Characteristics of Ischemic Brain Lesions After Stenting or Endarterectomy for Symptomatic Carotid Artery Stenosis

Results From the International Carotid Stenting Study–Magnetic Resonance Imaging Substudy

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Background and Purpose—In a substudy of the International Carotid Stenting Study (ICSS), more patients had new ischemic brain lesions on diffusion-weighted magnetic resonance imaging (MRI) after stenting (CAS) than after endarterectomy (CEA). In the present analysis, we compared characteristics of diffusion-weighted MRI lesions.

Methods—Number, individual and total volumes, and location of new diffusion-weighted MRI lesions were compared in patients with symptomatic carotid stenosis randomized to CAS (n=124) or CEA (n=107) in the ICSS-MRI substudy.

Results—CAS patients had higher lesion numbers than CEA patients (1 lesion, 15% vs 8%; 2–5 lesions, 19% vs 5%; >5 lesions, 16% vs 4%). The overall risk ratio for the expected lesion count with CAS versus CEA was 8.8 (95% confidence interval, 4.4–17.5; \( P<0.0001 \)) and significantly increased among patients with lower blood pressure at randomization, diabetes mellitus, stroke as the qualifying event, left-side stenosis, and if patients were treated at centers routinely using filter-type protection devices during CAS. Individual lesions were smaller in the CAS group than in the CEA group (\( P<0.0001 \)). Total lesion volume per patient did not differ significantly. Lesions in the CAS group were more likely to occur in cortical areas and subjacent white matter supplied by leptomeningeal arteries than lesions in the CEA group (odds ratio, 4.2; 95% confidence interval, 1.7–10.2; \( P=0.002 \)).

Conclusions—Compared with patients undergoing CEA, patients treated with CAS had higher numbers of periprocedural ischemic brain lesions, and lesions were smaller and more likely to occur in cortical areas and subjacent white matter. These findings may reflect differences in underlying mechanisms of cerebral ischemia.

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Key Words: carotid stenosis • cerebral embolism • diffusion-weighted imaging lesions • endarterectomy • stenting • stroke

Carotid artery stenting (CAS) has emerged as an alternative to endarterectomy (CEA) for treatment of atherosclerotic stenosis of the internal carotid artery. The International Carotid Stenting Study (ICSS) was a randomized trial comparing CAS with CEA in patients with symptomatic carotid stenosis.\(^1\) An analysis of short-term outcome data in ICSS revealed a significantly increased risk in the incidence of death, stroke, or myocardial infarction within the first 120 days after randomization in the CAS group compared with the CEA group, mainly driven by a higher rate of nondisabling periprocedural stroke in the stenting arm. The ICSS–Magnetic Resonance Imaging (MRI) substudy compared the risk of periprocedural cerebral ischemia on MRI between the 2 groups.\(^2\) We previously reported our initial finding that a proportion of 50% of patients treated with CAS and 17% of those undergoing CEA had ≥1 new ischemic brain lesions on diffusion-weighted imaging (DWI) a median of 1 day after
treatment (adjusted odds ratio [OR], 5.21; 95% confidence interval [CI], 2.78–9.79; P<0.0001).

The previous analysis relied on a binary outcome measure, defined as the presence or absence of ≥1 new DWI lesions after treatment, irrespective of the total number of lesions, their volume, and location. A comparison of the total number of lesions per patient retains more information and might be better-suited to compare the risk of periprocedural embolism between treatments. In the present analysis of the ICSS-MRI substudy, we compared the number of new DWI lesions after CAS versus CEA overall, as well as in subgroups of patients. In addition, we compared the volume of ischemic lesions and their location between treatments.

Methods

MRI Substudy of the ICSS

The ICSS-MRI substudy was a prospective multicenter substudy in ICSS. The design of ICSS and the ICSS-MRI substudy has been described previously.1–3 Patients with symptomatic moderate or severe carotid artery stenosis (defined by a luminal narrowing of ≥50% according to the measurement of degree of stenosis used in the North American Symptomatic Carotid Endarterectomy Trial)1 were randomized in a 1:1 ratio to CAS or CEA. All of the patients included at 7 ICSS centers who took part in the ICSS-MRI substudy had the option of participation in the substudy, if no contraindications to MRI were present. The study was approved by local ethics committees for non-United Kingdom centers and by the Northwest Multicentre Research Ethic Committee in the United Kingdom. All of the patients provided written informed consent. At the 7 participating centers, CAS procedures were performed by 9 different interventionists, who had performed 8, 16, 18, 28, 36 (2 interventionists), 60, 61, and 68 procedures before and within the ICSS trial combined, before having performed the first procedure within the ICSS-MRI substudy.

