Carotid Artery Stenting

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Summary

Carotid atherosclerotic disease forms an important cause of stroke which is the leading cause of serious morbidity amongst patients. In symptomatic patients medical therapy has been demonstrated to be inferior to surgical carotid endarterectomy, whereas in asymptomatic patients no clear cut benefit is observed. Recently, carotid artery stenting has become an investigational tool and although several series have shown beneficial immediate and intermediate results there is a lack on long-term data. The article provides a critical analysis of carotid artery stenting. The adavantages and disadvantages with respect to carotid endarterectomy are discussed in view of the reduction of the risc of strokes and surgical complications, e.g., wound complications, cranial nerve injuries, and other medical or anesthetic complications.

Key Words
Carotid artery stenting, surgical carotid endarterectomy, carotid atherosclerotic disease

Introduction

Stroke affects 600,000 [1] to 700,000 [2] people annually in the United States and is the third leading cause of death after heart disease and cancer. It is the leading cause of serious morbidity. In addition stroke imposes a great financial drain on the health resources. The annual cost of stroke is close to $ 40 billion [3] and the lifetime cost for stroke is in the range of $ 90,000 – $ 230,000 per patient. Ischemic cerebral infarctions form 70 – 80 % of causes of stroke. Atherosclerotic internal carotid artery disease is responsible for approximately 9 % of all ischemic strokes [4]. Addition of embolism from the internal carotid artery brings this figure close to 35 % of all ischemic strokes [5]. This forms an important cause of stroke both in the general population and also constitutes a significant proportion of strokes associated with cardiovascular bypass surgery.

Carotid Endarterectomy (CEA)

The earliest report of carotid endarterectomy dates back to as early as 1954 [6] where a patient with imminent stroke was successfully treated by removal of the carotid artery stenosis. This was a building block on which subsequent attempts at carotid endarterectomy evolved. Previous randomized trials comparing medical with surgical treatment showed no benefit of carotid endarterectomy [7,8] and one report demonstrated a high (10 %) 30 day death and stroke incidence [9]. Subsequently trials [10-12] demonstrated a clear benefit of carotid endarterectomy over medical treatment and was most profound in the group with symptomatic high grade stenosis (≥ 70 %) with an absolute risk reduction of 13 % to 16 % [10,11] (Table 1). Patients with symptomatic moderate carotid stenosis (50 – 69 %) derived only moderate benefit. In order to prevent one ipsilateral stroke 15 patients with moderate grade stenosis would have to be treated by endarterectomy.

Factors determining the magnitude of benefit derived from carotid intervention are symptomatic or asymptomatic carotid stenosis, degree of carotid artery stenosis (Figure 1), and perioperative stroke or death (Table 2). Complication rates at 30 days after CEA range from 6 – 7 % for overall stroke and death rate and the major stroke and mortality rate is approximately 3 % [10,11]. The risks of stroke differ when reported by the surgeons as compared with neurologist controlled results as demonstrated by a metaanlysis of 17,105 operations [13].

	Stenosis (%)	Perioperative Stroke or death rate (%)	Ipsilateral Stroke Medical (%)	Ipsilateral Stroke CEA (%)
NASCET [10]	70 – 99	5.8	26	9*
NASCET [10]	50 – 69	6.7	22	16**
NASCET [10]	< 50	6.7	19	15
ECST [11]	60 – 99	7.5	17	3*

*) P < 0.001 **) P = 0.045

Table 1. Medical treatment versus carotid endarterectomy; symptomatic patients.

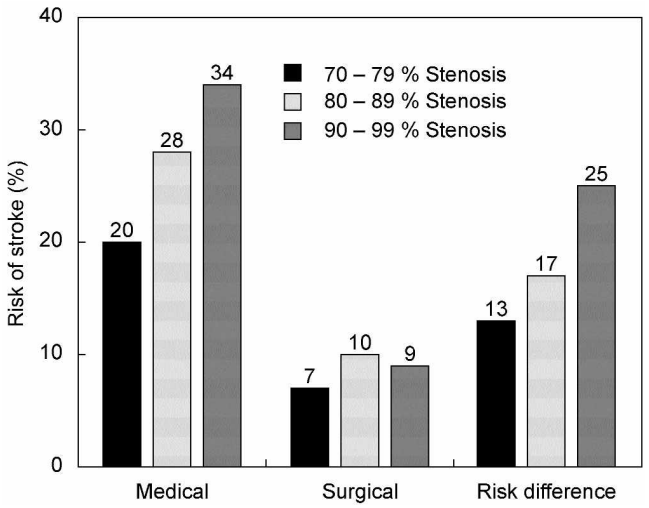

Figure 1. Risk of an ipsilateral stroke at 2 years depending on stenosis severity and mode of treatment : Data adapted from the North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET).

