

## Carotid angioplasty is an alternative therapeutic option to carotid endarterectomy for a defined group of patients

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Stroke is the third cause of death and the leading cause of disability worldwide. In the United States approximately 795000 cases of stroke are produced annually with a mortality rate of 17%. (1) Atherosclerotic disease of the extracranial internal carotid artery (ICA) is responsible for 20% to 25% of all ischemic strokes, and both medical therapy (MT) and carotid endarterectomy (CE) have been previously used to prevent them.

Medical therapy is currently considered the first choice in the treatment of asymptomatic patients with  $\leq 80\%$  carotid obstruction. Regarding CE, both American and European guidelines recommend its use in symptomatic patients with stenosis between 70 % and 99% (Class I, level of evidence A). Carotid percutaneous transluminal angioplasty (PTA) is the third therapeutic option which started to be used 15 years ago and several randomised studies have attempted to better define its role with respect to MT and CE.

CAVATAS (2) was the first multicentric, randomised study, which included 504 patients with symptomatic carotid artery disease for PTA and CE. There were no significant differences between both treatments in the endpoint of death or stroke at 30 days (10%) and at 3 years (14%). The surgical team had a greater rate of cranial nerve paralysis (CE: 8.7%, PTA: 0%;  $p < 0.0001$ ). No cerebral protection (CP) system was employed and stenting was used only in 26% of the cases.

SAPPHIRE (3) included 334 symptomatic and asymptomatic (70%) patients with high risk surgical criteria. According to protocol, CP was used in all PTA patients. The primary endpoint of death, stroke or acute myocardial infarction (AMI) at 30 days plus ipsilateral stroke or death due to neurological causes between 31 days and 1 year occurred in 12.2% of the PTA group patients and 20.1% of the CE group patients ( $p = 0.004$  for noninferiority and  $p = 0.05$  for superiority). The rates of stroke and death at 30 days were similar in both groups and in the CE group there was a greater proportion of infarction (6.6% vs. 1.9%;  $p = 0.04$ ) and cranial nerve paralysis (5.3% vs. 0%;  $p = 0.003$ ).

SPACE (4) and EVA-3S (5) published in 2006, were multicentric, randomised and noninferiority studies.

The SPACE study enrolled 1200 symptomatic patients and CP was used in 27% of the PTA group patients. The primary endpoint of ipsilateral stroke or death from any cause at 30 days, occurred in 41 patients of the PTA group (6.84%) and in 37 patients in the CE group (6.34%) (absolute difference 0.51%;  $p = 0.09$  for noninferiority). No significant differences were found for death, global stroke, non-fatal ipsilateral ischemic stroke, disabling stroke and non-fatal ipsilateral intracerebral bleeding. Even though the SPACE study could not prove noninferiority of PTA compared with CE, the difference between both treatments was of only four events in almost 600 patients treated per group.

The EVA-3S study also included symptomatic patients and CP was used in 92% of the PTA group patients. It was prematurely discontinued for safety reasons after including 527 patients. The primary endpoint of stroke, global death or death at 30 days was reached in 9.6% of the PTA group and in 3.9% of the CE group [RR 2.5 (95% CI, 1.2-5.1);  $p = 0.01$ ]. No significant differences were found for death, major, minor and non-disabling stroke or death (PTA 3.4%, CE 1.5%) and there was a greater proportion of cranial nerve paralysis with CE (7.7% vs. 0.1%;  $p < 0.001$ ). The main criticism to this study was the scarce experience of the participating interventional physicians. Since PTA is a highly operator-dependent procedure, lack of adequate training may have negatively conditioned the PTA group study results. Comparing SPACE and EVA-3S studies, it can be seen that that the rate of CP in the former was only 27%, while in the latter it reached 92% of the cases, and even so, stroke or death rates at 30 days were 7.68% in the SPACE study and 9.6% in the EVA-3S study.

Finally, the larger, randomized, multicentric studies [ICSS (6) and CREST, (7)] were published in 2010.