MRI scans at field strengths of 1.5 T or 3.0 T were specified to take place 1 to 7 days before treatment (pretreatment MRI), 1 to 3 days after treatment (posttreatment MRI), and 27 to 33 days after treatment (1-month follow-up MRI). Sixty-six patients were studied with 3-T scanners (CAS, n=57; CEA, n=29) and 165 were studied with 1.5-T scanners (CAS, n=87; CEA, n=78). Each scan included DWI sequences, whereas fluid-attenuated inversion recovery sequences were only mandatory in pretreatment and 1-month follow-up scans. Assessment of MRI scans was performed through consensus reading by a neuroradiologist (L.H.B.) and a neuroradiologist (L.M.J.) who were blinded to treatment allocation. In case of disagreement between the 2, a third reviewer (S.T.E.) made the final decision.

Imaging Outcome Measures

The present analysis was based on acute periprocedural ischemic brain lesions, defined as hyperintense DWI lesions on posttreatment MRI that were not present on pretreatment MRI. The following imaging outcome measures were specified: (1) the total number of new DWI lesions per patient (lesion count); (2) total lesion volume per patient, defined as the sum of all volumes of separate DWI lesions; (3) volume of separate DWI lesions (calculated by multiplying lesion diameters in 3 axes and dividing the obtained volume in milliliters by 2);2,4 and (4) location of lesions. We classified the location of lesions according to previously published templates.5 We discerned the carotid circulation (including anterior cerebral artery [ACA] and middle cerebral artery [MCA]) and the vertebrobasilar circulation (including both vertebral arteries, basilar artery, cerebellar arteries, and both posterior cerebral arteries [PCAs]). We further differentiated between superficial brain areas (including cortex and subjacent white matter) supplied by leptomeningeal branches of the ACA, MCA, and PCA (also known as superficial or pial arteries) and deep brain areas supplied by perforating arteries. Vascular border zones were defined as the area between ACA and MCA, between MCA and PCA, and between ACA, MCA, and PCA territories, as well as the area between territories supplied by leptomeningeal branches and perforating branches of the ACA, MCA, or PCA. We compared the likelihood of lesions occurring in the following locations between CAS and CEA: (1) in a territory supplied by leptomeningeal branches of the ACA, MCA, or PCA as opposed to any other territory; (2) in a border zone territory as opposed to any other territory; and (3) outside (located in the contralateral carotid or in the vertebrobasilar circulation) as opposed to within the territory supplied by the treated carotid artery. Lesions were considered separate if there was no continuity between them on the same slice as well as on adjacent slices.6 Age-related white matter changes were quantified on pretreatment fluid-attenuated inversion recovery sequences, using a published scale.7

Subgroup analyses were performed comparing lesion count between CAS and CEA with regard to the following baseline characteristics dichotomizing continuous and ordinal scaled variables at the median values of the study population: age (<71 vs ≥71 years); sex; hypertension; systolic blood pressure at randomization (<158.5 vs ≥158.5 mm Hg); diabetes mellitus; hyperlipidemia; any smoking (current smoking or history of); coronary heart disease; type of qualifying event (defined as the most recent ipsilateral ischemic event before randomization: retinal ischemia or transient ischemic attack versus hemispheric stroke); interval between qualifying event and treatment (<14 days vs ≥14 days); degree of stenosis (70%–99% [severe], 50%–69% [moderate]); side of treated stenosis (left vs right); presence vs absence of hyperintense DWI lesions on pretreatment MRI, and age-related white matter changes (sum score, 0–4 vs ≥5). To assess the impact of cerebral protection device (CPD) use on DWI lesion count, we investigated for any difference in treatment effect of CAS versus CEA between centers adopting a policy of routine CPD use and centers performing CAS without CPD. Centers performing protected CAS in the ICSS-MRI substudy chose to use filter-type devices.

