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# New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS)

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## Summary

**Background** The International Carotid Stenting Study (ICSS) of stenting and endarterectomy for symptomatic carotid stenosis found a higher incidence of stroke within 30 days of stenting compared with endarterectomy. We aimed to compare the rate of ischaemic brain injury detectable on MRI between the two groups.

**Methods** Patients with recently symptomatic carotid artery stenosis enrolled in ICSS were randomly assigned in a 1:1 ratio to receive carotid artery stenting or endarterectomy. Of 50 centres in ICSS, seven took part in the MRI substudy. The protocol specified that MRI was done 1–7 days before treatment, 1–3 days after treatment (post-treatment scan), and 27–33 days after treatment. Scans were analysed by two or three investigators who were masked to treatment. The primary endpoint was the presence of at least one new ischaemic brain lesion on diffusion-weighted imaging (DWI) on the post-treatment scan. Analysis was per protocol. This is a substudy of a registered trial, ISRCTN 25337470.

**Findings** 231 patients (124 in the stenting group and 107 in the endarterectomy group) had MRI before and after treatment. 62 (50%) of 124 patients in the stenting group and 18 (17%) of 107 patients in the endarterectomy group had at least one new DWI lesion detected on post-treatment scans done a median of 1 day after treatment (adjusted odds ratio [OR] 5·21, 95% CI 2·78–9·79;  $p < 0\cdot0001$ ). At 1 month, there were changes on fluid-attenuated inversion recovery sequences in 28 (33%) of 86 patients in the stenting group and six (8%) of 75 in the endarterectomy group (adjusted OR 5·93, 95% CI 2·25–15·62;  $p = 0\cdot0003$ ). In patients treated at a centre with a policy of using cerebral protection devices, 37 (73%) of 51 in the stenting group and eight (17%) of 46 in the endarterectomy group had at least one new DWI lesion on post-treatment scans (adjusted OR 12·20, 95% CI 4·53–32·84), whereas in those treated at a centre with a policy of unprotected stenting, 25 (34%) of 73 patients in the stenting group and ten (16%) of 61 in the endarterectomy group had new lesions on DWI (adjusted OR 2·70, 1·16–6·24; interaction  $p = 0\cdot019$ ).

**Interpretation** About three times more patients in the stenting group than in the endarterectomy group had new ischaemic lesions on DWI on post-treatment scans. The difference in clinical stroke risk in ICSS is therefore unlikely to have been caused by ascertainment bias. Protection devices did not seem to be effective in preventing cerebral ischaemia during stenting. DWI might serve as a surrogate outcome measure in future trials of carotid interventions.

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## Introduction

Percutaneous stenting is an alternative to endarterectomy for the treatment of internal carotid artery stenosis. The International Carotid Stenting Study (ICSS) recently completed random assignment of patients with symptomatic carotid stenosis to stenting or endarterectomy, and the interim results have been published.<sup>1</sup> The risk of procedural stroke, myocardial infarction, or death within the first 120 days after randomisation was significantly higher with stenting than with surgery (intention-to-treat analysis 8·5% vs 5·2%,  $p = 0\cdot006$ ), as was the risk within 30 days of treatment in the per-protocol analysis (7·4% vs 4·0%,  $p = 0\cdot003$ ). This difference was mainly caused by a higher number of non-disabling strokes in the stenting group (36 vs 11 within 30 days of treatment); the rate of disabling stroke or death did not differ significantly (26 vs 18).

Clinical follow-up of patients in ICSS was not masked to treatment allocation; therefore, there was the possibility of potential bias in ascertainment of non-disabling strokes. We used multimodal MRI as an additional outcome measure of procedural cerebral ischaemia that could be analysed without knowledge of treatment allocation. We aimed to compare the risk of procedural ischaemia and persistent infarction on MRI between patients randomly allocated to receive stenting or endarterectomy and to investigate the effect of cerebral protection devices on the risk of ischaemia associated with stenting.

## Methods

### Patients

The ICSS-MRI study is a prospective multicentre substudy of ICSS. Details of centre and investigator requirements,

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eligibility criteria, method of randomisation, nature of interventions, follow-up requirements, and the definition and assessment of outcome events have been described.<sup>1-3</sup>

Briefly, patients with recently symptomatic, at least moderate carotid artery stenosis ( $\geq 50\%$  measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria<sup>4</sup>) were randomly allocated to treatment with stenting or endarterectomy.

ICSS centres with sufficient neuroimaging facilities were invited to take part in the ICSS-MRI study. All patients randomly assigned to treatment in ICSS were eligible to participate if they had no contraindications to MRI.

The study was approved by local ethics committees for non-UK centres and by the Northwest Multicentre Research Ethics Committee in the UK. Patients provided written informed consent to undergo MRI when the scans were not part of clinical routine.

### Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to receive stenting or endarterectomy by use of a computerised service provided by the Oxford Clinical Trials Service Unit staff who were not involved in other parts of the trial. The allocated treatment was communicated to investigators or one of their research team by telephone after they provided baseline data of the patient. Randomisation was stratified by centre with minimisation for sex, age, contralateral occlusion, and side of the randomised artery. Investigators were masked to the randomisation program. Patients and individuals who delivered the interventions were not masked to treatment assignment. Patients were followed up, and clinical outcome events reported to the central trial office, by independent clinicians who were not masked to treatment assignment but who were not directly involved in delivering the randomly allocated treatment. Adjudication of outcomes was blinded. Apart from the trial statistician and the data monitoring committee, all ICSS investigators, including the chief investigator,

remained masked to the results of the trial, including the ICSS-MRI study, until after recruitment was completed.

### Procedures

Stents and other devices used for carotid stenting were chosen by the treating physician but had to have a CE mark. The protocol recommended that a cerebral protection device should be used whenever the local investigator thought that one could be used safely, but this was not mandatory. A combination of aspirin and clopidogrel to cover stenting procedures was recommended. Use of heparin during the procedure was mandatory. Surgeons could use standard or eversion endarterectomy. The use of local or general anaesthesia, shunts, and patches was at the discretion of the surgeon.

