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A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting

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Objective: **The purpose of this systematic review and meta-analysis was to synthesize the available evidence derived from randomized controlled trials (RCTs) regarding the relative efficacy and safety of endarterectomy vs stenting in patients with carotid artery disease.**

Methods: **We searched MEDLINE, EMBASE, Current Contents, and Cochrane CENTRAL through July 2010 to update previous systematic reviews. Two reviewers determined trial eligibility and extracted descriptive, methodologic, and outcome data (death, nonfatal stroke, and nonfatal myocardial infarction). Random-effects meta-analysis was used to pool relative risks and the I^2 statistic was used to assess heterogeneity.**

Results: **Thirteen RCTs proved eligible enrolling 7484 patients, of which 80% had symptomatic disease. Methodological quality was moderate to high, with better quality among RCTs published after 2008. Compared with carotid endarterectomy, stenting was associated with increased risk of any stroke (relative risk [RR], 1.45; 95% confidence interval [CI], 1.06-1.99; I^2 = 40%), decreased risk of periprocedural myocardial infarction (MI; RR, 0.43; 95% CI, 0.26-0.71; I^2 = 0%), and nonsignificant increase in mortality (RR, 1.40; 95% CI, 0.85-2.33; I^2 = 5%). When analysis was restricted to the two most recent trials with the better methodology and more contemporary technique, we found stenting to be associated with a significant increase in the risk of any stroke (RR, 1.82; 95% CI, 1.35-2.45) and mortality (RR, 2.53; 95% CI, 1.27-5.08) and a nonsignificant reduction of the risk of MI (RR, 0.39; 95% CI, 0.12-1.23). For every 1000 patients opting for stenting rather than endarterectomy, 19 more patients would have strokes and 10 fewer would have MIs. Outcome data in asymptomatic patients were sparse and imprecise; hence, these conclusions apply primarily to symptomatic patients.**

Conclusion: **Compared with endarterectomy, carotid artery stenting (CAS) significantly increases the risk of any stroke and decreases the risk of MI. (J Vasc Surg 2011;53:792-7.)**

Carotid endarterectomy has been established as an effective treatment for patients with advanced symptomatic or asymptomatic carotid disease.[1,2] Carotid stenting has emerged as a less invasive treatment alternative to endarterectomy. Stenting was originally proposed as a safer procedure with lower perioperative morbidity and lower incidence of cranial nerve injury and local complications.[3] However, several randomized clinical trials (RCTs) and subsequent meta-analysis demonstrated possible increased risk of stroke associated with stenting.[4] Conversely, long-term follow-up (10 years) of patients randomized to endarterectomy showed continued benefit compared to deferral of carotid procedures.[5]

The Society for Vascular Surgery developed clinical practice guidelines in 2008 in which they highlighted the clinical dilemma associated with selecting the optimal intervention strategy for carotid bifurcation stenosis.[6] Compared to carotid endarterectomy, stenting was associated with lower perioperative morbidity, particularly, myocardial infarction (MI), but increased the incidence of stroke. The carotid committee acknowledged the uncertainty and imprecise meta-analytic estimates (confidence intervals [CIs] that include both harms and benefits) and issued relatively weak recommendations based on the literature available at the time. The committee recommended endarterectomy and left stenting to be used based on the patients' values and preferences (ie, trading a stroke for MI).

However, since 2008, several larger RCTs have been published[7,8] and hence, the purpose of this systematic

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Table I. Description of included trials

Trial	*No. of patients*	*Cerebral protective devices, %*	*Mean age (year)*	*% asymptomatic*	*Degree of stenosis, %*
Naylor, 1998[13]	23	0	67.2	0	>70
Alberts, 2001[14]	219	0	68.3	0	>60
Brooks, 2001[15]	104	0	68.0	0	>70
CAVATAS, 2001[3]	504	0	67.0	3	NR
Brooks, 2004[16]	85	0	68.2	100	>80
Yadav, 2004[21]	334	96	72.6	71	>50; >80[a]
Mas, 2004[19]	527	92	69.7	0	>60
The SPACE Group, 2006[20]	1200	NR (mixed)	67.9	0	>70
Ling, 2006[18]	166	100	63	Mixed, % unclear	>50; >70[b]
Hoffman, 2006[17]	20	NR	NR	0	>70
Steinbauer et al[12]	87	0	69	0	>70
CREST, 2010[6]	2502	96	69	47	>50 (angio) >70 (US) >70 (CTA/MRI)
ICSS, 2010[7]	1713	72	70	0	>50