Statistical Analysis

Negative binomial regression models were used to compare DWI lesion counts between CAS and CEA. Patients without new DWI lesions after treatment were assigned a lesion count of 0. In these models, a difference in lesion count between CAS and CEA was expressed by a risk ratio and 95% CI with CEA as the reference group. This risk ratio expresses how many times more or fewer lesions are expected to occur in a CAS patient than in a CEA patient. The same models also were used for subgroup analyses as defined, including a multiplicative subgroup variable by posttreatment variable interaction term. In case of significant interactions (interaction P<0.05), explorative post hoc analyses of the associations between the subgroup variables and DWI lesion counts in each treatment group were performed.

All of the patients were included in the analysis of total lesion volumes. Patients without new DWI lesions after treatment were assigned a total lesion volume of 0. We used generalized linear models with Poisson-γ (Tweedie) distribution to compare total lesion volumes per patient between the CAS and CEA groups. Furthermore, among patients who had new DWI lesions after treatment, individual log-transformed volumes of separate lesions were compared between treatment groups using linear mixed-effects models, with a separate intercept for each patient. At the level of the DWI lesion, the odds of whether a lesion was located in a leptomeningeal territory versus any other territory, border zone versus any other territory, and outside versus within the territory supplied by the treated carotid artery were compared between treatment groups with generalized linear mixed-effects models with binomial error distribution. ORs and 95% CIs were expressed with CEA as the reference group. All of the models were adjusted for the delay between treatment and the posttreatment MRI scan, which was significantly longer in the CEA arm (median, 1 day; interquartile range, 1–2) than in the CAS arm (median, 1 day; interquartile range, 1–1), as reported previously.2

Finally, we compared the power of the negative binomial regression model (using lesion count as the outcome measure) with the original binary logistic regression model (using presence or absence of any new DWI lesions after treatment as the outcome measure) to find a statistically significant difference between CAS and CEA in the respective DWI outcome measures. For each sample size, starting
at 50 patients and stepwise increasing by 5 patients, the negative binomial regression and logistic regression models were fit for 1000 random samples of the ICSS-MRI substudy population. For each sample size, the statistical power of both models was estimated by the proportion of significant test results of all 1000 tests. For all of the analyses, P<0.05 was considered statistically significant. All of the analyses were conducted with R version 2.15.0.4

Results
Baseline Characteristics and Clinical Outcomes
The present analysis of the ICSS-MRI substudy was based on the same patient population as reported previously.2 A total of 231 patients were included, of whom 124 were randomly assigned to CAS and 107 were assigned to CEA. Seventy-three patients in the CAS group were treated in centers without and 51 patients were treated in centers with a policy of routine CPD use. The mean age of the patients was 70 years, 71% were men, and 89% had severe degree of stenosis (≥70%). Demographic, clinical, and MRI baseline characteristics did not differ significantly between the 2 groups. In the first 30 days after treatment, there was 1 sudden cardiac death in the CAS group; 10 patients (8%) in the CAS group and 5 (5%) in the CEA group had a stroke (10 strokes in the CAS group and 3 in the CEA group were ischemic, and 2 strokes in the CAS group were hemorrhagic); and 3 patients (2%) in the CAS group had a transient ischemic attack.3

DWI Lesion Count
In the negative binomial regression analysis, CAS was associated with higher DWI lesion count than CEA (Figure 1). The proportion of patients with 1 lesion was 15% for CAS versus 8% for CEA; for those with 2 to 5 lesions the proportion was 19% versus 5%; and for those with >5 lesions the proportion was 16% versus 4%. The risk ratio (RR) for the expected lesion count with CAS compared with CEA was 8.8 (95% CI, 4.4–17.5; P<0.0001), meaning that patients in the CAS group had, on average, 9-times as many DWI lesions after treatment as CEA patients. Subgroup analysis showed that this RR was higher in the following patient groups: (1) patients with blood pressure equal to or above the median (RR, 4.2; 95% CI, 1.7–10.3; interaction P=0.009); (2) patients with a history of diabetes mellitus (RR, 5.7; 95% CI, 1.4–25.3; interaction P=0.032); (3) patients with hemispheric stroke as the qualifying event (RR, 3.2; 95% CI, 1.0–10.1; interaction P=0.004); (4) patients with carotid stenosis on the left side (RR, 3.9; 95% CI, 1.6–9.6; interaction P=0.032; Figure 2); and (5) patients with blood pressure higher than median systolic blood pressure was associated with higher DWI lesion count in the CEA group (RR, 4.2; 95% CI, 1.0–16.7; P=0.044) but not in the CAS group. There was a trend toward a lower lesion count among patients with history of diabetes mellitus in the CEA group (RR, 0.17; 95% CI, 0.03–1.05; P=0.056), whereas diabetes mellitus had no effect on lesion count in the CAS group. Hemispheric stroke as the qualifying event (RR, 2.5; 95% CI, 1.2–5.5; P=0.021) and, by trend, stenosis on the left side (RR, 2.1; 95% CI, 1.0–4.7; P=0.062) increased the number of DWI lesions on posttreatment MRI in the CAS group but not in the CEA group.

