

## Carotid Endarterectomy is the Best Choice for Patients with Carotid Disease

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### Introduction

The good long term outcome of carotid endarterectomy (CE) was recognized for the first time after publication of the seminal study by Prof. DeBakey in 1975<sup>1</sup>. Since then, CE has been one of the most analyzed and investigated vascular surgical procedures. In the beginning of the 1990s, the results and surgical indications for carotid disease were well established for symptomatic patients with the publication of NASCET (*North American Symptomatic Carotid Endarterectomy Trial*) and ECST (*European Carotid Surgery Trial*) in 1991 and for asymptomatic patients, with ACAS (*Executive Committee for the Asymptomatic Carotid Atherosclerosis Study*) in 1994<sup>2-4</sup>.

With the advent of the endovascular technique, carotid stent-angioplasty (CSA) has been proposed to treat patients with carotid disease, with some supposed advantages, such as preventing cervical incision and general anesthesia, reduction in length of stay and occurrence of injury to cranial nerves. Some evidence relating to the risk/benefit of CSA has been reported in non-randomized studies. In a comprehensive review of more than 5,000 endovascular procedures published by Coward et al<sup>5</sup> in 2005, the authors identified an average rate of cerebrovascular accidents (CVA) and death of 4.7%, varying from 2 to 9%. These results, in addition to the motivation of the industry, have encouraged more and more the ample use of CSA in patients with carotid disease; however, it's dangerous to consider only these results, as there are several types of bias in some studies. Before the CSA becomes widely used, randomized studies should assess the efficacy of this type of treatment as compared with the conventional treatment (ECA). In this scenario, ECA champions are again placed in the position of accepting the challenge of maintaining their good results, publicize them and provide clarification to readers as to what is best for the patients. So far there are eight randomized studies comparing CSA and ECA, and five of them were interrupted early in the procedure because of the elevated risk of CSA or due to difficulties in recruiting patients. Therefore, there is no evidence of the benefit of CSA over ECA for the treatment of carotid disease so far,

### Key words

Endarterectomy, carotid; carotid artery injury.

this being the reason why an appropriate technical analysis is required which is based on evidence and on the history of the procedure. This paper aims to analyze the results of the randomized studies comparing CSA and ECA, and highlights some specificities of each study (Table 1).

### Comparative studies between CSA and ECA

The LEICESTER study, published in 1998, carried out in England, assessed symptomatic patients with stenosis above 70%<sup>6</sup>. It was interrupted early in the procedure after 23 patients had been randomized. Only 17 patients were treated and 10 underwent ECA and 7 underwent CSA. There was no death or cerebrovascular accident (CVA) in the group of patients treated with ECA; however, 5 patients of the CSA group (45.5%) had CVA in the immediate perioperative period, this being the reason why the study was suspended<sup>6</sup>. In this study, the degree of experience of the person who performed the procedure and the age of patients were not reported, and therefore conditions are lacking which would allow us to draw definitive conclusions. This was a historical study, but it served as a warning to the Department where the procedures were performed as to the poor outcomes of the endovascular technique.

The WALLSTENT, a North American study sponsored by the industry, in which 219 patients were randomized, was interrupted for presenting a high risk of CVA and death in the patients treated with the endovascular technique (12.1%) as compared with 4.5% for patients in the ECA group. Their results have never been published, and have only become known through rumors in medical conferences<sup>7</sup>. The veto to the publication of the WALLSTENT study results from the intervention of the sponsors themselves.

CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study) was the first comparative randomized study completed, involving 22 centers in Europe, Australia and Canada, and was published in 2001<sup>8</sup>. In this study, 504 patients were randomized, with 251 patients in the CSA group and 253 patients in the ECA group. The percentage of CVA and death in 30 days was 10.0% in the CSA group and 9.9% in the ECA group. The authors of this study declared that the risks associated with cervical incision and the use of general anesthesia during ECA might be a favorable factor for indicating the endovascular technique. Additionally, they attributed the higher mortality in this study, as compared with ECST and NASCET, to what would be merely an issue of statistical analysis. On the other hand, it's impressive that the authors of CAVATAS<sup>8</sup> have been able, by means of statistical analysis, to obtain similar results for both techniques, with a

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**Table 1 – Comparative and randomized studies of the treatment of carotid injury using the endovascular (CSA) and conventional (ECA) techniques**

Study	Year	Multi-center	Patients (CSA-ECA)	Symptomatic/ asymptom (n)	CVA/death 30 days (CSA-ECA)
Leicester	1998	No	7-10	17-0	45%-0%
Wallstent	2001	Yes	107-112	219-0	12.1%-4.5%
Cavatas	2001	Yes	251-253	488-16	10%-9.9%
Lexington I	2001	No	53-51	104-0	0%-1.9%
Lexington II	2004	No	43-42	0-85	0%-0%
Sapphire	2004	Yes	167-167	96-238	4.8%-5.4%
EVA-3S	2006	Yes	265-262	527-0	9.6%-3.9%
Space	2006	Yes	605-595	1.200-0	7.7%-6.5%

stratagem that does not analyze the real cause of mortality. We should point out the fact that, in the endovascular group, all the 7 deaths were due to CVA, which is obviously linked to the performance of the procedure. However, in the ECA group only one out of 4 deaths was caused by a CVA. The other three deaths were determined by: pulmonary embolism, rupture of abdominal aortic aneurysm (AAA) and acute respiratory failure secondary to a large cervical hematoma. Accepting this last cause means accepting a type of “undertreatment”, as the mere opening of the incision at the bedside could probably have prevented the death of the patient with cervical hematoma. The important thing is to note that this paper was published in the Lancet in 2001, with a foreword by professors Spence and Eliasziw, who highlighted the causes of the deaths occurred, and the insufficient results for both groups (surgery and endovascular procedure) of the CAVATAS study, pointing out the great number of patients who would need to be treated (NBT) with ECA (21) and with CSA (24) to prevent a CVA within 3 years as compared with an NBT of 6 obtained in the NASCET study<sup>9</sup>. These authors concluded furthermore that “at present, carotid angioplasty should clearly not be done routinely for patients with severe symptomatic stenosis, and it definitely should not be done for patients with moderate symptomatic or any degree of symptomless stenosis”. Recently, results relative to carotid restenosis in patients treated in the CAVATAS study were published in Stroke. Significant restenosis ( $\geq 70\%$ ) was significantly more common in the endovascular group (18.5%) than in the surgical group (5.2%)<sup>10</sup>.

The LEXINGTON I and II studies<sup>11,12</sup>, for symptomatic and asymptomatic patients, respectively, were published in 2001 and 2004. No adverse events (CVA or death) occurred in the 85 asymptomatic patients randomized in LEXINGTON II, whereas the CVA/death rates in the 104 symptomatic patients was equal to zero in the CSA group and 1.9% in the ECA group, with no statistically significant difference.

In 2004, the SAPPHERE study (*Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy*) was published. This study was also sponsored by the industry with the purpose of demonstrating that CSA was not inferior to ECA, with the use of a protective filter in patients who were considered of “high risk” for the surgery<sup>13</sup>. With the

