long-term result on the incidence of stroke (pooled OR, 1.27; 95% CI, 0.98 to 1.64, fixed effects) at a borderline level (P=0.067).

Metaregression did not reveal any significant modifying associations; details are provided in Supplemental Table VII. Nevertheless, the more elaborate analysis adopting a cutoff level of 68 years (P=0.14) (or 70 years) revealed that the difference in long-term stroke events was particularly sizeable for patients >68 years (pooled HR, 1.71; 95% CI, 1.19 to 2.45; P=0.004, fixed effects), whereas no significant difference was noted for patients <68 years (Figure 3). The exploratory metaregression analysis did not reveal any significant modifying effect by cardiovascular disease, diabetes, hypertension, or hyperlipidemia/dyslipidemia (data not shown).

Significant publication bias was demonstrated only regarding short-term death (P=0.03). The visual inspection of the funnel plot (Supplemental Figure VIII) revealed potentially unpublished small studies favoring CEA in terms of periprocedural mortality (asymmetry at the upper right quadrant).

Given that the definition concerning the long-term outcome “death or stroke” in SPACE3 and CREST3 studies was limited to postprocedural ipsilateral strokes, a sensitivity analysis was performed excluding these 2 sizeable studies. Despite the lower statistical power, the result shifted to the
Indeed, the majority of individual studies, despite their large rates of stroke and “death or stroke” in both timeframes. Long-term results emerged: CEA seemed to exhibit lower periprocedural stroke and consequently the combined outcome “death or stroke” were significant levels the conclusions reached by Meier et al about CAS vs CEA: Meta-Analysis of Long-Term Outcomes.

Figure 1. Forest plot of short-term ORs for (A) stroke, (B) death or stroke, (C) myocardial infarction, and (D) cranial nerve injury.

Discussion

This meta-analysis points to the significantly less frequent stroke events after CEA at the long-term context; importantly, this has been confirmed both at the level of ORs and HRs, pointing to the validity of the underlying association. The sizeable difference at the level of stroke events has resulted in a similar significant result concerning the combined outcome “death or stroke.” Noticeably, the difference in the incidence of stroke was marginally replicated at the analysis focusing especially on the postprocedural phase (later than 30 days after the intervention), pointing to the secondary preventive efficacy of CEA. No long-term differences became evident regarding the isolated outcome of mortality.

Concerning short-term outcomes, the present meta-analysis confirms and essentially expands at a formally statistically significant level the conclusions reached by Meier et al about stroke. Specifically, the rate of periprocedural stroke and consequently the combined outcome “death or stroke” were in favor of CEA, whereas the numerically favorable for CEA OR concerning death was only of borderline significance. Consequently, an impressive analogy between short-term and long-term results emerged: CEA seemed to exhibit lower rates of stroke and “death or stroke” in both timeframes. Indeed, the majority of individual studies, despite their large sample size, seemed deprived of adequate power for the documentation of such a long-term finding; the meta-analytic approach, however, was capable of reaching this composite conclusion.

The present meta-analysis confirms the increased risk for periprocedural cranial nerve injuries and myocardial infarction after CEA. Rather expectedly, the outcome “death or stroke or myocardial infarction” pointed to a null association at the short-term analysis, because its constituents pointed to opposite directions. Noticeably, the larger newly published studies (CREST, CAVATAS, SPACE, Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis [EVA-3S])1,5,8,13,14,17,18 did not provide a cardiological follow-up capable of monitoring myocardial infarction as time progressed.

A notion that has been extensively discussed is the existence and importance of a learning curve in CAS. It has been postulated that inherent difficulties of CAS placement may have created unfavorable events in CAS arms.2,7,13,24,25 As reflected on the most recent trials, the complication rates of CAS seem to continuously decline; it is tempting to envisage a parallel trend concerning the hazards of CEA so that the ORs do not change very much along with publication year. Nevertheless, metaregression pointed to trials showing a parallel trend concerning the hazards of CEA so that the overall meta-analytic findings of this study did not reach formal significance.

This meta-analysis extrapolated the short-term findings of the recent individual patient data meta-analysis by the Carotid Stenting Trialists’ Collaboration26 on long-term stroke
events. Our meta-analysis suggested that the difference in long-term stroke events was particularly sizeable in patients >68 years, whereas no significant difference was observed in those <68 years. This represents an important finding because, despite the superiority of CEA, there may be certain subgroups, for instance, younger patients, in whom the results seem equivalent. Nevertheless, longer follow-up from numerous studies would be desirable to establish the meaningfulness of age as a long-term effect modifier, because metagression with mean age of patients did not yield a significant result.

