

# Proximal protection with the Gore PAES can reduce DWI lesion size in high-grade stenosis during carotid stenting

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## KEYWORDS

- carotid artery stenting
- carotid stenosis
- cerebral protection
- diffusion-weighted imaging

## Abstract

**Aims:** The aim was to determine the incidence of new ischaemic lesions on diffusion-weighted MR imaging (DWI) in a non-randomised cohort of patients after protected and unprotected carotid artery stent placement using the Parodi Anti-Emboli System (PAES).

**Methods and results:** A retrospective review was conducted on 269 patients who received DWI prior to, and 24-72 hours after, stent placement. All patients were enrolled in one centre. Forty patients stented with the PAES device were matched with 229 patients stented without protection (control group). New diffusion restriction on DWI was detected in 25.8% (PAES) versus 32.3% (control group);  $p=0.64$ . On average there were 0.7 lesions (PAES) versus 0.8 lesions (control group) per patient. The area of lesions was 1.7 (PAES) versus 5.6 mm<sup>2</sup>. In a subanalysis of patients (32 PAES, 148 non-protected) with >80% stenosis, the area of restricted diffusion was less when proximal protection was used ( $p<0.05$ ). The number and area of DWI lesions did not differ on the contralateral, non-stented side. When the PAES system was used, patients were more likely not to have any lesion at all ( $p=0.028$ ).

**Conclusions:** In high-grade stenosis, the use of the Gore PAES device significantly reduced the area of new DWI lesions and patients were more likely not to have any new DWI lesion at all.

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## Introduction

Cerebral protection devices were developed to reduce the risk of stroke caused by thromboembolic events during carotid artery stenting. The application of protection devices has been demonstrated to be feasible but there is, as yet, no level 1 evidence of benefit<sup>1-3</sup>.

Currently, three types of temporary cerebral protection are being used. These are devices with distal balloon occlusion or filtration baskets, as well as proximal occlusion devices with flow arrest or flow reversal in the internal carotid artery (ICA). However, in the large investigations in which carotid artery stenting (CAS) was compared with carotid endarterectomy (CEA)<sup>4,5</sup> only distal protection devices were used.

The current study was undertaken to determine the incidence of new ischaemic lesions detected on diffusion-weighted MR imaging (DWI) in a non-randomised cohort of patients after protected and unprotected carotid artery stent placement using a proximal protection device, namely the Parodi Anti-Emboli System (PAES) (WL Gore & Associates Inc., Flagstaff, AZ, USA). Diffusion-weighted imaging (DWI) was used as it has the ability to visualise changes in diffusion within minutes after the onset of ischaemia, allowing it to become a powerful tool in the evaluation of patients with stroke syndrome<sup>6,7</sup>. DWI has been suggested as a surrogate outcome measure for treatment safety in future pilot studies of carotid interventions<sup>8</sup>.

## Methods

Over a six-year period from 2000 to 2006, a retrospective review was conducted in our centre on 269 patients who received DWI imaging prior to, and 24-72 hours after, stent placement. Data were collected as part of an audit. All patients agreed that their data could be used for research purposes.

Patients with both symptomatic and asymptomatic stenosis were included. Symptomatic patients were defined as those with transient ischaemic attacks (TIA), or minor or major stroke in the territory of the stent-treated side within the previous four weeks. All patients were surveyed on a dedicated stroke unit after the procedure, and neurological examination was conducted by an experienced neurologist before and after the intervention and on the day of discharge. All neurological changes were recorded.

The following stents were used: WALLSTENT® (Boston Scientific, Natick, MA, USA); S.M.A.R.T.® nitinol stent (Cordis Corporation, Johnson & Johnson, Warren, NJ, USA) or Cordis PRECISE® nitinol stent system (Cordis Corporation); and Zilver vascular stent (William Cook Europe, Bjaeverskov, Denmark).

All patients received adjunctive dual antiplatelet therapy with ASA and clopidogrel. Interventionalists had a minimum experience of 25 CAS procedures. Forty patients were stented using the Gore Parodi Anti-Emboli System (PAES). Data from these patients were compared to data from 229 patients who were stented without a protection device. Patients where distal protection devices were used were excluded.

PAES was only used in patients who had a good circle of Willis with no haemodynamically relevant stenosis on the contralateral side. PAES was used at the operator's discretion and discussed with

the patient. It was not used in cases of estimated high-risk carotid disease, such as floating thrombus or ulcerated plaque.