objective of having the device approved by the FDA (*Food and Drug Administration*) for commercial purposes, the study was widely publicized to cardiologists in congresses, and its publication was delayed for approximately two years. It also adopted the non-inferiority principle to compare the results with the ECA group. This statistical stratagem could facilitate permission for the sale of the devices by the FDA. The problems evidenced in these studies are numerous. These “high risk” patients included almost 70% of the asymptomatic patients. In the ECA group, the CVA/death rate was 6.1%, almost double the rate obtained for the patients of the ACST study (*Asymptomatic Carotid Surgery Trial*), that was 3.1%<sup>14</sup> and for the patients operated under the North American Medicare system (3%)<sup>15</sup>, and in large centers worldwide, where CVA and death rates are in the region of 3%<sup>16-18</sup>, which is not defensible, because the intervention determined more deaths than the natural course of the disease. The conflict of interests also became apparent on the declaration made by all the co-authors of the study. Prof. Peter Bell, from England, emphasizes the characteristics of this study and pointed out that “this trial should be shown to every undergraduate as an example of how not to do a trial”<sup>19</sup>. Following the publication of SAPPHERE, Mozes et al<sup>20</sup>, from the Mayo Clinic, demonstrated CVA and death rates of only 1.7% in “high risk” patients using SAPPHERE criteria. We should not accept that the SAPPHERE study become a valid parameter for selecting the best treatment for patients with carotid stenosis. It is important to highlight that, in the patients of the surgical group, 23.4% were submitted to coronary angioplasty and 30.8% were submitted to myocardial revascularization surgery prior to the ECA, as compared with 34.8% and 43.4%, respectively, for the endovascular group. This type of approach could account for the higher rates of heart events in the ECA group. The heart event analyzed in the study was the perioperative elevation of serum levels of creatine-kinase (MB-fraction); however, long term implications of this “chemical” infarction look uncertain. In the very well structured analysis by Naylor and Golledge, from England, for a procedure with surgical risk of 6% (results demonstrated by the SAPPHERE study), it would be necessary to treat 1000 patients to prevent only 22 CVAs over a period of five years,

which obviously wouldn't justify its indication<sup>21</sup>.

Recently two other comparative studies were published: EVA-3S (*Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis*)<sup>22</sup> and SPACE (*Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy*)<sup>23</sup>, both in 2006. The multi-center study SPACE involved 35 centers in Germany, Austria and Switzerland, with 1,200 randomized patients (symptomatic), and was the largest comparative study made to date. The EVA-3S study, sponsored by the French government randomized 527 symptomatic patients. Both studies used pre-defined non-inferiority margins and the SPACE study failed in proving the non-inferiority of CSA as compared with ECA; that is, if its non-inferiority was not proven, the superiority of ECA is proven. In the SPACE study, the CVA and death rate in the group submitted to ECA was 6.5% (above the rate accepted for this type of patient) and in the CSA group the rate was 7.7%. The EVA-3S study, after being interrupted twice because of the excessive risk in the group of patients treated with the endovascular technique, concluded that, for symptomatic patients with carotid injury equal to or above 60%, the CVA and death rates were lower in the ECA group (3.9%) when compared with the CSA group (9.6%).

A systematic review of the records of the Cochrane Library analyzed the results of randomized and comparative studies published up until October 2004; that is, before the publication of the SPACE and EVA-3S studies<sup>5</sup>. The analysis included 1,269 patients, with CVA and death rates of 8.1% for the CSA group and 6.3% for the group treated with ECA. The authors of this review concluded that *"there is insufficient evidence to support a move away from recommending carotid endarterectomy as the treatment of choice for suitable carotid*

*stenosis"*. We shouldn't forget that one of the authors of that study, Dr. Martin Brown, is one of the organizers of the CAVATAS<sup>8</sup> study, and therefore has a very clear conflict of interest. Even so, these authors stated that *"stenting should only be offered within the ongoing trials of stenting versus surgery"*. After the publication of the SPACE and EVA-3S studies, it is very likely that these considerations should not be changed, because if the data of these two studies are added to the analysis of the Cochrane Library, we obtain CVA and death rates of 8.1% in the CSA group and 5.9% in the ECA group, with a difference in the results (p=0.02) (Table 2).

Despite these results, there is still reluctance and broad discussion about the matter, with some authors challenging this data in view of the use of different devices and different degree of experience of the interventionist doctor that performs the procedure. Since the first reports on CSA, 20 years have elapsed and the argument that better devices are needed to obtain better results is often used. The SPACE study is the eighth comparative randomized study conducted and results in favor of CSA have not been demonstrated yet, and new comparative studies are still underway in the hope of achieving the "expected" results.