The protocol initially specified MRI scans to take place 1–3 days before treatment (pretreatment scan), 1–3 days after treatment (post-treatment scan), and 27–33 days after treatment (1-month follow-up scan). During the study, the window for the pretreatment scan was extended to 7 days before treatment to allow for more flexibility. Diffusion-weighted imaging (DWI) sequences were used at each scan to detect acute ischaemic brain lesions. Fluid-attenuated inversion recovery (FLAIR) sequences were used at pretreatment scans to measure cerebral white matter changes and at 1-month follow-up scans to investigate whether acute ischaemic brain lesions led to persistent tissue changes. Centres were allowed to use scanners with field strengths of 1.5 Tesla or 3 Tesla, as long as the same scanner and the same imaging parameters were used in both treatment groups (table 1).

A neurologist and a neuroradiologist, both masked to treatment, analysed all scans. Disagreement was resolved by consensus or, if no consensus could be reached, a third reviewer had the final decision. On each scan, the number, vascular territory according to previously published templates,<sup>5</sup> and volume of hyperintense lesions on DWI, signifying acute cerebral ischaemia, were measured. Volumes of separate lesions were calculated by measuring lesion diameters in three axes, converted to mL.<sup>6</sup> Lesions were considered separate if there was no continuity between them on the same slice as well as on adjacent slices. Baseline white-matter changes were semiquantitatively assessed on FLAIR sequences of the pretreatment scan by use of the sum of the age-related white matter changes (ARWMC) score.<sup>7</sup> The sites of hyperintense lesions on post-treatment DWI sequences were investigated for corresponding hyperintense signal on FLAIR sequences at 1-month follow-up, signifying persistent infarction.

The primary imaging outcome was the presence of any new hyperintense DWI lesion on the post-treatment scan that was not present on the pretreatment scan. Secondary imaging outcome measures were hyperintensity on FLAIR images at 1-month follow-up at the site of at least one post-treatment DWI lesion that was not present on the pretreatment scan; and the presence of any

	Tesla	Slice thickness (mm)	Gap thickness (mm)	Matrix	Field of view (mm)	Echo time (ms)	b* (s/mm <sup>2</sup> )
Amsterdam	3	3	0	256×256	230	94	1000
Basel	1.5	5	2	128×128	230	105	1000
London	1.5	5	1.5	256×256	230	96	1000
Newcastle	3	4	1	256×256	230	70	2500
Rotterdam	1.5	5	0	256×256	240	85	1000
	3	5	0	256×256	250	65	1000
Sheffield	1.5	5	1	130×130	240	102	1000
Utrecht	1.5	5	0	128×128	230	79	1000
	3	5	0	256×256	230	71	2500

\*The b value is a function of diffusion gradient strength, the duration of the gradient, and the interval between diffusion gradients. The higher the b value, the stronger the diffusion weighting, with a resulting increase in contrast between lesions and normal brain tissue.

Table 1: DWI parameters used at participating centres

hyperintense DWI lesion at 1-month follow-up that was not present on the post-treatment scan.

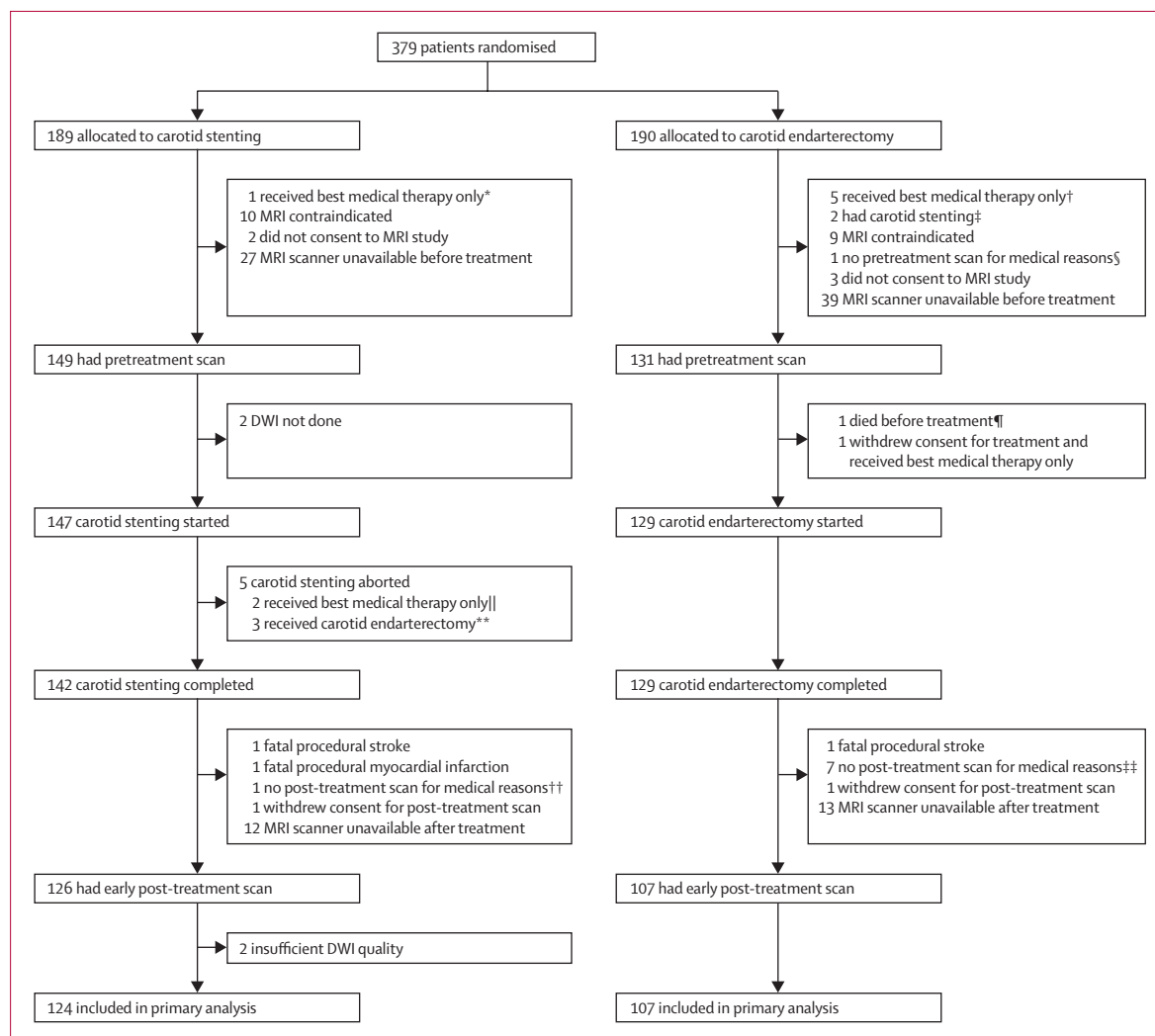
### Statistical analysis

A sample size of at least 100 patients per treatment group was chosen on the basis of detecting an increase in the proportion of patients with the primary outcome measure in the stenting group of two times compared with the endarterectomy group at a significance level of 0.05 and 90% power, assuming 25% of patients in the endarterectomy group would have new DWI lesions after treatment. SPSS Statistics software version 17.0 was used for statistical analysis (SPSS, Chicago, IL, USA).