angio, Angiography; *CTA,* computed tomography angiography; *MRI,* magnetic resonance imaging; *NR,* not reported; *US,* ultrasound.
All angioplasties were performed with stenting except in Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS; only 26%).
[a]Stenosis in symptomatic patients was >50% and in asymptomatic patients was >80%.
[b]Stenosis in symptomatic patients was >50% and in asymptomatic patients was >70%.

review was to update the current literature base and evaluate the relative effects of endarterectomy and stenting on death, stroke, and MI.

METHODS

Studies that enrolled patients with carotid artery disease regardless of symptoms and allocated them at random to either carotid artery endarterectomy or to endovascular treatment (stenting) were eligible for review. Studies were included regardless of size or language of publication. Included studies had to measure the outcomes of interest (stroke, death, or MI).

A comprehensive literature search of electronic databases (MEDLINE, EMBASE, Web of Science, and Cochrane CENTRAL) was conducted from 2008 through July 2010 using the appropriate terms and text words. Trials published before 2008 were obtained from our previous systematic review.[4] The details of the search strategy are available from the authors upon request. Two reviewers, working independently determined trial eligibility, and extracted descriptive, methodologic, and outcome data from each eligible RCT.

Random-effects meta-analysis[9] was used to assess relative risks and the I^2 statistic was used to assess heterogeneity of treatment effect among trials. The I^2 statistic represents the proportion of heterogeneity of treatment effect across trials that were not attributable to chance or random error. Hence, a value >50% reflects significant heterogeneity that is due to real differences in study populations, protocols, interventions, and outcomes.[10] The three main patient-important[11] outcomes of interest were death, stroke, and MI measured at the longest follow-up. We did not use a composite endpoint of these vascular morbidities because the results of published trials violated the assumptions of a common underlying treatment effect needed for proper interpretation of composite endpoints (ie, death, MI, and stroke, the components of the composite endpoints responded to the intervention in different directions). Intention-to-treat analyses data were extracted whenever possible. Absolute effects were estimated using pooled relative risks and median control event rates from patients undergoing carotid endarterectomy in the included trials. The GRADE framework was used to determine the quality of evidence.[12] Subgroup analyses that were established a priori and conducted in the original meta-analysis were repeated (subgroups based on the patients' symptoms, the use of protective devices, and stopping trials prematurely). We excluded two older RCTs in sensitivity analysis in which the interventions may be deemed less relevant to current practice (Carotid and Vertebral Artery Transluminal Angioplasty Study [CAVATAS] in which only 26% of patients received stents; and Leicester in which there was no preprocedural imaging of the origin of the major head and neck vessels to exclude contraindications to carotid artery stenting (CAS), use of nondedicated stents, and lack of routine predilation techniques).[3,13]

RESULTS

The original search identified 10 RCTs.[3,13-21] The updated search identified 418 potentially eligible references; of which only three new RCTs were identified.[7,8,22] Thus, the total body of evidence included 13 RCTs enrolling 7484 patients; of which 4302 (57%) were participants of the three new RCTs. One of these three trials is a long-term update[22] of a previously published preliminary report.[23] The majority of patients (80%) enrolled in these 13 RCTs was symptomatic. We also identified one publication describing an individual patient-pooled analysis of Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE), International Carotid Stenting Study, and Endarterectomy vs Angioplasty in Patients with Symptomatic

Table I. Continued.