- **Presence or absence of symptoms**
  - symptomatic patients: benefit
  - asymptomatic patients: dependent on other factors
- **Degree of carotid artery stenosis**
  - > 50 % stenosis: benefit
  - < 50 % stenosis: no benefit
- **Rate of perioperative stroke and death**
  - symptomatic patients: < 6 %
  - asymptomatic patients: < 3 %

Table 2. Variables influencing CEA benefit.

CEA in Asymptomatic Carotid Disease

The role of carotid endarterectomy in symptomatic high grade stenosis is well established [10-12], but the role in asymptomatic carotid artery stenosis is still ambiguous (Table 3). The Asymptomatic Carotid Atherosclerosis Study (ACAS) [12] study found a mere 6 % reduction in the risk of stroke at 5 years which is less than half of that reported in patients with symptomatic carotid stenosis. This was obtained by using stringent selection criteria and concerns persist that whether these results can be generalized to all surgical centers.

	Stenosis (%)	Perioperative Stroke or Death Rate (%)	Relative Risk Reduction (%)	Benefit
ACAS [12]	> 60	2.3	53	Yes
VA Trial [14]	> 50	4.7	10	No

Table 3. Medical treatment versus carotid endarterectomy; asymptomatic patients.

Similarly the Veterans Affair Asymptomatic Carotid Stenosis [14] study randomized 444 patients to either CEA or optimum medical therapy with a mean follow up of 4 years which also did not demonstrate statistical significant reduction in ipsilateral strokes (4.7 % vs 9.4 %). Studies with carotid stenting (CS) have not shown any significant benefit in patients with asymptomatic carotid stenosis either.

Carotid Stenting (CS)

Evolution

Carotid endarterectomy is an established treatment modality of symptomatic carotid artery stenosis. Some of the reservations or shortcomings of this procedure prompt the search for alternate means of treatment for symptomatic carotid stenosis. They are briefly summarized in tables 4 and 5. Carotid stenting may provide an answer to this predicament. CS has been increasingly performed around the globe since first reports came out as early as 1996 [15]. It is still an investigational tool in the United States. CS does not need to be proved superior to CEA in the management of symptomatic carotid stenting but should be an equally viable option i.e. it should have acceptable complication rates [16] i.e. < 6 % for symptomatic and < 3 % for asymptomatic stenoses.

Results of CS

Some of the complications seen with CEA can be avoided or largely attenuated by CS for e.g. wound

- Carotid lesions higher than cervical vertebrae C2-3
- Carotid lesions at the ostium or origin of the common carotid artery
- Cervical spine disease or fixation preventing extension beyond neutral
- Prior radical neck dissection
- Prior radiation therapy to the neck

Table 4. Anatomic considerations; not suited for CEA.

- Unstable angina
- Myocardial infarction within previous month
- Critical coronary artery disease requiring revascularization
- Congestive heart failure
- Severe pulmonary disease
- Bleeding diathesis

Table 5. Clinical comorbidity associated with high risk for CEA.

complications, cranial nerve injuries, other medical and anesthetic complications [17] (Figure 2). These very disadvantages form advantages for CS. It can be performed in patients with NASCET exclusion criteria [18]. In a recent large center 5 year experience [19], NASCET ineligible patients constituted approximately 50 % of patients studied and only one patient (0.2 %) experienced a myocardial infarction.

Recent data from round the globe have demonstrated that CS can now be performed with low complication rates [19-22] (Table 6). A worldwide registry of carotid stenting reports a technical success rate of 98.4 %, a major stroke and death rate of 2.4 %, and an overall minor stroke rate of 2.7 % [23]. Minor stroke rates were defined as a new neurologic event that resulted in slight functional impairment that either completely resolved within 7 days or caused an increase of less than four points in the patient's score on the National Institutes of Health (NIH) stroke scale. Major stroke rates were defined as a new neurologic event that persisted after 7 days and increased the patient's score on the NIH stroke scale by four points or more.