## Conclusion

Based on the results of these studies and with the conviction that we can offer the best treatment to patients with carotid disease, we believe that there is no ample indication for CSA for patients with atherosclerotic carotid injury, as some vascular interventionists have been proposing; on the contrary, we believe that such procedure could play a complementary role in few situations, such as a hostile neck due to previous radiation therapy or restenosis due to recurrent atherosclerotic injury, and in case of upper carotid injury. We therefore conclude that ECA is the best alternative to treat patients with atherosclerotic carotid injury.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This study is not associated with any graduation program.

**Table 2 – Results of the comparative studies between CSA and ECA for patients with carotid injury**

Study (Ano)	Patients (CSA-ECA)	CVA-death CAS-ECA)
Cochrane (2005)	632-637	51-40
EVA-3S (2006)	265-262	25-10
Space (2006)	605-595	46-38
TOTAL	1502-1494	122-88
		(8.1% vs. 5.9%) p = 0.02*

\*Chi-square (p<0.05).

## References

- DeBaKey ME. Successful carotid endarterectomy for cerebrovascular insufficiency: nineteen-year follow-up. JAMA. 1975; 233 (10):1083-5.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. N Engl J Med. 1991; 325: 445-53.
- MRC European Carotid Surgery Trial: interim results of symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Surgery Trialists' Collaborative Group. Lancet. 1991; 337: 1235-41.
- Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995;

- 273 (18): 1421-8.
5. Coward LJ, Featherstone RL, Brown MM. Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomized evidence. *Stroke*. 2005; 36: 905-11.
  6. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg*. 1998; 28: 326-34.
  7. Alberts MJ. Results of a multicenter prospective randomized trial of carotid artery stenting versus carotid endarterectomy. [oral abstract]. *Stroke*. 2001; 32: 325-d.
  8. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Lancet*. 2001; 357: 1729-37.
  9. Spence D, Eliasziw M. Endarterectomy or angioplasty for treatment of carotid stenosis? *Lancet*. 2001; 357: 1722-3.
  10. McCabe DJH, Pereira AC, Clifton A, Bland JM, Brown MM, on behalf of the CAVATAS Investigators. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Stroke*. 2005; 36: 281-6.
  11. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol*. 2001; 38: 1589-95.
  12. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: randomized trial in a community hospital. *Neurosurgery*. 2004; 54: 318-25.
  13. Yadav JS, Wholey MH, Kuntz RE, SAPHIRE investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004; 351: 1493-501.
  14. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurologic symptoms: randomised controlled trial. *Lancet*. 2004; 363: 1491-502.
  15. Hsia DC, Moscoe LM, Krushat WM. Epidemiology of carotid endarterectomy among medicare beneficiaries: 1985-1996 Update. *Stroke*; 29 (2): 346-50.
  16. Riles TS. Surgical management of internal carotid artery stenosis: preventing complications. *Can J Surg*. 1994; 37 (2):124-7.
  17. Sundt TM Jr, Ebersoldt MJ, Sharbrough FW, Piepgras DG, Marsh WR, Messick JM Jr. The risk-benefit ratio of intraoperative shunting during carotid endarterectomy: relevancy to operative and postoperative results and complications. *Ann Surg*. 1986; 203 (2):196-204.
  18. Hertzner NR, O'Hara PJ, Mascha EJ, Krajewski LP, Sullivan TM, Beven EG. Early outcome assessment for 2228 consecutive carotid endarterectomy procedures: the Cleveland Clinic experience from 1989 to 1995. *J Vasc Surg*. 1997; 26 (1): 1-10.
  19. Bell PR. Limitations to the value of the SAPHIRE trial. *Acta Chir Belg*. 2006; 106: 141-3.
  20. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC. Carotid endarterectomy in SAPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg*. 2004; 39: 958-65.
  21. Naylor AR, Golledge J. High risk plaque, high risk patient or high risk procedure? *Eur J Vasc Endovasc Surg*. 2006; 32 (5): 557-60.
  22. Mas JL, Chattelier G, Beyssen B, Branchereau A, Moulin T, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006; 355 (16): 1660-71.
  23. SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G, Hartmann M, et al. 30 days results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006; 368: 1239-47.