All patients were evaluated with cerebral DW MRI prior to and after stent placement the day before, and up to 72 hours after CAS. Whole-brain diffusion-weighted images were acquired with an echo-planar sequence. An isotropic sequence was used (repetition time: 4,000 m/s; echo time: 133 m/s; field of view: 210 mm; matrix: 128×128; and number of excitations: 4), with b values of 0 and 972 s/mm<sup>2</sup>. All new hyperintensities on the brain scans were noted and categorised according to size, frequency and location. Lesions were counted and then categorised by size in mm<sup>2</sup>. This was done for the vessel-dependent (stented side) and vessel-independent (contralateral) areas.

Comparison was made between preprocedural and post-procedural diffusion-weighted imaging. All new lesions on DWI which occurred after CAS were counted, and the number and area (mm<sup>2</sup>) of lesions were measured.

Statistical analysis was done using Statistical Product and Service Solutions (SPSS) (SPSS Inc., Chicago, IL, USA). Non-parametrical tests (chi-square test, Mann-Whitney test) were used. A significance was established at p<0.005 (Table 1).

**Table 1. Overview of both groups.**

	PAES group	Non-protected group
Mean age	64.1±7.5 (46-81 yr) median: 68 IQR: 11.5	67.9±8.3 (43-85 yr) median: 68 IQR: 11
Female	7 (17.5%)	57 (24.9%)
Male	33 (82.5%)	172 (75.1%)
Stented stenosis	88.8%±9.8 median: 95 IQR: 7.5	87%±10.1 median: 90 IQR: 15
Asymptomatic	12 (30%)	69 (30.1%)
Symptomatic	28 (70%)	160 (69.9%)
Barthel index before stent	96.4±5 median: 100 IQR: 5	91.2±20.1 median: 100 IQR: 5
mRS before stent	1.2±0.8 median: 1 IQR: 1	1.3±1.2 median: 1 IQR: 2

IQR: interquartile range; mRS: modified Rankin Scale

## Results

Patients were asymptomatic in 81 cases and symptomatic in 188 cases. The age range of the patients was 43-85 years, with a mean of 67.3±8.3. We had 64 female and 205 male patients (Table 1). The mean degree of stenosis (according to the North American Symptomatic Carotid Endarterectomy Trial) on the treated side was 87.3%±10 (Table 2).

There were no discernible differences between the two groups in terms of degree or appearance of stenosis, patient age, gender, risk factors such as hypertension, smoker, former smoker, diabetes, hyperlipidaemia, stent type used and symptomatic and asymptomatic patients (p>0.05).

**Table 2. Overview of the different degrees of stenosis.**

Degree of stenosis	PAES	Non-protected group
<70%	5 (12.5%)	21 (9.2%)
71-80%	3 (7.5%)	60 (26.2%)
>80%	32 (80%)	148 (64.6%)

Two patients did not tolerate temporary occlusion of the common carotid artery (CCA). These patients were therefore stented without protection and were excluded from the study. In both of these cases, absence of new lesions was detected at post-interventional MRI.

The number of new DWI lesions that occurred on the stented side was  $0.81 \pm 1.8$ , and the mean area ( $\text{mm}^2$ ) of fresh DWI lesions on the stented side was  $5.0 \pm 14.3 \text{ mm}^2$ .

There was no significant difference concerning clinical outcome or fresh DWI lesions when comparing the two groups. The Barthel index score before stent placement was  $91.6 \pm 19.3$ , and the Barthel index score after stent placement was  $92.5 \pm 18.3$ .

After the stent procedure 74.2% of patients in the PAES group had no new diffusion restriction on DWI. In the non-protected group only 67.8% showed absence of new lesions. However, this was not statistically significant.

The mean number of new DWI lesions was 0.7 in the PAES group vs. 0.8 in the non-protected group. Although the area of lesions was  $1.7 \text{ mm}^2$  (PAES group) versus  $5.6 \text{ mm}^2$  (non-protected group) on the stented side, this was not significant ( $p=0.064$ ; Mann-Whitney U test) (Table 3, Table 4).