DWI Lesion Volume and Location
The estimated distribution of total DWI lesion volume per patient in the 2 groups is shown in Figure 3. There was no significant difference in total lesion volume per patient between the CAS and the CEA groups in the entire study population (P=0.18). Among patients with new DWI lesions after treatment (CAS, n=62 patients; CEA, n=18), volumes of separate lesions were significantly smaller in the CAS group (median volume, 0.02 mL) than in the CEA group (0.08 mL; P<0.0001; Figure 3). Periprocedural DWI lesions in the CAS group were more likely to occur in cortical or subjacent white matter areas supplied by leptomeningeal arteries than lesions occurring in the CEA group (OR, 4.2; 95% CI, 1.7–10.2; P=0.002). CAS lesions were, by trend, less often located in vascular border zone territories than CEA lesions (OR, 0.5; 95% CI, 0.2–1.1; P=0.092). There was no significant difference between treatment groups in the likelihood of DWI lesions occurring in the territory supplied by the contralateral carotid artery or the
vertebrobasilar arteries (OR CAS vs CEA, 3.9; 95% CI, 0.5–33.4; P=0.220). The estimated powers to find a statistically significant difference between CAS and CEA using the negative binomial regression model (DWI lesion count) and the binary logistic regression model (presence vs absence of any DWI lesion) were 76% and 65% for a sample size of 50 patients, 91% and 87% for 75 patients, and 97% and 95% for 100 patients, respectively (Figure 4).

Discussion
In the present study, we found that in patients randomly assigned to CAS or CEA for symptomatic carotid stenosis, ischemic brain lesions on DWI were higher in number but smaller in size after CAS than CEA, resulting in no significant difference in total ischemic lesion volume per patient; low blood pressure at randomization, diabetes mellitus, stroke as the qualifying event, left-side stenosis, and center policy of routine filter-type CPD use increased the excess in DWI lesions with CAS over CEA; and lesions associated with CAS were located more often in cortical areas or subjacent white matter than lesions associated with CEA.

Previous nonrandomized studies have reported a more frequent occurrence of periprocedural DWI lesions after CAS than CEA. A meta-analysis of these studies comparing the odds of having ≥1 new DWI lesion after treatment revealed an OR of 6.71 (95% CI, 4.57–9.87) favoring CEA, which was comparable with the initial report of the ICSS-MRI substudy.2 In most of these studies, a binary MRI end point (presence of any number of DWI lesions vs absence of DWI lesions) was chosen. The negative binomial regression model used in the present analysis retained more information by comparing the actual number (count) of new DWI lesions after treatment between groups. We found that the expected number of ischemic lesions with CAS was ≈9-fold higher than with CEA. The negative binomial regression analysis of DWI lesion count had higher statistical power to demonstrate a difference between CAS and CEA than the logistic regression model if <100 patients were randomly sampled from the ICSS-MRI substudy population. Assessment of DWI lesion count therefore may be the preferred method to monitor procedural risks in future pilot studies of carotid revascularization.

Increased statistical power of the negative binomial regression model was also of advantage in subgroup analysis seeking to identify baseline variables that influence the difference in cerebral embolism between treatments. Higher
Blood pressure has been identified previously as a risk factor for periprocedural stroke or death in CEA in the European Carotid Surgery Trial (systolic blood pressure >180 mm Hg) and the North American Symptomatic Carotid Endarterectomy Trial (diastolic blood pressure >90 mm Hg). In line with these findings, we observed that in the CEA group, patients with higher than median systolic blood pressure at baseline had more DWI lesions after treatment than patients with lower systolic blood pressure; in contrast, blood pressure did not significantly alter DWI lesion count in CAS. As a consequence, the difference in lesion count between CAS and CEA was greater among patients with low blood pressure and lower among patients with high blood pressure (albeit still in favor of surgery).