These findings have been substantiated in a recent 5 year prospective study by Roubin et al [19]. They studied 528 consecutive patients. Follow up was available in 99.6 % of patients at a mean of 17 ± 12 months. The inhospital follow up and subsequent follow up was performed by a

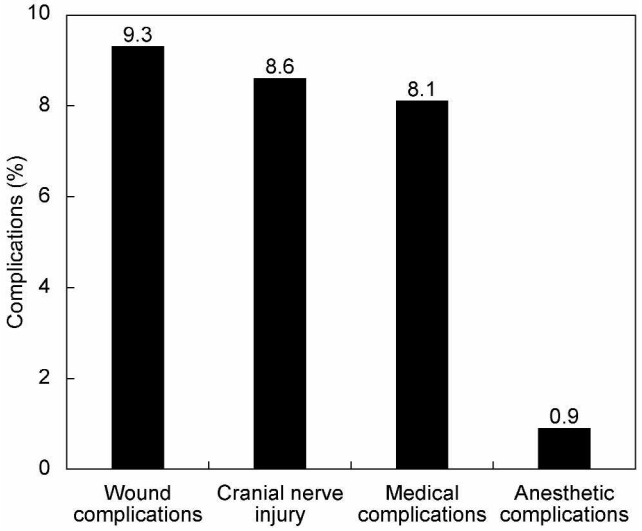

Figure 2. Surgical and medical complications of CEA (30 day results). Data adapted from the North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET).

Study	Year	Patients	Success	Major Stroke	Minor Stroke	Death	Total 30 day
		(n)	(%)	(%)	(%)	(%)	(%)
Diethrich [25]	1996	110	99	1.8	9.1	0.9	11.8
Yadav [15]	1997	107	100	1.9	6.7	0.9	7.9
Wholey [42]	1997	108	95	1.9	6.5	1.9	10.2
Mathur [39]	1998	231	100	0.9	7.4	0.9	8.2
Leisch [43]	1998	65	98	1.5	3.1	1.5	6.2
Bergeron [26]	1999	99	97	0	5.0	0	5.0
Shawl [44]	2000	170	99	0.6	2.4	0	2.9
Henry [45]	2000	290	99	1.4	2.6	0.3	4.3
Average		1180	99	1.2	5.3	0.7	6.9

Table 6. Carotid artery stenting; safety and feasibility: 30 day results.

neurologist. They used a different definition of minor and major nonfatal strokes (Minor stroke was less than 30 days and raised the NIH stroke score by less than three and major stroke was more than 30 days and raised the NIH stroke score by more than three). In 10 % of arteries dilated there was a contralateral occluded inter-

nal carotid artery and 15 % patients underwent bilateral carotid artery stenting. Only 2 % of patients could not be successfully stented. The overall 30 day stroke or death rate was 7.4 % and the major stroke or death rate was 2.6 %. The 5 year follow up showed a significant reduction trend in minor stroke rates from 7.1 % for the first year to 3.1 % for the fifth year ($p < 0.05$). Three year freedom from all fatal and non fatal strokes was 88 ± 2 %, which was 95 ± 2 % if the 30 day periprocedural period was not included in the analysis. This study also included patients ≥ 80 years of age. The 3 year freedom from all fatal strokes for < 80 vs ≥ 80 years of age was 90 ± 2 % vs 73 ± 4 %. Age ≥ 80 years was a predictor of periprocedural adverse events and late stroke. Similar results have been reported in observational studies for CEA [24]. The restenosis rate was 3 % which is comparable to other studies with CS and is much less than the approximate 13 % with CEA. Follow up results of the worldwide registry and other smaller studies have been comparable [23,25,26].

Subsets of Patients Benefiting From CS Over CEA

Patients with previous CEA have a high risk of strokes and death after reoperations [27,28]. Stenting has provided comparable to lower complication rates in these patients [29] (Figure 3). Similarly 94 high surgical risk patients at Cleveland Clinic referred by vascular surgeons for interventional carotid stenting could be performed with a 99 % success rate with acceptable stroke and death rates [5]. Another subset of patients that tend to perform better with carotid stenting are the ones with combined coronary and carotid artery disease [30,31] and patients with previous radiation to the neck. As described earlier, NASCET ineligible patients can be successfully treated with CS (Figure 4). CEA has demonstrated skewed results in favor of men [10-12,32]. The study by Roubin et al [19] have found similar immediate and late outcomes for men and women using CS. Thus CS may be more helpful in women but this needs revalidation in randomized studies.