The ICSS study enrolled 1713 patients with symptomatic carotid stenosis and CP was used in 72% of the patients in the PTA group. The 120-day safety analysis evaluating death rate, stroke or AMI, favoured CE (CE: 5.2%, PTA: 8.5%;  $p = 0.006$ ). However, no significant differences were obtained in the rates of death or disabling stroke. The effect in the 120-day safety analysis with a 3% risk increase in

the PTA group was due to a greater number of non-disabling strokes in this group. There was a greater rate of cranial nerve paralysis in the CE group (CE: 5.28%, PTA: 0.12%;  $p < 0.0001$ ) and few cases of AMI in both groups (CE: 3, PTA: 4). The sub-group analysis suggests that patients  $< 70$  years and women have a similar risk in both groups.

The CREST study included 2502 patients with severe carotid stenosis, 47% of which were asymptomatic. CP was used in 96.1% of the patients in the PTA group and no significant difference was detected in the primary endpoint (global stroke, AMI or death in the periprocedural period, or ipsilateral stroke within 4 years since randomization): PTA: 7.2%, CE: 6.8%;  $p = 0.51$ . Global periprocedural stroke was greater in the PTA group (4.1% vs. 2.3%;  $p = 0.01$ ), essentially at the expense of a greater rate of minor ipsilateral strokes, while the incidence of AMI was lower in the PTA group (1.1% vs. 2.3%;  $p = 0.03$ ). Similarly to the ICSS and SPACE studies, PTA involved increased risk in elderly patients. The CREST study showed the best periprocedural outcome results, distant from those of randomized studies published up to the present, both for PTA as CE (Table 1).

This issue of the *Revista Argentina de Cardiología* publishes the work of Dr. Bettinotti and collaborators. (8). It is a descriptive, observational and prospective carotid PTA study, conducted at two centers in the Ciudad Autónoma de Buenos Aires and one center in the suburbs of Buenos Aires, incorporating symptomatic patients with  $\geq 50\%$  stenosis and asymptomatic patients with  $\geq 60\%$  stenosis, all with at least one high risk surgical criterion and with the distinctive feature that all the procedures were performed by the same operator. This is not a lesser fact, since as previously explained in the EVA-3S study analysis, angiographic and clinical results are directly associated with the operator's experience. In the work of Bettinotti and collaborators, the analysis was performed dividing the sample into two periods, the first with 54 patients treated between 1998 and 2003 and the second with 171 patients treated between 2004 and 2010. The rate of clinical success was greater in the second period (96.1% vs. 87%;  $p = 0.016$ ) and this could be due to a number of reasons: 1) the patients were different: 72% were symptomatic in the first period and only 17.5% in the second, 2) the increased operator experience and the greater number of procedures performed in the second period: 171 PTAs (24/year) between 2004 and 2010 and 54 PTAs (9/year) between 1998 and 2003, 3) the improved materials and systematic use of CP. In the overall population analysis ( $n = 255$ ), the study showed values in accordance with international guidelines and with the previously analyzed multicentric studies.

To conclude, three comments: 1) The value of this study lies in the knowledge it provides on PTA

**Table 1.** Stroke or death in symptomatic patients. Periprocedural and late outcome

	CREST		SPACE		ICSS		EVA-3S	
	PTA	CE	PTA	CE	PTA	CE	PTA	CE
Stroke or death in symptomatic patients (30 days), %	6,0	3,2	6,0	3,2	6,0	3,2	6,0	3,2
Stroke or death in symptomatic patients (late follow-up: > 30 days up to 4 years), %	2,0	2,4	2,0	2,4	2,0	2,4	2,0	2,4

results in national centers, in accordance with the requirements of American and European guidelines ( $< 6\%$  death or stroke in symptomatic patients). 2) PTA must reduce periprocedural events, specially non-disabling stroke. At present, its place is reserved for symptomatic patients, with severe carotid stenosis and high surgical risk. 3) Independently of guidelines and multicentric studies, we should reconsider indications for revascularization in patients with asymptomatic carotid stenosis, given the low rate of events with current medical treatment.

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