The role of diabetes mellitus as a complicating factor for carotid revascularization remains controversial. One study identified diabetes mellitus as an independent predictor for periprocedural DWI lesions in CAS and CEA (OR, 5.3; 95% CI, 1.9–14.8), without comparison between treatments. Another study found no association between history of diabetes mellitus and increased occurrence of DWI lesions after CAS. In 1 nonrandomized study, diabetes mellitus was a predictor of perioperative stroke or death in CEA patients (RR, 2.83; 95% CI, 1.05–7.61; \( P = 0.04 \)) but not in CAS patients (\( P = 0.72 \)). Why a history of diabetes mellitus should reduce the number of DWI lesions in CEA while having no effect on CAS, as the risk factor analysis in the present study suggested, lacks explanation and might represent a chance finding.

A higher risk of periprocedural stroke or death with left-side stenosis has been reported previously for CEA and for CAS. Mechanisms that have been discussed include right-handedness of the surgeon in CEA and a more difficult catheterization of the left common carotid artery compared with the brachiocephalic trunk on the right in CAS. In the randomized Stent-Protected Angioplasty Versus Carotid Endarterectomy trial, side of stenosis did not modify the difference in periprocedural stroke or death between CAS and CEA. In contrast, we observed that the increase in DWI lesions with CAS compared with CEA was higher among patients with stenosis on the left than in those with stenosis on the right.

The strongest subgroup interaction was found for the type of the qualifying event. Patients with hemispheric strokes before randomization had more DWI lesions after CAS than those presenting with a retinal event or transient ischemic attack, an effect that was not observed in the CEA arm. Hence, the difference in DWI lesion count between CAS and CEA was highest among those patients. Interestingly, patients with symptomatic carotid stenosis presenting with strokes also had the highest risk of a recurrent stroke while using medical therapy in a pooled analysis of randomized trials comparing CEA with medical care. Stroke as a clinical manifestation of carotid stenosis therefore may be considered a marker of increased plaque instability. Plaque instability, in turn, may be more likely to increase the risk of periprocedural embolism during CAS (because of dislodgment of plaque debris or thrombi); this is less the case with CEA, in which the artery is clamped off. CEA, therefore, appears to be the safer treatment in these patients. An alternative possible mechanism is that collateral blood supply might be impaired in patients with carotid stenosis presenting with strokes.

The difference in DWI lesion count after CAS compared with CEA was greater at centers routinely using filter-type CPDs during CAS than at centers performing unprotected stenting. Although previous nonrandomized studies reported higher proportions of patients with new DWI lesions after unprotected than after protected CAS, 2 small randomized...
studies previously have shown higher rates of DWI lesions after filter-protected than after unprotected stenting.17,18 Our observation is in line with these findings and casts doubt on the beneficial effect of filter-type protection devices.19

Volumes of individual DWI lesions were significantly smaller after CAS compared with CEA, resulting in no significant difference in total lesion volume per patient between treatment groups. In addition, we found that DWI lesions in CAS were more likely to occur in cortical areas and subjacent white matter supplied by leptomeningeal arteries than lesions in CEA. These findings may suggest a difference in the underlying pathogenesis of cerebral ischemia between treatments. A shower of multiple, small emboli released during the procedure appears to be the predominant mechanism of cerebral ischemia in CAS. The clinical impact of small DWI lesions is still unknown. In general, smaller DWI lesions are more likely to be reversible and more often remain clinically silent compared with larger lesions.20,21 The impact of silent DWI lesions on cognition is the subject of current research. In line with 2 other studies,22,23 a single-center substudy in ICSS revealed a small but statistically significant decrease in global cognitive performance 6 months after CAS compared with baseline values, an effect that was not present in the CEA arm.24 Our finding that cortical areas were more likely to be affected by periprocedural emboli in CAS than in CEA may explain the effect on cognition.