The primary analysis of MRI outcome measures included all patients who completed the allocated treatment and who had both the pretreatment scan and

the post-treatment scan. A secondary sensitivity analysis excluded patients whose pretreatment scans were done more than 7 days before pretreatment or whose post-treatment scans were done more than 3 days after treatment. We used binary logistic regression models to compare MRI outcome measures between treatment groups, adjusted for any significant imbalances in baseline characteristics. Interactions between the effect of treatment on the primary outcome measure and selected baseline characteristics (age, sex, type of most recent ipsilateral event, presence of a hyperintense DWI lesion before treatment, and ARWMC score) were investigated, adjusted for any significant imbalances in baseline characteristics.

To assess the effect of cerebral protection devices in stenting, we separated centres into those with a policy of



**Figure 1: Study profile**

DWI=diffusion-weighted imaging. \*Carotid occlusion before scheduled treatment. †Carotid occlusion (n=4), patient was unfit for either procedure (n=1). ‡Suspected lung tumour in preoperative investigation (n=1), refused allocated treatment (n=1). §Hypotension. ¶Probable cardiac cause. ||Functional carotid occlusion (n=1) and stenosis <50% (n=1). \*\*Problems in getting access to stenosis (n=2) and severe back pain during the procedure (n=1). ††Hypotension. ‡‡Hypotension or hypertension (n=3), non-fatal procedural myocardial infarction (n=1), cardiac arrhythmia (n=2), surgical clips with uncertain MRI compatibility used (n=1).

using such devices wherever possible and those with a policy of using mainly unprotected stenting, and tested for an interaction between centre policy and treatment effect. To take into account the fact that centres with a policy of protected stenting did not use cerebral protection devices in every patient and that the devices were used in some patients at centres with a policy of unprotected stenting, we also did a direct comparison between patients treated with protection versus those treated without in the stenting group, adjusted for any significant imbalances in baseline characteristics between groups.

A non-randomised exploratory comparison of the total lesion number and total lesion volume was done in the subset of patients with new DWI lesions on the post-treatment scan by use of Mann-Whitney tests.

This is a substudy of a registered trial, ISRCTN 25337470.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. LHB, MMB, and STE had full access to all data in the study and had final responsibility to submit the manuscript for publication.

### Results

In ICSS, 1713 patients were randomly allocated to stenting (n=855) or endarterectomy (n=858) between May, 2001, and October, 2008. Seven centres used the ICSS-MRI study protocol: five had a policy of using cerebral protection devices during stenting and two had a policy of unprotected stenting. In these seven centres, 189 patients were randomly assigned to stenting and 190 patients to endarterectomy (figure 1). 124 patients in the stenting group and 107 patients in the endarterectomy group were included in the primary analysis. Figure 1 shows the reasons for exclusion and incomplete MRI. In the primary analysis population, the pretreatment scan was done more than 7 days before treatment in one patient in the stenting group (11 days) and in 14 patients in the endarterectomy group (maximum 29 days [median 9, IQR 8–16]). The post-treatment scan was done more than 3 days after treatment in five patients in the stenting group (maximum 6 days [5, 4–6]), and in eight patients in the endarterectomy group (maximum 8 days [5, 4–7]). In 203 patients (118 in the stenting group and 85 in the endarterectomy group), both pretreatment and post-treatment scans were done within the specified time limits.

Demographic, clinical and MRI baseline characteristics did not differ substantially between the two groups (table 2); however, the interval between treatment and the post-treatment MRI scan was longer in the endarterectomy group (p=0.008). Baseline characteristics were similar to those of patients in the main ICSS trial who were not included in this MRI substudy, with the exception of higher systolic blood pressure at randomisation in patients in the MRI substudy than in the other patients (mean 156 mm Hg [SD 27] vs 144 mm Hg [23]), p<0.0001.<sup>1</sup> In a post-hoc analysis, systolic blood pressure did not predict the occurrence of new DWI lesions after treatment (unadjusted OR 1.00 [95% CI 0.99–1.01], p=0.682; OR adjusted for treatment 1.00 [0.99–1.01], p=0.703).

11 (9%) of 124 patients in the stenting group had any procedural stroke or death (ie, occurring within 30 days of treatment) compared with five (5%) of 107 in the endarterectomy group (p=0.30, table 3). Although there were no fatal strokes, one sudden cardiac death occurred 25 days after stenting. 13 patients (10%) in the stenting group and three (3%) in the endarterectomy group had procedural transient ischaemic attack or ischaemic stroke (OR 4.06, 95% CI 1.20–13.63, p=0.035).

	Carotid stenting (n=124)	Carotid endarterectomy (n=107)
Age (years)	70.5 (9.4)	69.5 (8.8)
Men	87 (70%)	76 (71%)
Vascular risk factors		
History of hypertension	85 (69%)	74 (69%)
History of diabetes	24 (19%)	24 (22%)
History of hypercholesterolaemia	78 (63%)	72 (67%)
Smoking (past or present)	94 (76%)	80 (75%)
Coronary heart disease	30 (24%)	21 (20%)
Peripheral artery disease	22 (18%)	15 (14%)
Systolic blood pressure at randomisation (mm Hg)	156.3 (26.0)	155.7 (28.3)
Total cholesterol at randomisation (mmol/L)	4.8 (1.3)	5.0 (1.3)
Most recent ipsilateral event		
Amaurosis fugax	23 (19%)	21 (20%)
Retinal stroke	4 (3%)	1 (1%)
Transient ischaemic attack	42 (34%)	46 (43%)
Hemispheric ischaemic stroke	55 (44%)	39 (36%)
Modified Rankin scale score at randomisation		
0	54 (44%)	38 (36%)
1	29 (23%)	29 (27%)
2	31 (25%)	28 (26%)
3	7 (6%)	9 (8%)
4	3 (2%)	3 (3%)
Degree of ipsilateral carotid stenosis at randomisation*		
Moderate (50–69%)	17 (14%)	8 (8%)
Severe (70–99%)	107 (86%)	99 (93%)
Contralateral carotid occlusion	8 (6%)	2 (2%)
Interval between most recent ipsilateral event and treatment (days)	37 (14–82)	45 (23–85)
Interval between pretreatment scan and treatment (days)	1 (1–3)	1 (1–3)
Interval between treatment and post-treatment scan (days)	1 (1–1)†	1 (1–2)†
Presence of ischaemic lesion on DWI before treatment	54 (44%)	42 (39%)
ARWMC score	4 (2–7)	4 (2–8)
Interval between treatment and 1-month follow-up scan‡ (days)	33 (30–36)	33 (30–34)