Null findings of the metagression analyses, which are worth commenting on, pertain to distal protection, early termination of trials, area of study origin, commercial sponsor, and symptomatic/asymptomatic status of patients. Asymptomatic patients may well exhibit distinct rates of events; however, discrepancies between CEA and CAS seem not to be modified by asymptomatic status. Accordingly, the null finding regarding distal protection is in line with the results of the International Carotid Stenting Study-MRI (ICSS-MRI) substudy, which concluded that protection devices did not seem effective in preventing cerebral ischemia during CAS.22 Our analysis seems rather to portray early termination as a simple cause of low statistical power than as a factor creating systematic deviation from the nonterminated trials. Potentially meaningful risk factors for surgery (such as...
cardiovascular disease, diabetes, hypertension, hyperlipidemia/dyslipidemia) did not seem able to interfere with the generalizability of the results.

Despite the clinically expected heterogeneity between existing studies in terms of adopted outcome definitions, expertise of specialists and centers, concomitant antiplatelet drug treatment, type of stent, and/or distal protection devices used in CAS, formal statistical tests did not point to substantial heterogeneity with the exception of the outcome “death or stroke or myocardial infarction.” This may imply that the aforementioned factors could not distort the underlying differences between CAS and CEA. The lack of publication bias also points to the validity of the present results. A sole exception of publication bias emerged, indicating potentially unpublished small studies, which might have favored CEA in terms of periprocedural mortality.

Certain limitations of this meta-analysis should be acknowledged. Our approach was based on data abstracted from publications and not on individual patient data; thus, our results should be viewed as hypothesis-generating and not as definitive evidence. Moreover, the fact that each trial reported its own set of outcomes may have led to limited statistical power. Heterogeneity in definitions of outcomes may represent a potential limitation; however, the sensitivity analysis has not pointed to major differentiation of results. Moreover, the lack of universal reporting concerning the expertise and specialty of operators among trials may have interfered with the results of individual studies given that in the CREST lead-in phase, the periprocedural “death or stroke or myocardial infarction” rate ranged from 1.6% to 7.7% depending on the operator’s specialty; however, the effect of this phenomenon should not be overestimated given that no substantial heterogeneity was detected. It should be also declared that some studies exhibited particularities; for instance, in CAVATAS, only a minority of 26% had been treated with stents and the remaining with percutaneous transluminal angioplasty. As expected, this meta-analysis could not assess issues that have not been thoroughly examined. The present analysis lends support to the recent mounting evidence that CAS and increased risk for periprocedural cranial nerve injuries as well as myocardial infarction was confirmed. In addition, the results of individual studies given that in the CREST prospective, randomised trial with long term follow up (BACASS). Schweiz Arch Neurol Psychiatr. 2008;157:191–192.


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“CAROTID ENDARTERECTOMY VERSUS CAROTID ARTERY STENTING: A COMPREHENSIVE META-ANALYSIS OF SHORT-TERM AND LONG-TERM OUTCOMES.”
SUPPLEMENTAL METHODS

METHODS S1:

Trial identification

Eligible articles were identified by a search of MEDLINE bibliographical database from January 1, 1990 to May 31, 2010 using the following combination of the search strings: “(carotid endarterectomy OR carotid stenting) AND (randomized OR randomization)”. We also searched abstract lists and conference proceedings of the 2006-09 scientific sessions of the American College of Cardiology, the European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and the American Heart Association. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used and two investigators (KPE and TNS), working independently, searched the literature and extracted data from each eligible randomized controlled trial. All randomized controlled trials with any sample size comparing CAS with CEA for the treatment of unilateral or bilateral carotid artery stenosis were considered eligible for this analysis. Both asymptomatic and symptomatic patients were included in the systematic review. All endovascular techniques (use of simple balloon catheter or stent, use of cerebral protection device or not) and open surgical treatment approaches (use of a shunt or not, use of a patch or not, local or general anesthesia etc.) were allowed for the treatment of the internal carotid artery stenosis in all eligible trials.
METHODS S2:

Statistical analysis

The fixed-effects model (Mantel-Haenszel method), as well as the random effects (DerSimonian Laird) model, were used to calculate the pooled Odds Ratio (OR). ORs and HRs were calculated to express CAS versus CEA comparison; OR or HR values larger than 1 denote results favorable for CEA. The equivalent z test was performed for each pooled OR and HR; p<0.05 was considered statistical significant, whereas 0.10<p<0.05 was considered borderline (marginal) significance. To avoid reporting of numerous low-power findings of questionable significance throughout the manuscript, pooled ORs are reported only when at least two large (>250 patients per arm) trials presented the relevant data.

Between-study heterogeneity was assessed by using Cochran Q statistic and by estimating I² respectively. In the absence of significant heterogeneity, the fixed effects model was chosen. All analyses were performed according to the intention-to-treat principle. For studies with a zero cell we used a continuity correction of 0.5.

