Endarterectomy or Stenting in Severe Asymptomatic Carotid Stenosis

Dallit Mannheim MD, Batla Falah MD and Ron Karmeli MD

Department of Vascular Surgery, Carmel Medical Center, Haifa, Israel

ABSTRACT: **Background:** Stroke is a major cause of death in the western world, and carotid endarterectomy has been shown to be effective in treating both symptomatic and asymptomatic carotid stenosis. Carotid stenting is a relatively new form of treatment for carotid stenosis and few studies have looked specifically at asymptomatic patients.

Objectives: To retrospectively examine short- and long-term results in the treatment of asymptomatic carotid artery stenosis with surgery or stenting.

Methods: We retrospectively collected data of all patients with asymptomatic carotid stenosis treated by carotid artery stenting or carotid endarterectomy in our department from 2006–2007. The primary endpoints were stroke, myocardial infarction, or death during the periprocedural period; or any ipsilateral stroke, restenosis, or death within 4 years after the procedure.

Results: The study comprised 409 patients who were treated by either stenting or surgery. There was a low morbidity rate in both treatment groups with no significant difference in morbidity or mortality between the treatment groups, short-term as well as long-term.

Conclusions: Both treatment methods have a low morbidity and mortality rate and should be considered for patients with few risk factors and a long life expectancy. Treatment method should be selected according to the patient's individual risk factors and imaging data.

IMAJ 2017; 19: 289–292

KEY WORDS: carotid artery stenosis, carotid artery endarterectomy, carotid artery stenting, stroke, myocardial infarction

Stroke is a major cause of death in the western world, and carotid artery stenosis is the estimated cause in 8–20% of the patients [1]. Large randomized controlled trials conducted 20–30 years ago have shown carotid endarterectomy (CEA) to be an effective treatment in both symptomatic [2,3] and asymptomatic stenosis [4,5]. With the improvement of best medical therapy (BMT) and the reduction of stroke by 40–50%, it has been suggested that patients with severe asymptomatic carotid stenosis be treated by BMT [6]; however, some subgroups of patients are still at high risk for stroke despite BMT and might benefit from invasive treatment [7]. The emerging wide spread use endovascular techniques has added another aspect to the question of how to treat carotid stenosis, especially since CEA is a procedure with few perioperative complications (cerebral-vascular accident: CVA, 1–3%; cranial nerves injury 2–8%) and good long term results (5 year CVA; 5–6.5%).

Results of studies comparing carotid artery stenting (CAS) to endarterectomy have been conflicting [8-11]. These studies have looked at both symptomatic and asymptomatic patients, but few studies have looked specifically at asymptomatic patients.

In this study we examined short- and long-term results in the treatment of asymptomatic carotid artery stenosis with surgery or stenting.

PATIENTS AND METHODS

Data were retrospectively collected from patient charts of all asymptomatic patients treated for carotid stenosis by either CEA or CAS between 2006 and 2007 (n=409) in the Department of Vascular Surgery at the Carmel Medical Center. Asymptomatic patients with severe carotid artery stenosis > 70% were considered for invasive treatment if they were thought to be a low surgical risk and have a life expectancy of more than 5 years. Diagnosis of carotid stenosis was made by carotid duplex and confirmed with computed tomography angiography (CTA) or magnetic resonance angiogram (MRA). Demographic and medical data were collected for each patient. Data included gender, age, and risk factors such as hypertension, diabetes, hyperlipidemia treated by statins, chronic renal failure, ischemic heart disease, smoking, and previous vascular surgeries including coronary artery bypass graft (CABG), peripheral vascular bypass, and CEA.

Data were also collected from patient charts in the vascular clinic and included results of physical and neurological examinations as well as duplex ultrasonography after 1, 3, and 6 months, and then yearly up to 4 years after treatment.

End points included short-term conditions such as perioperative complications, cranial nerve injury, operation site hematoma or infection, transient ischemic attack (TIA), CVA (both ipsilateral and contralateral), and myocardial infarction (MI) as defined by clinical symptoms with elevated enzyme levels.

Long-term results included mortality, ipsilateral TIA or CVA, and restenosis defined as stenosis of 70% or more according to NASCET classification (residual lumen in comparison to the normal distal internal carotid artery lumen), as diagnosed by duplex ultrasound and confirmed by CTA.

TREATMENT METHODS

All patients were treated by either aspirin 75–100 mg or clopidogrel 75 mg pre-operatively. All patients after CAS were treated with a dual anti-platelet regimen (75–100 mg aspirin and 75 mg clopidogrel) for 45 days and after that by aspirin (75–100 mg) alone. Patients undergoing CEA were treated postoperatively with aspirin (75–100 mg) alone.