Data are mean (SD), number (%), or median (IQR). ARWMC=age-related white matter changes. DWI=diffusion-weighted imaging. \*According to NASCET method. †Mann-Whitney test p=0.008. ‡1-month follow-up scans were done in 86 patients in the stenting group and in 75 patients in the endarterectomy group.

Table 2: Demographics and baseline characteristics

62 (50%) of 124 patients in the stenting group had new DWI lesions on post-treatment scans compared with 18 (17%) of 107 patients in the endarterectomy group (OR 5.21, 95% CI 2.78–9.79;  $p < 0.0001$ , adjusted for interval between treatment and post-treatment scan; table 4). There were non-significant imbalances between treatment groups in the proportion of patients with hemispheric ischaemic stroke as qualifying event (55 [44%] of 124 in the stenting group and 39 [36%] of 107 in the endarterectomy group,  $p = 0.223$ ) and interval between most recent ipsilateral event and treatment (median 37 days [IQR 14–82] in the stenting group and 45 [23–85] in the endarterectomy group,  $p = 0.123$ ; table 2). In a post-hoc comparison adjusted for these variables in addition to interval between treatment and post-treatment scan, the OR for new DWI lesions was 5.30 (95% CI 2.80–10.05,  $p < 0.0001$ ). In patients who had pretreatment and post-treatment scans within the prespecified time limits, 58 (49%) of 118 patients in the stenting group and 15 (18%) of 85 patients in the endarterectomy group had new DWI lesions after treatment (adjusted OR 4.84, 95% CI 2.45–9.55;  $p < 0.0001$ ).

66 patients were studied in 3 Tesla scanners (37 in the stenting group and 29 in the endarterectomy group) and 165 in 1.5 Tesla scanners. Lesions were detected in 29 (44%) of 66 patients scanned with 3 Tesla compared with 51 (31%) of 165 patients scanned with 1.5 Tesla ( $p = 0.06$ ).

In eight of 62 patients with positive DWI after stenting, lesions were associated with symptoms of an ischaemic hemispheric stroke between initiation of treatment and the post-treatment scan, and one patient had an ipsilateral retinal stroke before the scan (table 4). In the other 53 patients with stents and new DWI lesions, no ischaemic events happened up to the time of the scan; however, one patient had an ischaemic stroke 4 days after the scan, and two had transient ischaemic attacks (26 and 28 days after the scan). In addition, one patient without new DWI lesions on the post-treatment scan had a transient ischaemic attack 19 days after the scan. In the endarterectomy group, three of 18 patients with new DWI lesions had ischaemic hemispheric strokes, whereas 15 did not have any ischaemic events up to the time of the scan; however, two patients who did not have any new lesions on post-treatment DWI had haemorrhagic strokes 1 and 3 days after the scan. No hemispheric ischaemic event occurred between treatment and the post-treatment scan without a corresponding lesion on DWI in any of the 231 patients included in the primary analysis.

In patients with hemispheric stroke as the qualifying event, 33 (60%) of 55 in the stenting group and four (10%) of 39 in the endarterectomy group had new DWI lesions on post-treatment scans (adjusted OR 15.04, 95% CI 4.38–51.67), whereas in those with a retinal ischaemic event or transient ischaemic attack as the qualifying event, 29 (42%) of 69 in the stenting group and 14 (21%) of 68 in the endarterectomy group had new DWI lesions (adjusted OR 2.89, 1.34–6.22; interaction  $p = 0.025$ ;

	Carotid stenting (n=124)	Carotid endarterectomy (n=107)	OR (95% CI)	p*
Any stroke or death	11 (9%)	5 (5%)	1.99 (0.70–5.66)	0.300
All cause death	1 (1%)	0	..	..
Any stroke	10 (8%)	5 (5%)	1.79 (0.62–5.17)	0.423
Stroke pathology				
Ischaemic	10 (8%)	3 (3%)	..	..
Haemorrhagic	0	2 (2%)	..	..
Stroke severity				
Non-disabling	7 (6%)	2 (2%)	..	..
Disabling	3 (2%)	3 (3%)	..	..
Fatal	0	0	..	..
TIA	3 (2%)	0	..	..
Ischaemic stroke or TIA	13 (10%)	3 (3%)	4.06 (1.20–13.63)	0.035

Data are number (%). TIA=transient ischaemic attack. \*Fisher's exact test.