Evidence of publication bias was determined using Egger’s formal statistical test. Given that the Cochrane Handbook for Systematic Reviews of Interventions dictates as a rule of thumb that tests for funnel plot asymmetry should be used only when there are at least ten studies included in the meta-analysis, we performed the Egger’s test only in case of nine or more studies. For the interpretation of Egger’s test, statistical significance was defined as p<0.1.

Meta-regression was performed to assess whether OR was modified by symptomatic/asymptomatic status in the study arms, use of distal protection devices in the CAS arm, early termination of trial, patients age (mean age), area of study origin (USA-based vs. other), commercial sponsor and publication year. Concerning the possible modifying effect of age an additional analysis was performed. Given that the recent meta-analysis by the Carotid Stenting Trialists’ Collaboration demonstrated that a cut-off age of 70 years may modify short-term discrepancies between CAS and CEA, we sought whether such a pattern exists regarding long-term stroke. Of note, concerning meta-regression with publication year special attention was paid so as to allocate the short-term results to the first, short-term publication and the long-term results to the subsequent publication, as appropriate. Meta-regression was performed post hoc only when the pooled OR was statistically significant, to detect only meaningful modifying effects upon demonstrated associations. As appropriate, we performed meta-regression only in case of nine or more studies. Nevertheless, an exploratory meta-regression analysis (i.e., occasionaly with less than nine studies) was performed to assess whether the results were modified by the conventional/high risk for surgery status; the effect of the most frequently reported and potentially meaningful risk factors (prevalence of cardiovascular disease, diabetes, hypertension, hyperlipidemia/dyslipidemia in the study) was assessed. Sensitivity analysis was performed in case of deviation in the definitions of outcomes adopted by various studies. All analyses were conducted using STATA 10.0 (STATA Corp. College Station, TX, USA).
## SUPPLEMENTAL TABLES

### Table S3: Characteristics of studies included in the meta-analysis

<p>| Study (year of the most recent publication) | Countries | Study type | Short term/long term data | Inclusion criteria | Duration of follow-up | Mean age (years) (CEA/CAS) | No of patients (CEA/CAS) | Hyper tension (%) | Diabetes (%) | Hypertigleneemia/ Dyslipidemia (%) | Cardiovascular disease (%) | Distal protection (%) | Asymptomatic (%) | Trial stopped early (reason) | Funding/Conflict of interest | CAS (Type of stent; antiplatelet therapy) | CEA (surgical technique; antiplatelet therapy) |
|---------------------------------------------|-----------|------------|--------------------------|-------------------|-----------------------|---------------------------|---------------------------|-----------------|-------------|-----------------------------------|---------------------------|-----------------|----------------|--------------------------------|---------------------------------|-----------------------------|
| LEICESTER (1998)†                          | UK        | Single center randomized | Yes/no | ≥70% symptomatic ICA stenosis | 30 days | 66.7±68 | 12/11 | NR| NR| NR | NR | 0 | 0 | Yes (inferiority of CAS at the interim analyses) | UK Stroke Associations and Schneider UK Ltd | Wallstent; aspirin before and after |
| LEXINGTON I (2001)                          | USA       | Single center randomized | Yes/yes | &gt;70% symptomatic ICA stenosis | 24 months | 69.6±66.4 | 51/53 | 89.4±29.3 | 55.7±67.3 | 0 | 0 | No | Boston Scientific Inc provided the endovascular device | Wallstent; aspirin and clopidogrel before and after |
| WALLSTENT (2001)                            | USA       | Multicenter randomized  | Yes/yes | ≥60% symptomatic ICA stenosis | 12 months | 70±66.5 | 112/107 | NR | NR | NR | NR | 0 | 0 | Yes (inferiority of CAS at the futility analysis) | NR | Wallstent; aspirin and ticlopidine for 4 weeks |
| LEXINGTON II (2004)                         | USA       | Single center randomized | Yes/yes | &gt;80% asymptomatic ICA stenosis | 48 months | 69.9±66.6 | 42/43 | 89.4±14.12 | 20.0±64.7 | 0 | 100 | No | No financial support | Wallstent; Dynalast; aspirin and clopidogrel before and after |
| TESCAS-Ca (2006)†                          | China     | Multicenter randomized  | Yes/no | ≥50% symptomatic or &lt;70% asymptomatic ICA stenosis | 6 months | 63±63 | 84/82 | 61.4±22.89 | 72.2±72.29 | NR | NR | No | Supported by State Funding | TCD monitoring, patch graft, shunting, general anesthesia, antiplatelet after |
| BACASS (2008)†                             | Switzerland | Single center randomized | Yes/yes | ≥70% symptomatic ICA stenosis | 48 months | 71±99 | 10±10 | 79.0±50.0 | 65.0±10.0 | 100 | 0 | No | NR | Wallstent; aspirin and clopidogrel prior or immediately after CAS and for 1 month | Wallstent; aspirin and clopidogrel prior or immediately after CAS and for 1 month |
| EVA-3S (2008)†                             | France    | Multicenter randomized  | Yes/yes | &gt;40% symptomatic | 42.5 months | 70.2±69.1 | 262/265 | 72.1±23.91 | 56.8±56.8 | NR | 92 | 0 | Yes (inferiority of CAS, both safety and effectiveness) | Supported by French Ministry of Health (Programme Hospitalier de Carrefour Wallstent, Menarini; Accele||</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Symptomatic</th>
<th>ICA stenosis</th>
<th>Length</th>
<th>Event Rates</th>
<th>Initial Results</th>
<th>Authors/Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPACE (2008)</td>
<td>Austria, Germany, Switzerland</td>
<td>Multicenter randomized</td>
<td>Yes/yes</td>
<td>≥50% symptomatic or &lt;80% asymptomatic ICA stenosis</td>
<td>24 months</td>
<td>68.7/68.1</td>
<td>589/607</td>
<td>75.59</td>
</tr>
<tr>
<td>SAPPHIRE (2008)</td>
<td>USA</td>
<td>Multicenter randomized</td>
<td>Yes/yes</td>
<td>≥50% symptomatic or &lt;80% asymptomatic ICA stenosis and ≥1 high-risk surgical criteria</td>
<td>36 months</td>
<td>72.6/72.3</td>
<td>167/167</td>
<td>85.30</td>
</tr>
<tr>
<td>Steinbauer et al (2008)</td>
<td>Germany</td>
<td>Single center randomized</td>
<td>No/yes</td>
<td>&gt;10% symptomatic ICA stenosis</td>
<td>66 months</td>
<td>68.4/67.9</td>
<td>44/43</td>
<td>78.16</td>
</tr>
<tr>
<td>CAVATAS (2009)</td>
<td>Australia, Italy, Spain, Switzerland, UK</td>
<td>Multicenter randomized</td>
<td>Yes/yes</td>
<td>≥10% symptomatic or asymptomatic ICA stenosis</td>
<td>60 months</td>
<td>68/68</td>
<td>253/251</td>
<td>54.76</td>
</tr>
</tbody>
</table>