Follow-up (months)	*Allocation concealment*	*Blinding*	*Early termination*	*Funding*
1	Yes	No	For harm	Mixed
12	Probably not	Probably not	For futility	For profit
48	Yes	No	No	Mixed
36	No	Outcome assessors	No	Not for profit
48	Yes	No	No	Not for profit
36	Yes	Probably not	For slow enrollment	Mixed
6	No	Outcome assessors	For futility and harm	Not for profit
1	Yes	No	For funding shortage	Mixed
6	Probably not	Probably not	No	Not for profit
45	Yes	Probably not	No	NR
64-66	No	None	No	For profit
30	Yes	Outcome assessors	No	Mixed (15% for profit)
3	Yes	Outcome assessors	No	Mixed

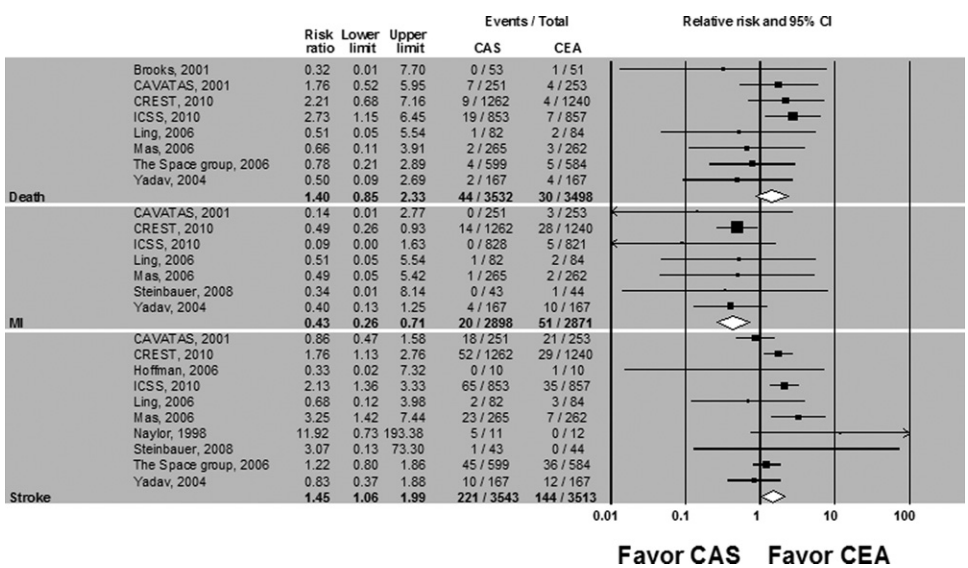

Fig. Random-effects meta-analysis comparing carotid artery stenting (*CAS*) to endarterectomy (*CEA*). *Diamonds* represent the pooled relative risk (relative risk). *Squares* and *lines* represent relative risks from individual studies and their 95% confidence intervals (CIs), respectively.

Severe Carotid Stenosis (ie, data sets of the three trials were merged and analyzed as one trial).[24]

In general, the overall quality of the body of evidence (13 RCTs) was high. Although methodological limitations were noted in the RCTs published before 2008 (allocation concealment was performed only in 6 of 11 studies, blinded outcome assessment in 2 of 11, and stopping early before full recruitment occurred in 5 of 11), the more recent and larger RCTs[7,8] that comprise 56% of all patients included in this meta-analysis did not have these limitations. Table I describes the 13 RCTs included in this systematic review and their methodological quality.

Meta-analysis. Compared with carotid endarterectomy, stenting was associated with increased risk of any stroke (relative risk [RR], 1.45; 95% CI, 1.06-1.99; I^2 = 40%) and decreased risk of periprocedural MI (RR, 0.43; 95% CI, 0.26- 0.71; I^2 = 0%). The increase in mortality associated with stenting was not statistically significant (RR, 1.40; 95% CI, 0.85-2.33; I^2 = 5%). Results are depicted in the Fig. Long-term outcomes of stenting (studies with follow-up ≥12 months) demonstrate similar increase in the risk of any stroke (RR, 1.74; 95% CI, 1.14-2.66) and no significant difference in mortality (RR, 1.02; 95% CI, 0.27-3.86), although the latter results are very