In summary the advantages of CS over CEA are

- Performed under local anesthesia hence other comorbid cardiac and pulmonary disease are no contraindications. In addition continuous neurological monitoring is possible during the intervention and any stroke can be immediately picked up and promptly managed.
- Absence of cranial nerve injuries
- Surgically inaccessible sites can be attempted
- Low restenosis rates

Cerebral Protection During Carotid Stenting

As seen with any vascular intervention microembolization forms an integral factor affecting immediate results. The same analogy seems to be a cause of cerebral embolization during CS. Microembolization detected by transcranial Doppler monitoring occurs both with CS and CEA [32-34]. Protection can be phar-

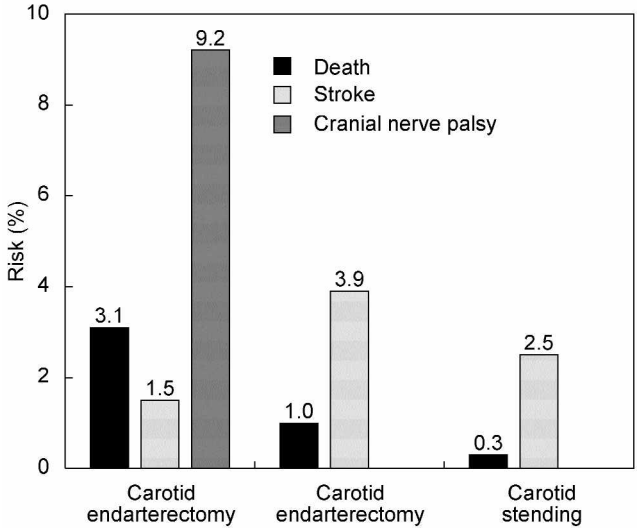

Figure 3. Risk of Death, stroke or cranial nerve palsy in patients with previous carotid endarterectomy treated with reoperation or carotid stenting. Data adapted from [27-29].

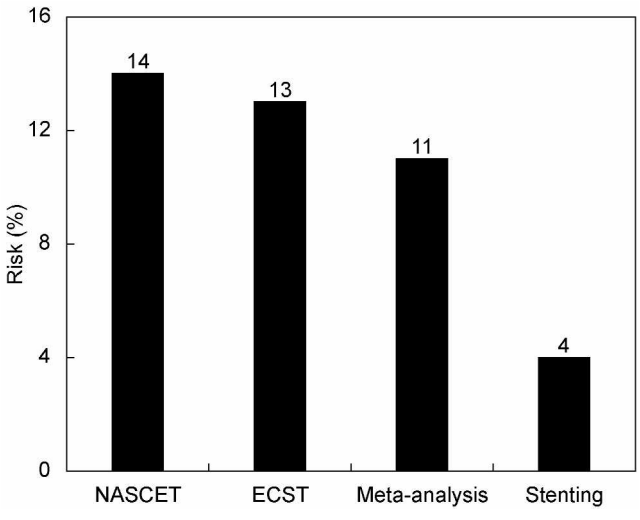

Figure 4. 30 day risk for death or stroke in patients with occluded contralateral coronary artery.

macological using glycoprotein IIb/IIIa inhibitors. A small series of 95 patients [5] patients showed no acute stroke or death with use of abciximab during CS, but there were 1 intracranial hemorrhage and five hematomas. This therapy is still in its infancy and needs further evaluation.

Multiple devices are available for mechanical cerebral protection [35]. They include distal balloon occlusions, filter devices. The principle of balloon protection is that the distal balloon temporarily occludes the runoff circulation to the brain, and thereby trapping the debris with it, which is then aspirated out of the guiding catheter prior to deflation of the balloon. Henry M [36] reported a small cohort of 58 patients undergoing balloon protection facilitated CS and compared it with 212 patients without protection. This was not a randomized study. The minor stroke rate was 1.5 % with as compared to 5.2 % without protection. The reservations with the balloon occlusion devices is the impact of temporary impairment of cerebral circulation, risk of endothelial damage by balloon inflation. Newer devices like the Angioguard (Cordis) is a filter-type device which permits continued cerebral perfusion and is being evaluated in the SAPPHIRE trial. The benefits will be known only after the results of these trials. At the present moment CS is performed only with neuroprotection in ≥ 80 year old patients as it is postulated to be associated with greater benefits.