**Study Design Notes:**
- **Multicenter randomized:** Multiple centers were involved in the study.
- **Single center randomized:** The study was conducted in a single center.
- **Yes/yes:** Indicates the percentage of patients in each group who met the criteria.
- **No/yes:** Indicates the percentage of patients in each group who did not meet the criteria.

**Event Rates and Initial Results:**
- **Event Rates:** The percentage of patients experiencing the primary outcome.
- **Initial Results:** The percentage of patients meeting the initial criteria.

**Authors/Supplements:**
- **SAPPHIRE (2008):** Supported by Cordis; consulting or educational support from Abbott, Boston Scientific, Cordis, Guidant and Sanoft-Aventis to some of the contributing authors.
- **SPACE (2008):** Supported by Cordis; consulting or educational support from Abbott, Boston Scientific, Cordis, Guidant, Johnson&Johnson, Kerberos to some of the contributing authors.
- **CAVATAS (2009):** Supported by British Heart Association, NHS Management Executive, the Stroke Association, the Wellcome Trust and the Neurosciences.

**Conclusion:**
- Studies varied in their primary outcomes, patient selection criteria, and the use of adjunctive therapies such as aspirin and clopidogrel.
| Study Abbreviation | Multicenter Randomized | Yes/No | Yes/No | 30 days | 48 months | Yes/No | ≥50% symptomatic ICA stenosis
≥70% on angiography, ≥70% on CTA or MRA
(CTA or MRA if ICA was ≥50-69% symptomatic ICA stenosis)
≥60% on angiography, ≥70% on US, or ≥80% CTA or MRA (CTA or MRA if ICA was ≥50-69% asymptomatic ICA stenosis) | Support
Funded by Gore Medical, Medical Research Council, the Stroke Association, Sanofi-Synthelabo, Reta Lila Weston Trust for Medical Research, Swiss National Science Foundation, University of Basel, Department of Health, National Institute for Health Research Biomedical Research Centres and the European Union; consulting support from Boston Scientific, CR Bard, W.L. Gore Carotid Wallstent, Precision, Protégé, Acculink, Xact, Stmary, Cristallo ideale, Exponent, Nest Suhn, aspirin and clopidogrel before and 1 month after
The use of standard or eversion endarterectomy, local or general anesthesia, shunts and patch was left to the discretion of the surgeon; NR
Supported by NINDS, NIH, Abbott Vascular Solutions (formerly Guidant), and Accuray and Accurix systems; educational or consulting or speaking support from various sponsors (not shown for reasons of brevity)
According to published guidelines; aspirin 48 hours before, aspirin or ticlopidine or clopidogrel or aspirin/extended-release dipyridamole indefinitely after
Cerebral ischemia or cerebral death or stroke before 48 months after
Death or recurrent ischemia or death or stroke after 48 months after
Stroke Foundation, again 1 day before and indefinitely after