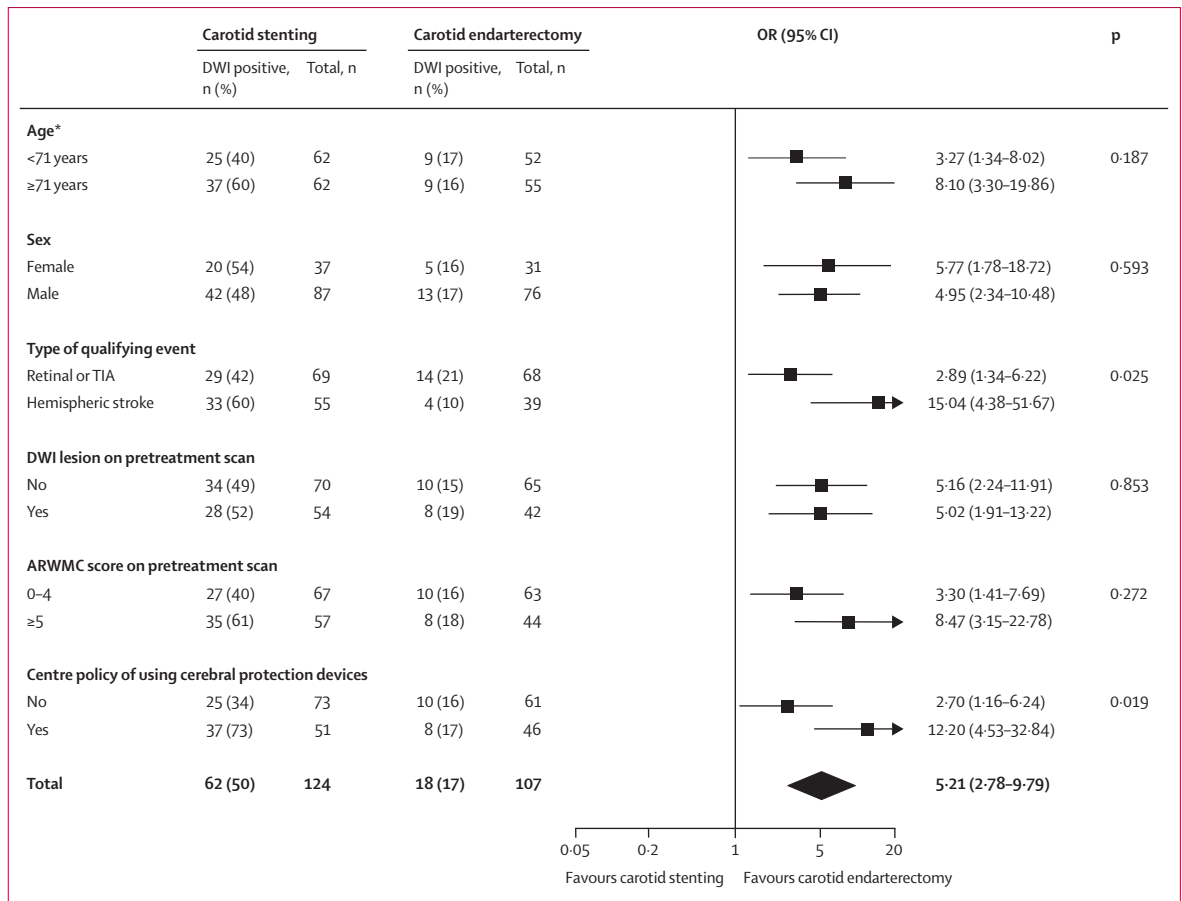
**Table 3: Clinical outcome within 30 days of treatment**

	Carotid stenting (n=124)	Carotid endarterectomy (n=107)	OR (95% CI)	p*
At least one new lesion	62 (50%)	18 (17%)	4.94 (2.67–9.16) <sup>†</sup> 5.21 (2.78–9.79) <sup>‡</sup>	<0.0001 <0.0001
Single lesion	18 (15%)	9 (8%)	..	..
Multiple lesions	44 (35%)	9 (8%)	..	..
Location of lesions				
Ipsilateral carotid circulation only	34 (27%)	14 (13%)	..	..
Ipsilateral carotid and non-ipsilateral (contralateral carotid or vertebralbasilar) circulations	22 (18%)	3 (3%)	..	..
Non-ipsilateral (contralateral carotid or vertebralbasilar) circulations only	6 (5%)	1 (1%)	..	..
Ischaemic events in patients with new DWI lesions <sup>§</sup>	9 (7%)	3 (3%)	..	..
Hemispheric stroke	8 (6%)	3 (3%)	..	..
Retinal infarct	1 (1%)	0	..	..
TIA	0	0	..	..
None	53 (43%)	15 (14%)	..	..

Data are number (%). DWI=diffusion-weighted imaging. TIA=transient ischaemic attack. \*Logistic regression.  
<sup>†</sup>Unadjusted. <sup>‡</sup>Adjusted for interval between treatment and post-treatment scan. <sup>§</sup>Events occurring between start of treatment and post-treatment scans only. No ischaemic event occurred between the start of treatment and the post-treatment scan in patients without new DWI lesions.

**Table 4: New DWI lesions on post-treatment scans**

figure 2). In patients treated at a centre with a policy of using cerebral protection devices, 37 (73%) of 51 in the stenting group and eight (17%) of 46 in the endarterectomy group had new DWI lesions on post-treatment scans (adjusted OR 12.20, 95% CI 4.53–32.84), whereas in those treated at a centre with a policy of unprotected stenting 25 (34%) of 73 patients in the stenting group and ten (16%) of 61 in the endarterectomy group had new lesions on DWI (adjusted OR 2.70, 1.16–6.24; interaction  $p = 0.019$ ). Both interactions remained significant after adjustment for each other ( $p = 0.040$  and  $p = 0.038$ , respectively). In the stenting group, cerebral protection



**Figure 2: New DWI lesions on post-treatment scans in patient subgroups**

Data are numbers of patients (%) with new DWI lesions on post-treatment scans (DWI positive) and total numbers of patients per treatment group. Squares and horizontal lines are adjusted odds ratios (OR) and 95% CIs. The diamond represents the overall adjusted OR and 95% CI. All OR and interaction p values are adjusted for interval between treatment and post-treatment scan. \*Dichotomised at the rounded median age of the study population. DWI=diffusion-weighted imaging. ARWMC=age-related white matter changes.

devices were used in 47 (92%) of 51 patients enrolled at centres with a policy of using protection, and in nine (12%) of 73 patients at centres with a policy of unprotected stenting. All cerebral protection devices used in the ICSS-MRI study were of the filter type. Compared with patients who had stenting without protection, in those who had cerebral protection devices a history of hypertension was more common (80% vs 59%,  $p=0.012$ ) and intervals between treatment and post-treatment scans were longer (median 1 day [IQR 1-2] vs 1 day [1-1],  $p=0.001$ ). When use of cerebral protection devices was compared irrespective of centre policy, 38 (68%) of 56 patients who had protected stenting and 24 (35%) of 68 patients who had unprotected stenting had new DWI lesions after treatment (OR 3.28, 1.50-7.20;  $p=0.003$ , adjusted for hypertension and delay to post-treatment scan).