**Table 3. Summary of the main findings.**

	PAES group	Non-protected group
Absence of new lesions	28 (74.2%)	155 (67.8%)
Number of new DWI lesions on stented side	$0.7 \pm 2$ median: 1 IQR: 1	$0.8 \pm 1.8$ median: 2 IQR: 2
Area of lesions on stented side	$1.7 \pm 4 \text{ mm}^2$ median: 3 IQR: 9	$5.6 \pm 15.3 \text{ mm}^2$ median: 9 IQR: 25
Number of lesions on contralateral side	0.18 median: 0 IQR: 0	0.55 median: 0 IQR: 0
Area of lesions on contralateral side	0.18 median: 0 IQR: 0	2.05 median: 0 IQR: 0
Fluoroscopy time	$18.2 \pm 9.6$ median: 19.4 IQR: 10.55	$16.1 \pm 8.9$ median: 13.05 IQR: 8.64
Barthel index after stent	$96.4 \pm 5$ median: 100 IQR: 5	$92.1 \pm 19$ median: 100 IQR: 5
mRS after stent	$1.2 \pm 0.8$ median: 1 IQR: 1	$1.2 \pm 1.1$ median: 1 IQR: 2
TIA	4 (10%)	4 (1.7%)
Stroke	0	1 (0.6%)
Death	0	0

IQR: interquartile range; mRS: modified Rankin Scale

**Table 4. Summary of results of subgroup with stenosis >80%.**

	PAES group	Non-protected group
Number of patients	32	148
Age (years)	67 median: 68 SD: 8.24 IQR: 11.5	69 median: 68 SD: 8.3 IQR: 11
Degree of stenosis	89.8 SD: 9.6 median: 95 IQR: 7.5	86.9 SD: 9.44 median: 90 IQR: 15
Area of lesions on stented side	$1.7 \pm 4 \text{ mm}^2$	$5.6 \pm 15.3 \text{ mm}^2$
Fluoroscopy time	19.9 median: 19.4 SD: 11.7 IQR: 10.55	16.6 median: 13 SD: 7.3 IQR: 8.64
Barthel index before stent	96.5 median: 100 SD: 4.7 IQR: 5	90.8 median: 100 SD: 20.9 IQR: 5
Barthel index after stent	96.5 median: 100 SD: 4.7 IQR: 5	90.4 median: 100 SD: 22.3 IQR: 5
mRS before stent	1.2 median: 1 SD: 0.6 IQR: 1	1.2 median: 1 SD: 1.2 IQR: 2
mRS after stent	1.2 median: 1 SD: 0.68 IQR: 1	1.2 median: 1 SD: 1.2 IQR: 2

IQR: interquartile range; mRS: modified Rankin Scale; SD: standard deviation

### Subanalysis of patients with >80% stenosis

We performed a subanalysis in those patients with a >80% stenosis. The group consisted of 32 PAES patients and 148 non-protected patients. We found:

#### 1. Total area of lesions

The overall area in  $\text{mm}^2$  (all new lesions added together) of diffusion restriction was less when proximal protection was used ( $p < 0.034$ ).

#### 2. Patients with new DWI lesions (>80% stenosis)

On the contralateral, non-stented side, the number and the area of fresh DWI lesions did not differ between the two groups.

#### 3. Patients without new DWI lesions (>80% stenosis)

When comparing patients where no fresh DWI lesions occurred after stenting we found that when the PAES system was used patients were more likely not to have any lesion at all ( $p = 0.028$ ).

### Clinical results

There was no difference in clinical outcome after the intervention between the PAES group and the non-protected group. This included technical success rate, Barthel index and mRS score before and after intervention, as well as peri-interventional and post-interventional TIA, minor and major stroke.

## Discussion

The use of distal cerebral protection devices has recently been the subject of debate in which it has been suggested that they may generate more microemboli than are demonstrated in unprotected CAS<sup>7-10</sup>.

The occurrence of DWI lesions in interventional procedures is considered a non-clinical measure of outcome. However, there are data supporting the finding that embolic events can also occur in the early post-procedural phase and that they are related to interactions between the stent frame and the plaque (poor stent scaffolding, plaque prolapse, platelet micro-aggregates, etc.)<sup>11,12</sup>. Some of the DWI spots detected in this study may thus not have been related to the use (or non-use) of a protection device.

A subgroup analysis of the International Carotid Stenting Study (ICSS) found that new DWI lesions occurred significantly less frequently when no distal protection was used (68% vs. 35%), OR 3.28 (1.50-7.20);  $p=0.003$ <sup>8</sup>.

The German Stent-Supported Percutaneous Angioplasty Carotid Artery versus Endarterectomy (SPACE) trial found no significant difference regarding the stroke/death rate in unprotected vs. protected CAS (6.2% vs. 8.3%;  $p=0.40$ )<sup>13</sup>.

Two randomised studies<sup>3,14</sup> evaluated the use of filter protection devices in CAS compared to non-protected stenting regarding the amount of distal cerebral emboli. Both found a non-significant increase in lesions on DWI in the filter-protected group.