case of zero long term events, short term events were evidently also zero;

| Study Abbreviation | Multicenter Randomized | Yes/No | Yes/No | 30 days | 48 months | Yes/No | ≥50% symptomatic ICA stenosis
≥70% on angiography, ≥70% on CTA or MRA
(CTA or MRA if ICA was ≥50-69% symptomatic ICA stenosis)
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According to published guidelines; aspirin 48 hours before, aspirin or ticlopidine or clopidogrel or aspirin/extended-release dipyridamole indefinitely after
Cerebral ischemia or cerebral death or stroke before 48 months after
Death or recurrent ischemia or death or stroke after 48 months after
Stroke Foundation, again 1 day before and indefinitely after
Cerebral ischemia or cerebral death or stroke before 48 months after
Death or recurrent ischemia or death or stroke after 48 months after
Stroke Foundation, again 1 day before and indefinitely after

case of zero long term events, short term events were evidently also zero;
Table S4: Reporting of outcomes in the eligible trials of the meta-analysis.

| Study (year of the most recent publication) | Death short-term | Death long-term | Stroke short-term | Stroke long-term | Myocardial infarction short-term | Myocardial infarction long-term | Death or stroke short-term | Death or stroke long-term | Death or ipsilateral stroke short-term | Death or ipsilateral stroke long-term | Death or disabling stroke short-term | Death or disabling stroke long-term | Death or stroke or myocardial infarction short-term | Death or stroke or myocardial infarction long-term | Cranial nerve injury short-term |
|---------------------------------------------|------------------|----------------|------------------|------------------|---------------------------------|---------------------------------|-------------------------------|---------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|----------------------------------------|----------------------------------|
| LEICESTER (1998)                            | +                | -              | -                | -                | +                               | -                               | +                             | -                         | +                                   | -                                   | +                                   | +                                      | +                                      | -                                |
| LEXINGTON I (2001)                          | C^i              | +              | C                | +                | C                               | C                               | C                             | C                         | C                                   | C                                   | C                                   | C                                      | C                                      | +                                |
| WALLSTENT (2001)                            | -                | -              | -                | -                | +                               | -                               | -                             | -                         | -                                   | -                                   | -                                   | -                                      | -                                      | -                                |
| LEXINGTON II (2004)                         | +                | -              | +                | -                | +                               | -                               | C                             | -                         | -                                   | -                                   | -                                   | -                                      | +                                      | +                                |
| TESCAS-Ca (2006)                            | +                | -              | +                | -                | -                               | -                               | C                             | -                         | -                                   | -                                   | -                                   | -                                      | -                                      | -                                |
| BACASSb (2008)                              | +                | +              | +                | +                | +                               | +                               | C                             | C                         | C                                   | C                                   | C                                   | C                                      | C                                      | +                                |
| EVA-3Sc (2008)                              | C                | C              | C                | C                | +                               | -                               | C                             | -                         | -                                   | +                                   | -                                   | C                                      | -                                      | +                                |
| SAPPHIREd (2008)                            | +                | +              | +                | +                | +                               | +                               | CM^j                          | CM                        | -                                   | -                                   | -                                   | -                                      | +                                      | -                                |
| SPACEe (2008)                               | +                | +              | +                | +                | -                               | -                               | +                             | +                         | +                                   | -                                   | +                                   | -                                      | -                                      | -                                |
| Steinbauer et al (2008)                     | C                | +              | -                | -                | -                               | -                               | C                             | -                         | -                                   | -                                   | -                                   | -                                      | +                                      | +                                |
| CAVATASf (2009)                             | +                | +              | +                | +                | -                               | -                               | +                             | -                         | +                                   | +                                   | +                                   | C                                      | -                                      | +                                |
| ICSSg (2010)                                | +                | -              | -                | -                | -                               | -                               | +                             | -                         | -                                   | -                                   | -                                   | -                                      | +                                      | +                                |
| CRESTb (2010)                               | +                | +              | +                | +                | -                               | -                               | +                             | -                         | -                                   | -                                   | +                                   | -                                      | +                                      | +                                |

^aTESCAS-C: Trial of Endarterectomy versus Stenting to Carotid Atherosclerotic Stenosis-China; ^bBACASS: Basel Carotid Artery Stenting Study; ^cEVA-3S: Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis; ^dSAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; ^eSPACE: Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy; ^fCAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study; ^gICSS: International Carotid Stenting Study; ^hCREST: Carotid Revascularization Endarterectomy versus Stent Trial; ^iC: Calculated; ^jCM: Calculated from the meta-analysis sharing co-authors with the SAPPHIRE trial.
Table S5: Definitions of outcomes in the eligible trials of the meta-analysis.