Table II. Absolute risk difference per 1000 patients

Outcome	*RD (95% CI)*	*Quality of evidence*	*Interpretation*
Death	3.44 (-1.29, 11.44)	Moderate[a]	CAS is associated with 3 more deaths (from 1 fewer to 11 more)
MI	−10.15 (-13.17, -5.16)	High	CAS is associated with 10 fewer MI's (from 13 fewer to 5 fewer)
Stroke	18.77 (1.96, 42.23)	High	CAS is associated with 19 more strokes (from 2 more to 42 more)

CAS, Carotid artery stenting; *CEA,* carotid artery endarterectomy; *CI,* confidence interval; *MI,* myocardial infarction; *RD,* risk difference presented as a percentage with endarterectomy as a reference.
Analysis assumed the median control event rate from patients undergoing carotid endarterectomy in the included trials and relative risks from random effects meta-analyses.
[a]Quality of evidence downgraded due to imprecision of meta-analytic estimate.

imprecise. When analysis was restricted to major or disabling stroke, the effect on stroke was not significant (RR, 1.00; 95% CI, 0.62-1.62). However, this analysis is underpowered and the result is very imprecise as well.

Absolute treatment effects. Using the median event rate observed in patients undergoing endarterectomy across all RCTs as a control event incidence (ie, death 0.86%, MI 1.78%, and stroke 3.91%), we estimated the risk difference per 1000 patients. Results are summarized in Table II with the associated quality of evidence.

Subgroup and sensitivity analyses. We found no significant treatment-subgroup interaction for subgroups based on whether the patient had symptoms or not, the use of protective devices, and stopping trials prematurely. However, these analyses were highly underpowered and their results are likely unreliable. Within-trial subgroup analyses also failed to identify significant treatment interactions based on the severity of stenosis,[3] patient gender,[7,20] the presence of symptoms,[7,21] or whether MI was associated with Q wave.[21] Age seemed to interact with treatment effect in the individual patient-pooled analysis,[24] Carotid Revascularization Endarterectomy vs Stenting Trial (CREST),[7] and to a lesser extent in SPACE,[20] suggesting CAS is more efficacious in the young (age <70).

The exclusion of the two older RCTs[3,13] does not change study conclusions; that is, increased risk of stroke, decreased risk of MI with stenting, and an unclear effect on mortality. When analysis is restricted to the two most recent trials[7,8] with the better methodology and with techniques and skills that arguably are more contemporary, we find CAS to be associated with a significant increase in the risk of any stroke (RR, 1.82; 95% CI, 1.35-2.45) and mortality (RR, 2.53; 95% CI, 1.27-5.08), and a nonsignificant reduction of the risk of MI (RR, 0.39; 95% CI, 0.12-1.23).

Asymptomatic patients. Outcome data in asymptomatic patients are sparse and imprecise. The number of patients who were asymptomatic across all trials was 1513 (20%); however, these patients had a small number of events. Only one trial exclusively enrolled asymptomatic patients and there were no events in either study arm.[16] In a second trial by Yadav et al,[21] the cumulative incidence of the primary composite endpoint of death, MI, or stroke was not statistically different between CAS and carotid endarterectomy (CEA). In asymptomatic patients enrolled in CREST,[7] the rates of death, MI, and any stroke were (0%, 1.2%, and 2.5% for CAS; and 0%, 2.2%, and 1.4% for CEA). CREST findings are consistent with our main findings in all patients (ie, suggest a trend for increased MI with CEA and increased stroke with CAS); however, these data are also very sparse and inference is limited.

DISCUSSION

We conducted a systematic review and meta-analyses comparing CAS and CEA. These analyses update the evidence base by more than doubling the number of randomized patients. CAS is associated with increased risk of stroke but decreased risk of perioperative nonfatal MI. The effect on mortality remains unclear. The meta-analytic estimates seem to be reliable with no significant heterogeneity. Outcome data were derived mainly from symptomatic patients. There may be an age-benefit interaction suggesting that CAS should be particularly avoided in patients over 70.