In patients with new DWI lesions on the post-treatment scan, the median number of lesions in patients in the stenting group was 3 (IQR 1-9) compared with 2 (1-5) in patients in the endarterectomy group ( $p=0.073$ ). Median total lesion volume was 0.17 mL (IQR 0.06-0.58) in the

stenting group and 0.19 mL (0.06-0.58) in the endarterectomy group ( $p=0.800$ ). In both groups combined, median total lesion volume was 9.40 mL (IQR 2.26-12.83) in the 11 patients (eight in the stenting group and three in the endarterectomy group) with corresponding symptoms of ischaemic hemispheric stroke and 0.12 mL (0.05-0.40) in the 69 patients (54 in the stenting group and 15 in the endarterectomy group) with silent lesions ( $p<0.0001$ , figure 3).

1-month follow-up MRI scans were not done routinely at one centre (17 patients in the stenting group and 16 in the endarterectomy group). In the other centres, all three scans were done in 86 (80%) of 107 patients in the stenting group and in 75 (82%) of 91 patients in the endarterectomy group. Within this population, 89 (17%) of 537 DWI lesions detected at post-treatment scans in the stenting group and 18 (53%) of 34 DWI lesions in the endarterectomy group had a corresponding hyperintense FLAIR signal at follow-up. FLAIR signals were present at follow-up at the site of at least one post-treatment DWI lesion in 28 patients (33%) in the stenting group and six

patients (8%) in the endarterectomy group (adjusted OR 5.93 [95% CI 2.25–15.62];  $p=0.0003$ ; table 5). Six patients in the stenting group and one in the endarterectomy group had new hyperintense DWI lesions on the 1-month follow-up scan.

The two reviewers initially disagreed and reached consensus on the presence or absence of hyperintense DWI lesions in two of 231 pretreatment scans that were included in the primary analysis, eight of 231 post-treatment scans, and one of 161 scans at 1-month follow-up. In addition, there was initial disagreement on the number of lesions in 25 of the 80 patients who had new DWI lesions on post-treatment scans.

## Discussion

In this MRI substudy of ICSS, about three times more patients had new ischaemic lesions on DWI after stenting than after endarterectomy, and the risk of cerebral ischaemia was higher among patients undergoing stenting with cerebral protection devices than without.

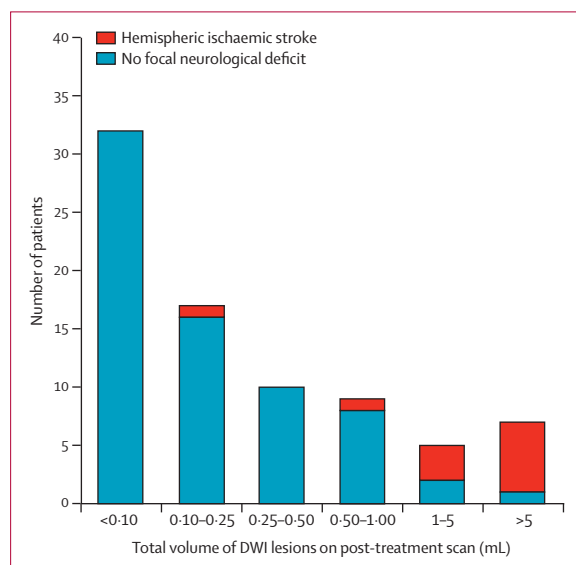
Non-randomised studies have suggested a higher rate of postprocedural ischaemic lesions on DWI after

stenting compared with endarterectomy.<sup>8–16</sup> In a meta-analysis of these studies the aggregate OR of new ischaemic lesions after treatment was 6.71 (95% CI 4.57–9.87) favouring endarterectomy (figure 4). However, whether this was because more patients who had high cardiovascular risk profiles were assigned to stenting is unclear. The OR for DWI lesions in our randomised study was very similar, arguing against such a bias.

At most centres in ICSS, patients were sent to neurological wards after stenting, whereas patients who had endarterectomy were transferred to high-dependency units or were sent to surgical wards for care after treatment. Thus, non-disabling strokes might have been detected more readily among patients who had stenting than among those who had endarterectomy. However, the results of the ICSS-MRI study confirm an increased risk of cerebral ischaemia associated with stenting in comparison with endarterectomy by using a separate, blinded assessment of MRI; thus it is unlikely that ascertainment bias caused the difference in non-disabling strokes between the two groups.

Among the 62 patients in the stenting group who had new DWI lesions after treatment, 44 (71%) had more than one lesion, and 28 (45%) had lesions in the contralateral carotid or vertebrobasilar circulation (mostly in addition to lesions in the ipsilateral carotid circulation). These results support the notion of an embolic pathogenesis of cerebral ischaemia.<sup>17</sup> Embolism might have happened at any stage of the stent procedure, including angiography before stenting.<sup>18</sup> Thrombotic material or atherosclerotic debris dislodged during the stenting procedure seems to result in single or multiple small emboli, which might manifest as stroke if a large enough volume of eloquent brain tissue is affected.

The differential risk of cerebral ischaemia was modified by the type of the most recent ipsilateral event before randomisation: the proportion with DWI lesions associated with stenting was smaller for patients enrolled after a transient ischaemic attack or a retinal ischaemic event than for patients who were enrolled after a hemispheric stroke. This pattern might have developed because patients with strokes have less stable plaques compared with those presenting with other ischaemic symptoms, a hypothesis that is supported by a histological study of symptomatic carotid plaques.<sup>19</sup> Thus, increased