<table>
<thead>
<tr>
<th>Study (year of the most recent publication)</th>
<th>Death</th>
<th>Stroke</th>
<th>Myocardial infarction</th>
<th>Death or stroke</th>
<th>Death or ipsilateral stroke</th>
<th>Death or disabling stroke</th>
<th>Death or stroke or myocardial infarction</th>
<th>Cranial nerve injury</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEICESTER (1998)</td>
<td>death from any cause within 30 days</td>
<td>any new neurologic deficit persisting for more than 24 hours within 30 days from the procedure</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>death from any cause or any new neurologic deficit persisting for more than 24 hours within 30 days from the procedure</td>
</tr>
<tr>
<td>LEXINGTON I (2001)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>WALLSTENT (2001)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>LEXINGTON II (2004)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>TESCAS-Ca (2006)</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>BACASS Ca (2008)</td>
<td>NR</td>
<td>NR</td>
<td>neurologic deterioration evidenced</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Event Type and Criteria</td>
<td>Stroke Scale</td>
<td>Aphasia/Hemianopsia</td>
<td>Duration</td>
<td>Death Cause</td>
<td>Stroke Definition</td>
<td>Neurological Deficit</td>
<td>Q Wave</td>
<td>Death Definition</td>
</tr>
<tr>
<td>-------------</td>
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<td>-------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>EVA-3S (2008)</td>
<td>Stroke, other vascular cause, and other cause within 30 days from treatment</td>
<td>National Institute of Health stroke scale</td>
<td>No aphasia or hemianopsia</td>
<td>Longer than 24 hours</td>
<td>Any focal nonconvulsive neurological deficit in a</td>
<td>All strokes and deaths that occurred within 30 days after the procedure</td>
<td>All strokes and deaths from treatment to the end of the follow-up</td>
<td>Any Q wave in two or more contiguous electrocardiographic derivations</td>
<td>Any stroke or death</td>
</tr>
<tr>
<td>SAPPHIRE (2008)</td>
<td>Death from any cause</td>
<td>National Institute of Health stroke scale</td>
<td>No stroke or myocardial infarction</td>
<td>Any stroke or death</td>
<td>Any stroke or death</td>
<td>Death, stroke, or myocardial infarction</td>
<td>Any stroke or death</td>
<td>Any stroke or death</td>
<td>Any stroke or death</td>
</tr>
<tr>
<td>Study</td>
<td>Event Description</td>
<td>Vascular Territory</td>
<td>Neurological Symptom</td>
<td>Time Frame</td>
<td>Cause of Death or Stroke</td>
<td></td>
<td></td>
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<tr>
<td>SPACe+ (2008)&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td>Death between randomisation and day 30</td>
<td>Vascular territory that persisted for more than 24 hours</td>
<td>Aphasic leads or non-Q-wave (elevation of the creatine kinase level to more than twice the upper limit of the normal range, with a positive MB fraction)</td>
<td>-</td>
<td>Ipsilateral stroke or death of any cause between randomisation and 30 days after treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinbauer et al (2008)&lt;sup&gt;16,17&lt;/sup&gt;</td>
<td>Any death during the observation period</td>
<td>-</td>
<td>Neurological symptoms &gt;24 hours during the observation period</td>
<td>-</td>
<td>Any death or stroke at any time after randomisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAVATAS (2009)&lt;sup&gt;18,19&lt;/sup&gt;</td>
<td>Death within 30 days of treatment</td>
<td>Deaths from any cause from treatment to the end of the follow-up</td>
<td>A clinical syndrome of acute onset of a focal neurological deficit that lasted</td>
<td>NR</td>
<td>Any death or stroke among survivors requiring help from another person as required</td>
<td></td>
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</tr>
</tbody>
</table>