Previous studies reported that ≤29% of patients had new DWI lesions located in the contralateral carotid or vertebro-basilary circulation after CAS.25,26 In our study population, 28 (23%) of the 124 patients in the CAS group and 4 (4%) of 107 patients in the CEA group had DWI lesions outside of the territory supplied by the treated carotid artery.2 We performed a post hoc binary logistic regression analysis that found that the odds of any lesion located outside of the ipsilateral carotid territory were significantly higher in the CAS group than in the CEA group (OR, 8.8; 95% CI, 2.9–27.3; P<.0001, adjusted for interval between treatment and posttreatment MRI scan). In the prespecified present analysis, which looked at the location of each DWI lesion separately, the odds of a lesion being located outside versus within the ipsilateral carotid territory were also higher in the CAS group than in the CEA group, but the difference was not significant (OR, 3.9; 95% CI, 0.5–33.4; P=.220). The more frequent involvement of distant territories in CAS as opposed to CEA therefore may partly reflect the higher number of periprocedural ischemic brain lesions per se. However, it is also possible that the risk of embolism to distant territories is specifically increased in CAS, for example, arising from manipulation of the aortic arch.

We are aware of several limitations of this study. First, both 1.5-T and 3.0-T scanners were used in the study. Differences in magnetic field strengths may have led to differences in the sensitivity of detecting small ischemic brain lesions and differences in lesion volume on DWI. However, there was no difference in the proportion of patients analyzed with the higher field strength between the 2 arms. Second, we did not systematically assess the configuration of the circle of Willis. Therefore, we cannot exclude that some patients with lesions in the contralateral ACA or in the PCA territory that were classified as nonipsilateral had a common A1 segment of the ACA or fetal-type PCA, respectively, in which case the lesions would have occurred in the territory of the treated carotid artery. Furthermore, the use of CPDs during CAS was not subject to randomization. The ICSS protocol recommended their use whenever it was considered safe and feasible. Therefore, other center-related factors, such as the experience of the interventionalist, might have contributed to the observed effect of CPD policy. In addition, all of the CPDs used in the ICSS-MRI study were of the filter type, and we cannot draw any conclusions for other types of devices such as those with distal balloon occlusion or proximal embolic protection systems to induce flow arrest or flow reversal. Proximal embolic protection was shown to reduce the risk of DWI lesions in CAS compared with filter protection in 2 recent randomized studies.27,28

Conclusion
Patients treated with CAS had a higher lesion count on post-treatment MRI than patients undergoing CEA, whereas individual lesions were smaller and more likely to be located in cortical regions and subjacent white matter. These findings may reflect differences in underlying mechanisms of ischemia. The increase in DWI lesion count with CAS as compared with CEA was greatest in patients with low blood pressure at randomization, diabetes mellitus, stroke as the qualifying event, and left-side stenosis. In addition, a policy of routinely using filter-type CPDs during CAS increased the excess in DWI lesions over CEA. Analysis of lesion count might be the preferred method to compare treatments in DWI-based studies of carotid revascularization, especially in small sample sizes, because of higher statistical power.

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Disclosures
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Supplemental Material

ICSS-MRI Study centres and collaborators

The following centres enrolled patients in the ICSS-MRI Study [number of patients included in primary analysis per centre].

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Abstract

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背景および目的：International Carotid Stenting Study（ICSS）のサブスタディにおいて，MRIで検出された新たな虚血性脳病変は，頸動脈内膜剥離術（CEA）後よりも，頸動脈内ステント留置術（CAS）後において多く認められた。本研究の解析では，拡散強調MRI病変の特徴を比較した。

方法：ICSS-MRIサブスタディにおいて，CAS群（n = 124）またはCEA群（n = 107）に無作為に割り付けられた，症候性頸動脈狭帯症を有する患者を対象として，病変数，個々の病変体積，総病変体積，および新たな拡散強調MRI病変の発生部位を比較した。

結果：病変数は，CAS患者の方がCEA患者よりも多かった（1病変，15%対8%，2～5病変，19%対5%，>5病変，16%対4%）。病変数の予測値に対する全体のリスク比は，CAS群がCEA群の8.8倍[95%信頼区間（CI）：4.4～17.5，p < 0.0001]で，無作為化時点で有効化が低い患者，糖尿病，脳卒中，脳虚血の発症機序における差違を反映している可能性がある。

結論：CASを受ける患者は，CEAを受ける患者に比べ，周術期の虚血性脳病変の数が多く，CEAよりも，皮質野および手下にある皮質下白質に発生する傾向が強かった。

臨床試験登録：URL: http://www.isrctn.org，国際識別番号：ISRCTN25337470.