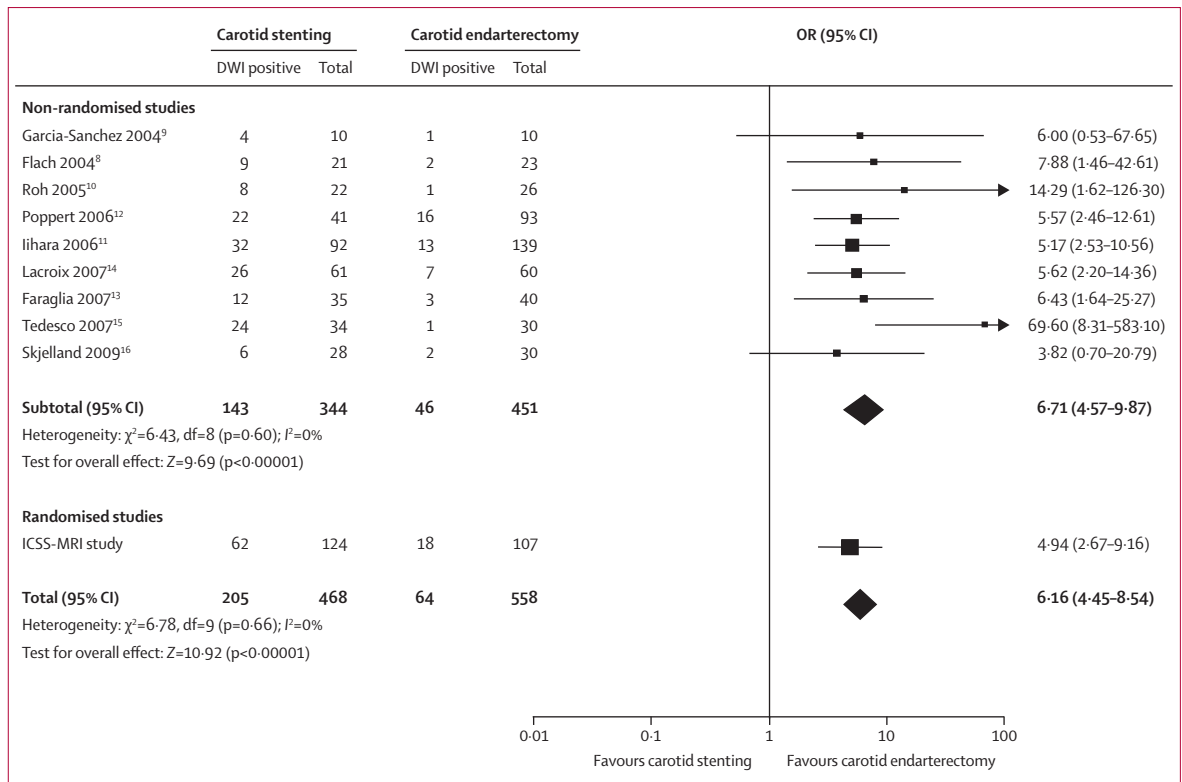
**Figure 3:** Distribution of DWI lesion volumes on post-treatment scans according to whether or not focal neurological deficits occurred  
DWI=diffusion-weighted imaging.

	Carotid stenting (n=86)	Carotid endarterectomy (n=75)	OR (95% CI)	p*
At least one new ischaemic lesion on post-treatment DWI	44 (51%)	10 (13%)	..	..
New hyperintensity on FLAIR at 1-month follow-up at site of at least one post-treatment DWI lesion	28 (33%)	6 (8%)	5.55 (2.15–14.33) 5.93 (2.25–15.62)	0.0004† 0.0003‡
New ischaemic lesion on DWI at 1-month follow-up not seen on post-treatment scan	6 (7%)	1 (1%)	5.55 (0.65–47.19)	0.117†

Data are number (%) or OR (95% CI). Patients with completed pretreatment, post-treatment and 1-month follow-up MRI scans are included. DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery imaging. †Logistic regression. ‡Unadjusted. †Unadjusted. ‡Adjusted for interval between treatment and post-treatment scan.

**Table 5: MRI findings at 1-month follow-up**





**Figure 4: Meta-analysis of studies comparing ischaemic lesions on DWI after carotid stenting versus carotid endarterectomy**  
Mantel-Haenszel fixed effect model comparing the proportions of patients with hyperintense DWI lesions after stenting versus endarterectomy in nine non-randomised studies, and in the ICSS-MRI study. Data are numbers of patients with new DWI lesions on post-treatment scans (DWI positive) and total numbers of patients in studies. Squares and horizontal lines are odds ratios (OR) and 95% CIs, with size of squares representing study weight. Diamonds represent aggregate OR and 95% CI. DWI=diffusion-weighted imaging.

plaque instability might pose a greater risk for cerebral embolism with stenting than with endarterectomy.

Five centres participating in the ICSS-MRI study had a policy of using filter-type cerebral protection devices during stenting, whereas at two centres stenting was mainly done without protection. The proportion of patients with DWI lesions in the stenting group was higher when centres used protection than when they did not. Our findings seem to contradict systematic reviews of observational studies reporting lower rates of stroke and ischaemia on DWI with protected than with unprotected stenting.<sup>20,21</sup> However, these studies either compared outcomes after protected stenting with historical controls of unprotected stenting (and thus might have been confounded by a learning curve effect) or were prone to selection bias. The results of the ICSS-MRI study are in agreement with two small randomised studies in which non-significant increases in the risk of cerebral ischaemia on DWI were reported after filter-protected stenting compared with unprotected stenting.<sup>22,23</sup> Together, these findings cast doubt on the efficacy of the routine use of filter-type cerebral protection devices in preventing cerebral embolism during stenting. Embolisation might develop during insertion of cerebral protection devices, especially in tortuous vessels and

stenoses, which are difficult to pass, and thromboembolism might result from damage to the endothelium. Nevertheless, some patients might benefit more than others from the use of filter-type cerebral protection devices, as suggested by a recent DWI study.<sup>24</sup> A randomised trial comparing protected versus unprotected stenting is required to investigate the safety and efficacy of cerebral protection devices.

Only 17% of DWI lesions in the stenting group and 53% in the endarterectomy group were associated with signal changes on FLAIR imaging 1 month later. This might be because full recovery of tissue injury occurred in the other lesions or because of differences in slice positioning between post-treatment scans and 1-month follow-up scans. However, more patients in the stenting group than in the endarterectomy group had at least one early DWI lesion leading to persistent tissue change. The finding of a higher proportion of DWI lesions after endarterectomy than stenting associated with permanent tissue damage on FLAIR might be explained by differences in volumes of individual lesions but might also suggest different pathogenetic mechanisms of cerebral ischaemia between stenting and endarterectomy.

New ischaemic lesions, even without corresponding focal deficit, might lead to clinical consequences in the

long term, including cognitive decline and dementia.<sup>25</sup> The effect of DWI lesions on cognitive function has been investigated in a single centre participating in the ICSS-MRI study and will be the subject of a separate report.