NR = Not Reported
<p>| | | | | | | | | | |
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| <strong>ICSS</strong> (2010)²⁰ | all-cause death within 30 days of randomization | - | any rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 h or leading to death with no apparent cause | - | the presence of two of the following three criteria: specific cardiac enzymes more than twice the upper limit of normal; history of chest discomfort for at least 30 min; or the development of specific abnormalities | - | any stroke or death within 30 days from the procedure | - | - | - | - | stroke or death or procedural myocardial infarction within 30 days of the procedure | - | NR | any stroke or death or procedural myocardial infarction |</p>
<table>
<thead>
<tr>
<th>Cause other than that of vascular origin within 30 days of the procedure</th>
<th>Cause other than that of vascular origin within 30 days of the procedure on a standard 12-lead electrocardiogram within 30 days of the procedure</th>
<th>Cause other than that of vascular origin within 30 days of the procedure on a standard 12-lead electrocardiogram within 30 days of the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
<th>any periprocedural stroke or death within 30 days after the procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST (2010)</td>
<td>all-cause death within 30 days of randomization</td>
<td>all-cause death from randomization to the end of the follow-up</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
<td>any acute neurologic event with focal symptoms and signs lasting for 24 hours or more that were consistent with focal cerebral ischemia within 30 days after the procedure</td>
</tr>
</tbody>
</table>

**Notes:**
- TESCAS-C: Trial of Endarterectomy versus Stenting to Carotid Atherovascular Stenosis-China;
- BACASS: Basel Carotid Artery Stenting Study;
- EVA-3S: Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis;
- SAPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy;
- SPACE: Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy;
- CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study;
- ICSS: International Carotid Stenting Study;
- CREST: Carotid Revascularization Endarterectomy versus Stent Trial;
- NR: Not reported
Table S6: Number of events and patients for the outcomes studied in the meta-analysis.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Short-term death</th>
<th>Short-term stroke</th>
<th>Short-term myocardial infarction</th>
<th>Short-term death or stroke</th>
<th>Short-term death or stroke or myocardial infarction</th>
<th>Cranial nerve injury</th>
<th>Long term death or stroke</th>
<th>Long term death or disabling stroke</th>
<th>Long term death</th>
<th>Long term stroke</th>
<th>Long term death</th>
<th>Long term stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEICESTER</td>
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<tr>
<td>(1998)</td>
<td>12</td>
<td>11</td>
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<td>0</td>
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<td></td>
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</tr>
<tr>
<td>LEXINGTON I (2001)</td>
<td>51</td>
<td>53</td>
<td>1</td>
<td>0</td>
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<tr>
<td>WALLSTENT (2001)</td>
<td>112</td>
<td>107</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
<td>LEXINGTON II (2004)</td>
<td>42</td>
<td>43</td>
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<td>0</td>
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<tr>
<td>TESCAS-C (2006)</td>
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<td>82</td>
<td>2</td>
<td>1</td>
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</tr>
<tr>
<td>BACASSS (2008)</td>
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<td>10</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
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<tr>
<td>EVA-3S (2008)</td>
<td>262</td>
<td>265</td>
<td>3</td>
<td>2</td>
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<td>SAPPHIRE (2008)</td>
<td>167</td>
<td>167</td>
<td>4</td>
<td>2</td>
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<tr>
<td>SPACE (2008)</td>
<td>589</td>
<td>607</td>
<td>5</td>
<td>6</td>
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</tr>
<tr>
<td>Steinbauer et al. (2008)</td>
<td>44</td>
<td>43</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>CAVATAS (2009)</td>
<td>253</td>
<td>251</td>
<td>4</td>
<td>7</td>
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<tr>
<td>ICSS (2010)</td>
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<td>853</td>
<td>7</td>
<td>19</td>
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</tr>
<tr>
<td>CREST (2010)</td>
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<td>1262</td>
<td>4</td>
<td>9</td>
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</tr>
</tbody>
</table>

CAS: Carotid Artery Stenting; CEA: Carotid endarterectomy; NR: Not Reported.
Table S7: Results of meta-regression analysis.