Trading benefits and harms requires presenting treatment effects to patients in absolute terms. As demonstrated in this report, stenting would lead to 19 more strokes and 10 fewer MIs per 1000 treated patients. Patients typically seek both procedures to prevent stroke as their primary indication for revascularization. Furthermore, the estimated average decrement in quality of life associated with stroke exceeds that of MI (a quality-of-life score of 0.52 for major stroke, 0.68 for moderate stroke, and 0.87 for minor stroke; compared to a score of 0.88 for MI).[25,26] However, this comparison remains challenging because of the lack of clarity in the published trials about the clinical significance and consequences of the MI described in these trials (clinically significant vs being demonstrated by electrocardiogram and enzymes only, associated with Q wave vs not). Moreover, it seems as if CAS was associated with an increase in primarily nondisabling strokes. From a societal perspective, Markovian analysis conducted using direct Medicare costs demonstrated that CAS produced less quality-adjusted life-years (8.97 vs 9.64) and an incremental cost of $17,700.[27] These analyses may not apply to patients at different ages or with different vascular anatomy. In all, the available evidence continues to support the previous iteration of the Society for Vascular Surgery guidelines on the management of carotid artery disease. These guidelines recommended that patients in need of carotid revascularization should be offered endarterectomy as their first choice. On the other hand, they recommended that stenting should be offered to patients who have high perioperative coronary risk or anatomic risk for endarterectomy such as previous CEA with recurrent stenosis, prior ipsilateral radiation therapy to neck with permanent skin changes, previous ablative neck surgery (eg, radical neck dissection, laryngectomy), common carotid artery stenosis below the clavicle, contralateral vocal cord paralysis, or presence of a tracheostomy stoma.[6]

The strengths of this review stem from the comprehensive literature search that follows an explicit protocol and bias protection measures undertaken by reviewers (such as selecting studies, evaluating studies quality, and extracting outcome data by two independent reviewers). The weaknesses stem from inability to evaluate patient-level covariates that are needed to conduct meaningful subgroup analyses. Such analyses may demonstrate differential benefit of CAS or CEA in a particular gender, age, or other patient groups. Another limitation is the paucity of data in asymptomatic patients making inferences in this subgroup of patients challenging. Compared with previous reviews,[4,28] this report has more randomized patients and higher precision and includes RCTs with fewer methodological shortcomings; therefore, these results offer higher-quality evidence, more precise results, and should yield stronger inferences.

The robustness of the currently available data and its relationship to the results of future and ongoing RCTs can be appreciated by estimating the Optimal Information Size.[29] This concept is based on the assumption that the sample size required for a reliable and conclusive meta-analysis is at least as large as that of a single optimally powered RCT. Using a desired power of 90%, two-sided α value of 0.05, the control event rate and relative risks observed in this meta-analysis, we find the optimal information size (sample size needed) to be 4516 and 4177 patients for stroke and MI, respectively. The current evidence base fulfills this assumption. Hence, it seems that our inferences are robust unless the stenting technique changes and the associated incidence of stroke significantly declines. On the other hand, if one considers the effect on major and disabling stroke (as opposed to any stroke), or considers inferences in asymptomatic patients, data remain sparse and definitive recommendations will be very sensitive to the results of future trials. Lastly, there is a growing consensus that future trials of carotid intervention in neurologically asymptomatic patients will have to include a nonintervention arm that receives the best available medical management. It is plausible that intensive medical treatment may trump all interventions if all three outcomes (MI, stroke, and death) were considered as primary outcomes. A medical intervention arm would preserve true equipoise.

The Society for Vascular Surgery is planning to update their clinical practice guidelines on the management of carotid artery disease. A panel of experts will use data from this report and other sources of evidence and incorporate additional relevant aspects such as patients' values, preferences, resource allocation, and clinical context to develop clinical recommendations.

CONCLUSION

Compared with endarterectomy, CAS increases the risk of any stroke and decreases the risk of MI. Outcome data in asymptomatic patients remain sparse and imprecise.

AUTHOR CONTRIBUTIONS

Conception and design: MM, AS, NS, VM, JR
Analysis and interpretation: MM, VM, JR
Data collection: MM, AS
Writing the article: MM
Critical revision of the article: MM, AS, NS, VM, JR
Final approval of the article: MM, AS, NS, VM, JR
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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