CEA was conducted under regional anesthesia, and the operative method (primary closure, patch or eversion) was decided by the surgeon intra-operatively.

CAS was considered for patients with a favorable anatomy, but patients with highly calcified plaque, suspected thrombus or ulcer in the preoperative imaging (CTA or duplex), and highly tortuous common or internal carotid artery were excluded. The stenting was done percutaneously via a transfemoral approach. All procedures were done with distal protection (Angioguard®, Cordis, USA) and all patients were stented (PRECISE®, Cordis, USA)

STATISTICAL METHODS

Statistical analysis was performed using SPSS software (SPSS Inc., version 22, Chicago, IL, USA). Continuous variables were presented by mean, median and standard deviation. Categorical variables were presented as percentages.

Comparison between the CAS group and the CEA group was done using chi-square analysis for the categorical variables, and independent *t*-test or Mann-Whitney test, as appropriate, for the continuous variables. A propensity score using logistic regression was computed to adjust for demographic and clinical variables between the groups.

Time distribution until death, CVA and restenosis were evaluated for each endpoint separately by Kaplan-Meier curve. Stratified Cox regression was conducted for computing the differences of the groups controlling for propensity score quartiles. $P < 0.05$ was considered statistically significant.

RESULTS

Patients were treated for significant asymptomatic stenosis (over 70%) from 2006–2007, 249 (61%) were treated by CEA and 160 (39%) by CAS. Follow-up data were available for 397 patients (97%) up to 4 years.

Ischemic heart disease, and a history of previous vascular surgery were more prevalent in the CAS group (50% vs. 40%, $P = 0.05$, 39% vs. 21%, $P < 0.0001$, respectively) [Table 1]. Most patients in the CEA group [193 (77.5%)] were treated by primary closure, 41 patients (16.5%) were treated with eversion and 15 (6%) with patch closure.

Table 1. Baseline characteristics of the study population

	CAS N=160	CEA N=249	*P*
Age (range)	70 (43–86)	69 (43–88)	NS
Gender (M/F)	107/53	172/77	NS
Hypertension (%)	123 (77)	192 (77)	NS
(%) Hyperlipedemia	110 (69)	151 (61)	NS
Diabetes (%)	64 (40)	108 (43)	NS
Chronic renal failure (%)	16 (10)	30 (12)	NS
Ischemic heart disease (%)	80 (50)	100 (40)	NS
Smoking (%)	20 (12)	40 (16)	NS
Previous vascular surgeries (%)	63 (39)	53 (21)	< 0.0001

CAS = carotid artery stenting, CEA = carotid endarterectomy, NS = not significant

The treatment results were divided into short-term (30 days post-treatment) and long-term (up to 4 year after treatment). Patients lost to follow-up did not change the distribution of risk factors or demographic data between the treatment groups.

There was no significant difference in morbidity or mortality between the treatment groups in the short-term (CVA: 2% in CAS and 1.5% in CEA, TIA: 1.4% in CAS vs. 0.7% in CEA, MI: 0 in CAS vs. 0.7% in CEA). There was also no difference in the long-term results (2.6% CVA in CAS and 4.2% in CEA) [Figures 1–3].

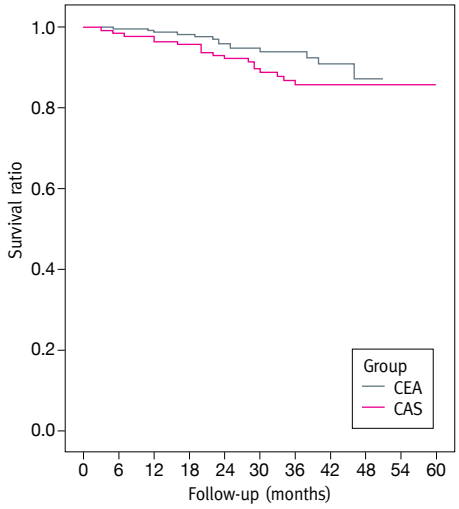
When examining the groups using propensity-matched comparison, there were no differences in the endpoint of mortality, CVA or restenosis [mortality hazard ratio (HR) = 1.78, 95% confidence interval (CI) 0.86-3.70, P = NS; CVA HR = 0.61, 95%CI 0.18–2.04, P = NS; restenosis HR = 0.64, 95%CI 0.33–1.24, P = NS].