<table>
<thead>
<tr>
<th>Meta-regression Variables</th>
<th>Short-term stroke</th>
<th>Short-term myocardial infarction</th>
<th>Short-term death or stroke</th>
<th>Short-term cranial nerve injury</th>
<th>Long-term stroke</th>
<th>Long-term death or stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic/asymptomatic status</td>
<td>p=0.99</td>
<td>p=0.99</td>
<td>p=0.65</td>
<td>p=0.87</td>
<td>p=0.95</td>
<td>p=0.85</td>
</tr>
<tr>
<td>Distal protection</td>
<td>p=0.15</td>
<td>p=0.71</td>
<td>p=0.56</td>
<td>p=0.44</td>
<td>p=0.50</td>
<td>p=0.97</td>
</tr>
<tr>
<td>Early termination of trials</td>
<td>p=0.61</td>
<td>p=0.73</td>
<td>p=0.57</td>
<td>p=0.22</td>
<td>p=0.59</td>
<td>p=0.72</td>
</tr>
<tr>
<td>Area of study origin</td>
<td>p=0.55</td>
<td>p=0.81</td>
<td>p=0.41</td>
<td>p=0.48</td>
<td>p=0.88</td>
<td>p=0.33</td>
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<tr>
<td>Commercial sponsor</td>
<td>p=0.08</td>
<td>p=0.79</td>
<td>p=0.15</td>
<td>p=0.99</td>
<td>p=0.56</td>
<td>p=0.77</td>
</tr>
<tr>
<td>Mean age of patients</td>
<td>p=0.19</td>
<td>p=0.92</td>
<td>p=0.49</td>
<td>p=0.35</td>
<td>p=0.67</td>
<td>p=0.53</td>
</tr>
<tr>
<td>Publication year</td>
<td>p=0.11</td>
<td>p=0.53</td>
<td>p=0.35</td>
<td>p=0.22</td>
<td>p=0.41</td>
<td>p=0.58</td>
</tr>
</tbody>
</table>
SUPPLEMENTAL FIGURE

Figure S8: Funnel plot for publication bias in the meta-analysis of a. short-term (periprocedurally) death and b. long-term death. OR: Odds ratio, CEA: Carotid endarterectomy, CAS: Carotid artery stenting.
SUPPLEMENTAL REFERENCES


Abstract 14

경동맥 스테닝 대 경동맥 내막절제술
단기 및 장기 결과의 포괄적 메타 분석

Carotid Artery Stenting Versus Carotid Endarterectomy
A Comprehensive Meta-Analysis of Short-Term and Long-Term Outcomes

Konstantinos P. Economopoulos, MD; Theodoros N. Sergentanis, MS; Georgios Tsigoulis, MD; Anargiros D. Mariolis, MD, PhD; Christodoulos Stefanadis, MD, PhD

(Stroke. 2011;42:687-692.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ meta-analysis ■ stenting

배경과 목적

경동맥 내막절제술(carotid endarterectomy, CEA)과 경동맥 스테닝(carotid artery stenting, CAS)의 비교는 여전히 논쟁이 되고 있으며, 특히 장기 결과(long-term outcome)에서 그러하다.

방법

단기(30일) 분석에 대하여 군당 결과의 수를 추출하였고, 장기 (1년 이상) 결과에 대하여 군당 결과와 위험도(hazard ratio)를 추출하였다.

결과

13개의 무작위 연구(CEA 3,723개와 CAS 3,754개)를 대상으 로 하였다. 단기 결과에서는 CAS가 뇌졸중과 ‘사망 또는 뇌졸중’의 위험을 증가시켰다. CEA는 사망과 ‘사망 또는 장애가 있는 뇌졸중’의 높은 발생에 비해한 경향성을 보였다. CAS는 심근경색과 심신경 손상의 높은 발생을 일으켰다. 장기 결과에서 CAS가 뇌졸중의 발생률 증가(pooled OR, 1.37; 95% CI, 1.13~1.65), ‘사망 또는 뇌졸중’의 발생률 증가(pooled OR, 1.25; 95% CI, 1.06~1.48)와 관련되어 있었다. 이러한 소견은 집단 위험도(pooled hazard ratio) 및 비약한 이차 예방 효과와 관련하여도 나타났다. 68세 초과의 환자에서는 장기 뇌졸중 발생률에서 상당한 차이를 보였으나, 68세 미만의 환자에서는 거의 차이를 보이지 않았다. 통계적으로 유의한 어떠한 이 절성(heterogeneity)도 보이지 않는 점은 명백했다. 메타 회귀 분석(metaregression)에서 증상의 유무, 말단 보호 장치(distal protection), 연구의 조기 종료, 연구가 진행된 지역, 또는 CAS 학습 곡선(learning curve)에 의한 통계적으로 유의한 어떠한 영향도 관찰되지 않았다.

결론

이 메타 분석은 임상적 관련에서 CEA 이후 뇌졸중 발생이 유의하게 낮았음을 보여 준다. CEA의 결과는 CAS에 비해 우수해 보이나, 하위 집단 중 특히 젊은 환자에서는 비슷한 결과를 보이기도 한다.

Figure 3. Forest plots depicting HRs concerning long-term stenosis for patients (A) <68 years old and (B) ≥68 years old.
Figure 1. Forest plot of short-term ORs for (A) stroke, (B) death or stroke, (C) myocardial infarction, and (D) cranial nerve injury.

Figure 2. Forest plot of long-term outcomes: (A) stroke (OR), (B) death or stroke (OR), (C) stroke (HR), and (D) death or stroke (HR).