In a total of 30 patients, Macdonald et al<sup>3</sup> detected significantly more transcranial Doppler (TCD) signals (426.5 vs. 165.2,  $p=0.01$ ) and emboli (251.3 vs. 92,  $p=0.03$ ) in procedures using filter protection than during interventions without protection. DWI at one to three hours post procedure and 24 hours after stenting showed 29% new lesions in the protected group and 18% (4 of 22) in the unprotected group ( $p=0.38$ ).

The most recent and largest randomised trial, namely the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)<sup>15,16</sup>, evaluated filter-protected CAS with carotid endarterectomy. The CREST investigators included 2,502 symptomatic and asymptomatic patients with carotid artery stenosis with (symptomatic,  $\geq 50\%$  stenosis detected by angiography or  $\geq 70\%$  stenosis detected by ultrasound) or without previous stroke (asymptomatic,  $\geq 60\%$  stenosis detected by angiography or  $\geq 70\%$  stenosis detected by ultrasound;  $n=1,181$ ).

The primary endpoint of the study was defined as the 30-day rate of stroke, myocardial infarction and death combined with the rate of ipsilateral stroke over four years after randomisation. The results revealed no significant difference between the CAS and the CEA groups (7.2% vs. 6.8%;  $p=0.51$ ; 95% CI) at a median follow-up of 2.5 years<sup>17</sup>. The event rate at 30 days was 5.2% in the CAS group versus 4.5% in the surgery group. The risk of stroke and death was slightly higher in CAS than in CEA (4.1% vs. 2.3;  $p=0.01$ , and 0.7% vs. 0.3%;  $p=0.18$ ). It seemed that patients older than 70 years had more benefit from surgery whilst younger patients benefited more from stenting. A disadvantage of the study might be that the combination of asymptomatic patients (with a lower risk for stroke)

and symptomatic patients might reduce periprocedural event rates, and could eventually disguise real differences between CAS and CEA. Long-term follow-up results showed that both approaches had comparable results and are equivalent regarding stroke prevention<sup>17</sup>.

Although distal protection devices might have been able to reduce the incidence of periprocedural complications, we cannot be certain of this. Distal protection devices first have to cross the (usually tight) carotid stenosis, thereby carrying the risk of dislodging debris. Often, predilatation of the stenosis is necessary to pass the filter or balloon device. Therefore, a system specifically protecting cerebral flow during the entire procedure seems an ideal option.

The Gore PAES proximal protection system consists of a balloon guide that is placed proximally to the stenosis, within the common carotid artery. By placing a second balloon within the external carotid artery it provides distal neuroprotection during CAS by means of continuous blood flow reversal, thereby directing emboli away from the brain. The procedure has been described elsewhere<sup>18</sup>, and there is robust evidence regarding the safety and feasibility of the device<sup>19</sup>.

Although the clinical relevance of silent microembolic events has not yet been established, an association with cognitive impairment<sup>20</sup> has been suggested. Purandare et al<sup>21</sup> discussed cerebral emboli as a potential cause of Alzheimer's disease and vascular dementia.

In the ICSS study, the median number of DWI lesions after intervention was three (IQR 1-9)<sup>8</sup>. In our single-centre experience the number of new DWI lesions that occurred on the stented side was  $0.81 \pm 1.8$ .

In the largest series of DWI controlled, unprotected carotid artery stent procedures so far, in 197 patients<sup>7</sup>, new DWI lesions occurred in 29.9% in the stented brain territory.

Although in our patient group we could not establish a significant difference regarding the number of new DWI lesions between the PAES and unprotected group (25.8 vs. 32.3;  $p=0.64$ ), the area of lesions was significantly smaller when a proximal protection device was used ( $p<0.05$ ). Former studies that only considered the number of lesions after CAS would have missed this important fact.

Lesions on diffusion-weighted magnetic resonance imaging are not necessarily associated with immediate neurological sequelae and often remain clinically silent. As expected, our clinical results with and without protection did not differ concerning morbidity and mortality, TIA and prolonged reversible ischaemic neurologic deficit (PRIND). The incidence of clinically symptomatic stroke during carotid artery stenting is so low that several thousand patients would be necessary to demonstrate significant differences between groups. DWI serves as a surrogate marker to analyse the differences between protected and unprotected CAS in this small number of patients.

Our results showed that, when the PAES system was used, patients were more likely not to have any lesion at all ( $p=0.028$ ). This is in accordance with previous results.