Randomized Trials of CS Versus CEA

The largest randomized trial comparing these techniques has been the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [37]. This trial enrolled symptomatic patients with ≥ 70 % stenosis. Both groups received identical medical treatment and were followed up for 3 years. In this study 25 % of patients with carotid angioplasty received additional stents. Both the groups had almost identical major stroke and death rates as well as identical minor and major stroke rates (Figure 5). The patients undergoing angioplasty demonstrated significant lower rates of wound hematomas (1.2 % vs 6.7 %, $p < 0.05$) and no cranial nerve palsies were observed (0 % vs 8.7 %, $p < 0.05$).

Ongoing Randomized Trials

The Carotid Revascularization Endarterectomy v/s Stent Trial (CREST) [38] will randomize low surgical risk patients to stenting or surgery. Approximately 2500 patients will be randomized. Acculink Nitinol

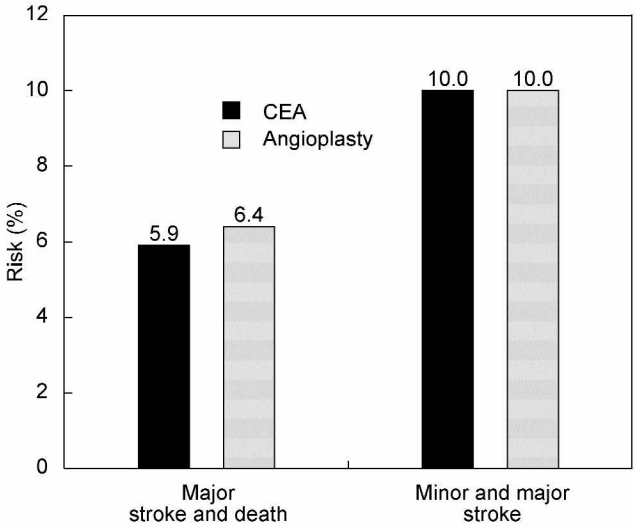

Figure 5. Data of death, minor and major stroke rates derived from the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).

stents (Guidant) will be employed. Primary endpoints will be one) 30 day composite rate of death, stroke or myocardial infarction two ipsilateral stroke after 30 days. Secondary endpoints will be 30 day morbidity and mortality, long term morbidity and mortality, restenosis rates, and cost effectiveness.

The SAPPHIRE (Study of Angioplasty with Protection in Patients at High-Risk for Endarterectomy) trial will randomize 720 high surgical risk patients (unstable angina, heart failure, cervical radiation therapy or radical neck dissection, need for CABG, contralateral occlusion) to CEA or CS. Angioguard (Cordis) will be the protection device and Smart Nitinol stents (Cordis) will be used. The primary endpoints will be as for the CREST study. Secondary endpoints will be 1 year ipsilateral stroke and death rate.

Predictors of High Risk for Stenting

There are various anatomic and clinical factors that constitute a high risk for carotid intervention and they should be specifically looked for. Anatomic predictors for high risk include tortuous course of the vessel and also of the aortic arch, presence of calcification, coexistent common carotid lesion, angiographic thrombus, occlusion and kinking of the vessel [39-41].

Clinical predictors of high risk include age ≥ 80 years, large deficit due to a previous stroke, cerebral atrophy, unstable neurologic symptoms and presence of peripheral vascular disease [39,40].

Conclusion

Carotid atherosclerotic disease forms an important cause of stroke which is the leading cause of serious morbidity amongst patients. In symptomatic patients medical therapy has been demonstrated to be inferior to surgical CEA. In asymptomatic patients no clear cut benefit is observed. CEA can be recommended in asymptomatic patients only if it can be performed with low complication rates.

CS is an investigational tool at the moment and although several series have shown beneficial immediate and intermediate results, only one long term result [19] is available which is comparable with CEA, but even in this study the results with asymptomatic patients were associated with higher than recommended complication rates. Results of CS in high risk groups and other NASCET ineligible patients have been very encouraging and are associated with acceptable periprocedural event rates. With the advent of cerebral protection CS may become safer and may result in better clinical outcomes. New randomized trial results are not yet available comparing CEA and CS with or without cerebral protection, To date CS can be recommended only in high risk surgical patients, patients turned down by the surgeon, previous neck surgery or neck irradiation and intervention for surgically inaccessible territories.

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