Subgroup analysis showed a higher mortality rate in hypertensive patients treated with endarterectomy (CAS HR = 0.80, 95%CI 0.29–2.23, P = NS; CEA HR = 0.33, 95%CI 0.13–0.80, $P = 0.015$). Further examination of these cases showed the cause of death to be related to infections and malignancies and was probably not connected to the treatment method. In addition, a higher percentage of restenosis was observed in woman treated by surgery (CAS HR = 1.14, 95%CI 0.27–4.80, P = NS; CEA HR = 2.6, 95%CI 1.06–6.42, $P = 0.037$).

DISCUSSION

The debate on the indications and best methods for treatment of asymptomatic carotid stenosis is still ongoing. The randomized controlled trials of the 1990s have shown carotid CEA to be an effective treatment in asymptomatic stenosis

Figure 1. Kaplan-Meier curve: 4 year survival



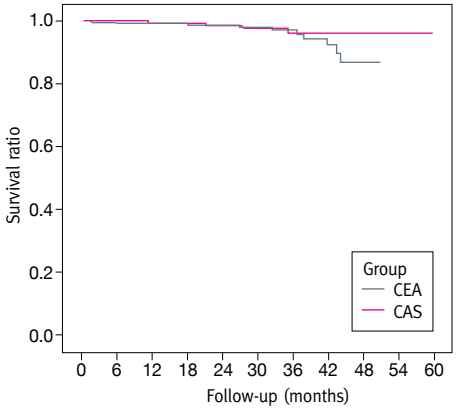
		1 month	6 month	12 month	24 month	36 month	48 month
CEA	Number remaining	241	224	207	176	108	14
	% survival	100	99.6	98.6	95.9	93.9	87.2
CAS	Number remaining	156	150	141	128	80	20
	% survival	100	98.7	96.6	92.3	85.8	85.5

[4,5]. With the improvement of BMT and the reduction of stroke by 40–50%, it has been suggested that patients with severe asymptomatic carotid stenosis be treated by BMT alone [6]. Researchers are currently conducting large randomized controlled trials to address these issues (ECST-2: trial number ISRCTN 97744893 and CREST-2: trial number NCT02089217). Early results are expected in 2018.

This study showed similar short- and long-term results for carotid endarterectomy and stenting in asymptomatic patients with significant carotid disease.

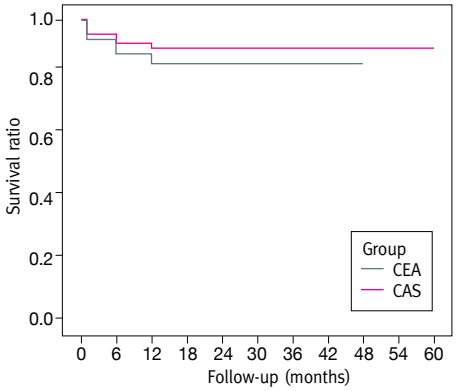
For an asymptomatic patient with severe carotid stenosis, the most important question is how to prevent an ischemic stroke. In large randomized controlled trials [4,5] CEA patients had a 5 year stroke rate of 5.1–6.5% compared to an 11% stroke rate in the medical treatment group. Recent studies have demonstrated that BMT might have a lower stroke rate than originally observed. The Asymptomatic Carotid Surgery Trial (ACST) [12] showed a rate 3.6% lower during the second 5 year follow-up period (years 6–10). Treatment with statins has generally been associated with stroke reduction [13], possibly due to stabilization of the carotid plaque by the treatment [14]. The CREAST [8] and SPACE [11] trials have shown similar rates of perioperative complications as well as long-term results for both CAS and CEA. Only the CREAST study looked at asymptomatic patients demonstrating similar results for stroke prevention in the perioperative and postoperative period for this group of patients [8] as well as a similar long-term restenosis rate [15]. In this study we showed a low perioperative stroke rate in both treatment groups (1.5–2%) as well as a low stroke rate during the 4 year follow-up (1.5–2.4%). This result might be due to the combination of our small sample size, the wide use of statins (61–69%) by our patients and a strict protocol for patient selection, including a CTA for all patients and a review of the imaging by the operating team, with special consideration for plaque morphology.

Figure 2. Kaplan-Meier curve: 4 year stroke-free survival



		1 month	6 month	12 month	24 month	36 month	48 month
CEA	Number remaining	241	222	205	174	105	13
	% survival	100	99.1	99.1	98.6	97	87
CAS	Number remaining	156	150	141	127	77	20
	% survival	100	100	99.3	98.5	96.4	96.4

Figure 3. Kaplan-Meier Curve: 4 year stenosis-free survival



		1 month	6 month	12 month	24 month	36 month	48 month
CEA	Number remaining	232	185	149	109	58	6
	% survival	93.5	89	85.4	85.4	85.4	85.4
CAS	Number remaining	146	127	106	83	53	12
	% survival	95.2	92.2	90.5	90.5	90.5	90.5

CAS has improved significantly over the past several years with the addition of protection devices and increased experience of the operators and will likely continue to improve as we better understand appropriate patient selection.