In a previously published evaluation of flow reversal in dogs, complete protection against embolic debris could be achieved<sup>22</sup>. Parodi et al<sup>23</sup> also described complete absence of microemboli with

flow reversal, whereas alternative methods were unable to achieve this level of protection. Rabe et al<sup>24</sup> also demonstrated complete absence of new DWI lesions following CAS with flow reversal.

Montorsi et al<sup>25</sup> conducted the first randomised study and compared the rate of cerebral microembolisation during CAS with proximal versus distal cerebral protection. Fifty-three patients were randomised to undergo CAS with proximal protection (Mo.Ma<sup>®</sup> Ultra proximal cerebral protection device; Medtronic/Invatec, Roncadelle, Italy) or distal filter protection (FilterWire EZ<sup>™</sup> Embolic Protection System; Boston Scientific). The authors assessed microembolic signals (MES) using TCD and lesions on diffusion-weighted MRI. In patients with high-risk, lipid-rich plaque, Mo.Ma<sup>®</sup> significantly reduced MES counts during lesion crossing, stent crossing, stent deployment, stent dilatation and in total. No significant difference was found in the number of patients with new post-CAS embolic lesions. Another study (PROFI)<sup>26</sup> compared embolic lesion load as seen on DWI between filter-protected and proximal balloon-protected CAS in a randomised trial. Compared with filter protection, proximal balloon occlusion resulted in a significant reduction in the incidence of new cerebral ischaemic lesions. Also, the number and the volume of new cerebral ischaemic lesions were significantly reduced by proximal balloon occlusion.

A recent European, prospective, multicentre study conducted in 2012 investigated the outcome of patients who underwent CAS for asymptomatic and symptomatic carotid artery stenosis (n=122; 28% symptomatic) using the GORE flow reversal system<sup>27</sup>. The primary and secondary endpoints of this study were stroke/death rate and myocardial infarction or a non-stroke-related neurological event within 30 days post intervention.

In three of the 122 patients the device could not be used, due to vessel tortuosity in one case and intolerance in two cases. No death or MI occurred during the 30-day period. The major adverse events rate at 30 days and the secondary endpoint rate were both 1.6%. A transient ischaemic attack was seen in one patient of each study arm.

Despite these and our positive results, a definitive identification of any substantial differences with the Gore PAES systems in carotid artery stenting will not be possible until a randomised trial has been conducted.

## Conclusion

Use of the Gore PAES device significantly reduced the area of new DWI lesions in patients with high-grade (>80%) stenosis. In addition, when the flow reversal system was used, patients were more likely not to have any DWI lesions at all. To establish the efficacy of proximal protection devices, a randomised comparison of non-protected versus filter-protected carotid artery stenting is warranted.

## Conflict of interest statement

I.Q. Grunwald, W. Reith and P. Papanagiotou have previously received consulting fees, travel expenses, congress support or study honoraria from Boston Scientific, Bard, ev3, Gore, Guidant, and Cordis. The other authors have no conflicts of interest to declare.

## References

1. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32:1769-818.
2. Cremonesi A, Setacci C, Castriota F, Valgimigli M. Carotid stent cell design: lack of benefit or lack of evidence? *Stroke*. 2008;39:e130.
3. Macdonald S, Evans DH, Griffiths PD, McKevitt FM, Venables GS, Cleveland TJ, Gaines PA. Filter-protected versus unprotected carotid artery stenting: a randomised trial. *Cerebrovasc Dis*. 2010;29:282-9.
4. International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985-97.
5. SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W. 30 day 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.
6. Grunwald IQ, Reith W. Non-traumatic neurological emergencies: imaging of cerebral ischemia. *Eur Radiol*. 2002;12:1632-47.
7. Grunwald IQ, Papanagiotou P, Roth C, Fassbender K, Karp K, Krick C, Schieber H, Müller M, Haass A, Reith W. Lesion load in unprotected carotid artery stenting. *Neuroradiology*. 2009;5:313-7.
8. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, Macdonald S, Gaines PA, Waaijer A, Stierli P, Jäger HR, Lyrer PA, Kappelle LJ, Wetzel SG, van der Lugt A, Mali WP, Brown MM, van der Worp HB, Engelter ST; ICSS-MRI study group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol*. 2010;9:353-62.
9. Aronow HD, Yadav JS. Embolic protection for carotid artery stenting--a 'no brainer'. *Acta Chir Belg*. 2004;104:65-70.
10. Eckert B, Zeumer H. Editorial comment--Carotid artery stenting with or without protection devices? Strong opinions, poor evidence! *Stroke*. 2003;34:1941-3.
11. Rapp JH, Wakil L, Sawhney R, Pan XM, Yenari MA, Glastonbury C, Coogan S, Wintermark M. Subclinical embolization