This study has several limitations. Although allocation of treatment was randomised, only 74% of patients randomly assigned treatment in ICSS at participating centres entered the ICSS-MRI study, 83% of whom completed post-treatment scanning. Thus, imbalances in unmeasured risk factors for DWI lesions between treatment groups might have influenced the results. Fewer patients allocated to have endarterectomy than to stenting completed the MRI study, suggesting a more restricted access to neuroimaging from surgical wards than from neurological wards. Clinically unstable patients with a higher risk for procedural ischaemia might have been less likely to complete the imaging protocol. However, any such bias is unlikely to explain the large difference in the occurrence of cerebral ischaemia between the two groups. The use of cerebral protection devices was not randomised in ICSS, and other centre-related factors (eg, experience of the interventionalist) might have contributed to the observed interaction. Also, because all cerebral protection devices used in the ICSS-MRI study were of the filter type, we cannot make any conclusions about the efficacy of other types of devices (eg, with distal or proximal balloon occlusion). Almost a third of patients in the ICSS-MRI study were studied in a 3 Tesla scanner and, although there was a higher DWI lesion detection rate than with 1.5 Tesla, there was no difference in the proportion of patients analysed with the higher magnetic field strength between the two treatment groups. The results were, therefore, probably not biased by detection of lesions at different field strengths.

By use of a separate masked assessment of MRI, we have shown in this substudy that the increased risk of cerebral ischaemia after stenting compared with endarterectomy reported in ICSS is unlikely to have been caused by ascertainment bias. DWI could be used as a surrogate outcome measure for treatment safety in future pilot studies of carotid interventions.

#### Contributors

LHB coordinated the study, analysed all scans, did statistical analysis, and wrote the manuscript. SH, HZF, PJJ, SM, PAG, AW, PS, HRJ, PAL, and LJK contributed to data acquisition. LMJ analysed all scans. JD supervised statistical analysis. LHB, SGW, AvdL, WPM, MMB, HBvdW, and STE designed the study. MMB is the chief investigator of ICSS, and co-supervised this study and took responsibility for final submission of the manuscript. STE supervised the study. All authors wrote and revised the manuscript.

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#### Conflicts of interest

PAG holds a research grant from Gore Medical and has a consultant and proctorship agreement with Boston Scientific. SM holds consultancy agreements with CR Bard and WL Gore. The other authors have no conflicts of interest.

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#### References

- 1 International Carotid Stenting Study investigators. 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; published online Feb 26. DOI: 10.1016/S0140-6736(10)60239-5.
- 2 Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. *Cerebrovasc Dis* 2004; **18**: 69–74.
- 3 International Carotid Stenting Study Protocol. 22-11-2007. [http://www.ion.ucl.ac.uk/cavatas\\_icss/protocol.pdf](http://www.ion.ucl.ac.uk/cavatas_icss/protocol.pdf) (accessed Feb 20, 2010).
- 4 North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke* 1991; **22**: 711–20.
- 5 Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of the human brain. In: Bogousslavsky J, Caplan LR, eds. *Stroke Syndromes*. 2nd edn. Cambridge, UK: Cambridge University Press, 2001: 375–404.
- 6 Pantano P, Caramia F, Bozzao L, Dieler C, von Kummer R. Delayed increase in infarct volume after cerebral ischemia: correlations with thrombolytic treatment and clinical outcome. *Stroke* 1999; **30**: 502–27.
- 7 Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001; **32**: 1318–22.
- 8 Flach HZ, Ouhlous M, Hendriks JM, et al. Cerebral ischemia after carotid intervention. *J Endovasc Ther* 2004; **11**: 251–57.
- 9 Garcia-Sanchez S, Millan-Torne M, Capellades-Font J, Muchart J, Callejas P, Vila-Moriente N. [Ischemic brain lesions following carotid revascularisation procedures: a comparative study using diffusion-weighted magnetic resonance imaging]. *Rev Neurol* 2004; **38**: 1013–17.
- 10 Roh HG, Byun HS, Ryo JW, et al. Prospective analysis of cerebral infarction after carotid endarterectomy and carotid artery stent placement by using diffusion-weighted imaging. *AJNR Am J Neuroradiol* 2005; **26**: 376–84.
- 11 Iihara K, Murao K, Sakai N, Yamada N, Nagata I, Miyamoto S. Outcome of carotid endarterectomy and stent insertion based on grading of carotid endarterectomy risk: a 7-year prospective study. *J Neurosurg* 2006; **105**: 546–54.

- 12 Poppert H, Wolf O, Theiss W, et al. MRI lesions after invasive therapy of carotid artery stenosis: a risk-modeling analysis. *Neurol Res* 2006; **28**: 563–67.
- 13 Faraglia V, Palombo G, Stella N, et al. Cerebral embolization in patients undergoing protected carotid-artery stenting and carotid surgery. *J Cardiovasc Surg (Torino)* 2007; **48**: 683–88.
- 14 Lacroix V, Hammer F, Astarci P, et al. Ischemic cerebral lesions after carotid surgery and carotid stenting. *Eur J Vasc Endovasc Surg* 2007; **33**: 430–35.
- 15 Tedesco MM, Coogan SM, Dalman RL, et al. Risk factors for developing postprocedural microemboli following carotid interventions. *J Endovasc Ther* 2007; **14**: 561–67.
- 16 Skjelland M, Krohg-Sorensen K, Tennoe B, Bakke SJ, Brucher R, Russell D. Cerebral microemboli and brain injury during carotid artery endarterectomy and stenting. *Stroke* 2009; **40**: 230–34.
- 17 Baird AE, Lovblad KO, Schlaug G, Edelman RR, Warach S. Multiple acute stroke syndrome: marker of embolic disease? *Neurology* 2000; **54**: 674–78.
- 18 Bendszus M, Koltzenburg M, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L. Silent embolism in diagnostic cerebral angiography and neurointerventional procedures: a prospective study. *Lancet* 1999; **354**: 1594–97.
- 19 Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. *Circulation* 2006; **113**: 2320–28.
- 20 Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke* 2003; **34**: 813–19.
- 21 Schnaudigel S, Groschel K, Pilgram SM, Kastrup A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. *Stroke* 2008; **39**: 1911–19.
- 22 Barbato JE, Dillavou E, Horowitz MB, et al. A randomized trial of carotid artery stenting with and without cerebral protection. *J Vasc Surg* 2008; **47**: 760–65.
- 23 Macdonald S, Evans DH, Griffiths PD, et al. Filter-protected versus unprotected carotid artery stenting: a randomised trial. *Cerebrovasc Dis* 2010; **29**: 282–89.
- 24 Kastrup A, Groschel K, Nagele T, et al. Effects of age and symptom status on silent ischemic lesions after carotid stenting with and without the use of distal filter devices. *AJNR Am J Neuroradiol* 2008; **29**: 608–12.
- 25 Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* 2009; **8**: 1006–18.