This study also showed that women have higher rates of restenosis in the surgical group without a significant difference in perioperative or long-term morbidity or mortality. These results were first demonstrated in the Asymptomatic Carotid Atherosclerosis Study (ACAS) [5] with a smaller risk reduction of stroke in asymptomatic women undergoing carotid surgery then in men (compared to medical treatment). The higher restenosis rate in women might be due to method of arteriotomy closure with a higher rate of restenosis in women treated by primary closure compared to a patch [16]. With the introduction of carotid stenting, the effect of gender on outcome after stenting was investigated with poorer results in women, especially in short-term morbidity and mortality [17]. Thus, treating women with asymptomatic carotid stenosis should be selective and patients should be counseled about lifestyle changes, and appropriate medical treatment of risk factors should be initiated.

The Society for Vascular Surgery recommends treating asymptomatic carotid stenosis in patients with low (< 3%) perioperative risk and patients with substantial risk factors should be considered for risk factor management and lifestyle changes over surgical treatment [18]. Although we have shown good results for both carotid surgery and stenting, invasive treatment of asymptomatic disease should be considered for patients with few risk factors and long life expectancy. Treatment method should be selected according to the patient's individual risk factors and imaging data.

Correspondence
Dr. D. Mannheim
Dept. of Vascular Surgery, Carmel Medical Center, Haifa 3436212, Israel
email: dallit@gmail.com

References

1. Flaherty ML, Kissela B, Khoury JC, et al. Carotid artery stenosis as a cause of stroke. *Neuroepidemiology* 2012; 40 (1): 36-41.
2. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998; 351 (9113): 1379-87.
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; 325 (7): 445-53.
4. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke* 2004; 35 (10): 2425-7.
5. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995; 273 (18): 1421-8.
6. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke* 2009; 40 (10): e573-83.
7. Paraskevas KI, Nicolaides AN, Veith FJ. Carotid endarterectomy may be required in addition to best medical treatment for some patient subgroups with asymptomatic carotid stenosis. *Vascular* 2015; 23 (1): 62-4.
8. Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010; 363 (1): 11-23.
9. Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008; 358 (15): 1572-9.
10. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006; 355 (16): 1660-71.
11. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008; 7 (10): 893-902.
12. Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? *Eur J Vasc Endovasc Surg* 2009; 37 (6): 625-32.
13. Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004; 35 (12): 2902-9.
14. Kadoglou NP, Gerasimidis T, Moumtzouoglou A, et al. Intensive lipid-lowering therapy ameliorates novel calcification markers and GSM score in patients with carotid stenosis. *Eur J Vasc Endovasc Surg* 2008; 35 (6): 661-8.
15. Lal BK, Beach KW, Roubin GS, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. *Lancet Neurol*; 11 (9): 755-63.
16. Mannheim D, Weller B, Vahadim E, Karmeli R. Carotid endarterectomy with a polyurethane patch versus primary closure: a prospective randomized study. *J Vasc Surg* 2005; 41 (3): 403-7; discussion 7-8.
17. Kuy S, Seabrook GR, Rossi PJ, Lewis BD, Dua A, Brown KR. Management of carotid stenosis in women. *JAMA Surg*; 148 (8): 788-90.
18. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease; executive summary. *J Vasc Surg*; 54 (3): 832-6.

Capsule

Countering chemo's effects on fertility

Conventional chemotherapy with DNA-damaging agents has helped countless cancer patients become cancer survivors. This successful outcome is sometimes accompanied by long-term side effects, however. In young female patients, for example, the alkylating agent cyclophosphamide can compromise fertility. This occurs because the drug causes inappropriate activation of ovarian follicular development, thereby exposing oocytes to its DNA-damaging effects. Studying a mouse model, Goldman et al. showed that ovarian function and fertility are preserved when cyclophosphamide is co-administered with drugs called mTORC1/2 inhibitors, which suppress a signaling pathway required for follicular activation. mTORC1/2 inhibitors are already clinically approved for other purposes, including treatment of certain forms of breast cancer, and may merit exploration as a fertility-preserving strategy in female cancer patients.

Proc Natl Acad Sci USA 2017; 114: 3186

Eitan Israeli