- after carotid artery stenting: new lesions on diffusion-weighted magnetic resonance imaging occur postprocedure. *J Vasc Surg.* 2007;45:867-72.
12. Palombo G, Faraglia V, Stella N, Giugni E, Bozzao A, Taurino M. Late evaluation of silent cerebral ischemia detected by diffusion-weighted MR imaging after filter-protected carotid artery stenting. *AJNR Am J Neuroradiol.* 2008;29:1340-3.
  13. Jansen O, Fiehler J, Hartmann M, Brückmann H. Protection or nonprotection in carotid stent angioplasty: the influence of interventional techniques on outcome data from the SPACE Trial. *Stroke.* 2009;40:841-6.
  14. Barbato JE, Dillavou E, Horowitz MB, Jovin TG, Kanal E, David S, Makaroun MS. A randomized trial of carotid artery stenting with and without cerebral protection. *J Vasc Surg.* 2008;47:760-5.
  15. Lal BK, Brott TG. The Carotid Revascularization Endarterectomy vs. Stenting Trial completes randomisation: lessons learned and anticipated results. *J Vasc Surg.* 2009;50:1224-31.
  16. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med.* 2010;363:11-23.
  17. Meier P. Carotid stenting or surgical carotid endarterectomy to prevent strokes? *Expert Rev Cardiovasc Ther.* 2010;8:1379-81.
  18. Grunwald IQ, Struffert T, Papanagiotou P, Politi M, Krick C, Reith W. Reversal of flow during carotid artery stenting: use of the Parodi antiembolism system. *Neuroradiology.* 2007;49:237-41.
  19. Clair DG, Hopkins LN, Mehta M, Kasirajan K, Schermerhorn M, Schönholz C, Kwolek CJ, Eskandari MK, Powell RJ, Ansel GM; EMPiRE Clinical Study Investigators. Neuroprotection during carotid artery stenting using the GORE flow reversal system: 30-day outcomes in the EMPiRE Clinical Study. *Catheter Cardiovasc Interv.* 2011;77:420-9.
  20. Stump DA, Rogers AT, Hammon JW, Newman SP. Cerebral emboli and cognitive outcome after cardiac surgery. *J Cardiothorac Vasc Anesth.* 1996;10:113-8.
  21. Purandare N, Burns A, Daly KJ, Hardicre J, Morris J, Macfarlane G, McCollum C. Cerebral emboli as a potential cause of Alzheimer's disease and vascular dementia: case-control study. *BMJ.* 2006;332:1119-24.
  22. Ohki T, Parodi J, Veith FJ, Bates M, Bade M, Chang D, Mehta M, Rabin J, Goldstein K, Harvey J, Lipsitz E. Efficacy of a proximal occlusion catheter with reversal of flow in the prevention of embolic events during carotid artery stenting: an experimental analysis. *J Vasc Surg.* 2001;33:504-9.
  23. Parodi JC, La Mura R, Ferreira LM, Mendez MV, Cersósimo H, Schönholz C, Garelli G. Initial evaluation of carotid angioplasty and stenting with three different cerebral protection devices. *J Vasc Surg.* 2000;32:1127-36.
  24. Rabe K, Sugita J, Godel H, Sievert H. Flow-reversal device for cerebral protection during carotid artery stenting--acute and long-term results. *J Interv Cardiol.* 2006;19:55-62.
  25. Montorsi P, Caputi L, Galli S, Ciceri E, Ballerini G, Agrifoglio M, Ravagnani P, Trabattoni D, Pontone G, Fabbicocchi F, Loaldi A, Parati E, Andreini D, Veglia F, Bartorelli AL. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. A randomized trial of proximal versus distal cerebral protection. *J Am Coll Cardiol.* 2011;58:1656-63.
  26. Bijuklic K, Wandler A, Hazizi F, Schofer J. The PROFi study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. *J Am Coll Cardiol.* 2012;59:1383-9.
  27. Nikas D, Reith W, Schmidt A, Duda S, Mathias K, Cremonesi A, Dill H, Formgren J, Pieniazek P, Musialek P, Hornung M, Sievert H, Reimers B. Prospective, multicenter European study of the GORE flow reversal system for providing neuroprotection during carotid artery stenting. *Catheter Cardiovasc Interv.* 2012;80:1060-8.