Predictors of Acute and Persisting Ischemic Brain Lesions in Patients Randomized to Carotid Stenting or Endarterectomy

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Background and Purpose—We investigated predictors for acute and persisting periprocedural ischemic brain lesions among patients with symptomatic carotid stenosis randomized to stenting or endarterectomy in the International Carotid Stenting Study.

Methods—We assessed acute lesions on diffusion-weighted imaging 1 to 3 days after treatment in 124 stenting and 107 endarterectomy patients and lesions persisting on fluid-attenuated inversion recovery after 1 month in 86 and 75 patients, respectively.

Results—Stenting patients had more acute (relative risk, 8.8; 95% confidence interval, 4.4–17.5; P<0.001) and persisting lesions (relative risk, 4.2; 95% confidence interval, 1.6–11.1; P=0.005) than endarterectomy patients. Acute lesion count was associated with age (by trend), male sex, and stroke as the qualifying event in stenting; high systolic blood pressure in endarterectomy; and white matter disease in both groups. The rate of conversion from acute to persisting lesions was lower in the stenting group (relative risk, 0.4; 95% confidence interval, 0.2–0.8; P=0.007), and was only predicted by acute lesion volume.

Conclusions—Stenting caused more acute and persisting ischemic brain lesions than endarterectomy. However, the rate of conversion from acute to persisting lesions was lower in the stenting group, most likely attributable to lower acute lesion volumes.

Clinical Trial Registration—URL: www.isrctn.org. Unique identifier: ISRCTN25337470.
(Stroke. 2014;45:00-00.)

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

I n the MRI substudy of the International Carotid Stenting Study (ICSS), acute ischemic brain lesions on diffusion-weighted imaging (DWI) were found more often after stenting than after endarterectomy.1,2 We investigated risk factors for acute periprocedural brain lesions and lesions persisting on follow-up imaging.

Methods

MRI was performed 1 to 7 days before (pretreatment scan), 1 to 3 days after (early post-treatment scan), and 27 to 33 days after treatment (follow-up scan, performed in 6 of 7 centers) among patients with symptomatic carotid stenosis randomized to stenting or endarterectomy. Acute ischemic brain lesions were defined as new hyperintense DWI lesions on the early post-treatment scan and persisting lesions as hyperintense signal on fluid-attenuated inversion recovery (FLAIR) imaging on the follow-up scan at the site of previous acute lesions.

Negative binomial regression models were used to compare the number of acute and persisting lesions (lesion count) between treatment groups. Negative binomial regression models with persisting lesion count as the dependent variable, which included an offset for acute lesion count, were used to compare the rate of conversion from acute to persisting lesions between treatment groups. The association between location (superficial versus deep and border-zone versus non border-zone) and volume (A×B×C/2 converted to cubic root) of
across lesions and their likelihood of persisting on follow-up FLAIR was investigated with generalized linear mixed models, including a separate intercept for each patient. Continuous variables were dichotomized at the population median. Models were adjusted for delay between treatment and the early post-treatment MRI scan. No adjustment for multiple comparisons was made because the analysis was considered exploratory.

### Results

At 7 centers taking part in the ICSS-MRI substudy, the numbers of patients randomized in ICSS and participating in the substudy were 189 and 124, respectively, in the stenting group and 190 and 107, respectively, in the endarterectomy group. Characteristics of patients participating and not participating in the substudy did not differ (Table I in the online-only Data Supplement). Stenting patients had more acute lesions than endarterectomy patients (relative risk [RR], 8.8; 95% confidence interval [CI], 4.4–17.5; *P*<0.001; Table). In the stenting group, acute lesion count was higher in older patients by trend (271 years; RR, 2.1; 95% CI, 1.0–4.6; *P*=0.067), men (RR, 2.4; 95% CI, 1.00–5.8; *P*=0.042), and patients with stroke as the qualifying event (RR, 2.5; 95% CI, 1.2–5.5; *P*=0.021; Figure). Higher systolic blood pressure (≥158.5 mm Hg) was associated with an increased acute lesion count in the endarterectomy group (RR, 4.2; 95% CI, 1.00–16.7; *P*=0.044). More severe white matter disease (age-related white matter changes3 sum score, ≥5) increased the number of acute lesions both in the stenting (RR, 2.4; 95% CI, 1.1–5.3; *P*=0.028) and in the endarterectomy group (RR, 4.1; 95% CI, 1.1–15.4; *P*=0.035).

Follow-up FLAIR was obtained at 6 centers, in 86 stenting and in 75 endarterectomy patients and showed signal-hyperintensity in 89 (27%) of 537 acute DWI lesions in the stenting group and 18 (53%) of acute DWI lesions in the endarterectomy group. Patients in the stenting group had more persisting lesions than patients in the endarterectomy group (RR, 4.2; 95% CI, 1.6–11.1; *P*=0.005; Table). However, the probability of conversion from acute to persisting lesions was lower in the stenting group (RR, 0.4; 95% CI, 0.2–0.8; *P*=0.007). None of the analyzed variables at patient level in both treatment groups combined predicted lesion conversion. At the lesion level, only the volume of the acute lesion was considered exploratory.

For 1 FLAIR lesion on follow-up MRI (n, %) 28 (64%) 6 (60%) 4.2 (1.6–11.1), *P*=0.005*.

### Discussion

Our study using DWI as surrogate outcome assessment is in line with previous research showing that procedural ischemic stroke risks are increased in elderly patients treated with stents and in patients with high blood pressure undergoing endarterectomy. The association between acute lesion count and type of qualifying event may indicate that patients with a preceding stroke have particularly unstable plaques that are vulnerable to dislodgment of plaque debris or thrombus during stenting. White matter disease might be considered an indicator for increased vulnerability of the brain toward periprocedural embolism.

In previous reports, the proportion of brain lesions persisting on follow-up FLAIR imaging ranged from 3% to 40% after stenting and 33% after endarterectomy. In contrast to these studies, we were able to compare the rate of conversion from acute to persisting lesions between patients randomized to stenting or endarterectomy. Although patients in the stenting group had more persisting lesions, their conversion rate from acute to persisting lesions was lower than in the endarterectomy group, which was most likely explained by smaller acute lesions. In line with previous studies, acute lesion volume was the only predictor for lesion persistence. This finding is in line with the clinical observation that in ICSS, most periprocedural clinical strokes associated with stenting recovered quickly and there was no difference in the proportion of patients with disabling symptoms after 1 month. The most important limitation of our study was the lack of power to perform interaction tests investigating whether risk factors for lesions differed significantly between treatment groups. Furthermore, FLAIR imaging may have missed small gliotic lesions at 1-month follow-up.

### Appendix

The following centers enrolled patients in the International Carotid Stenting Study (ICSS)-MRI Study (number of patients included per center): University Medical Centre, Utrecht, The Netherlands (129 patients); G.J. de Borst, G.A.P. de Kort, L.M. Jongen, L.J. Kappelle, T.H. Lo, W.P.T.H. Mali, F.L. Moll, H.B. van der Worp; University Hospital Basel, Switzerland (50 patients); L.H. Bonati, S.T. Engel, F. Fluri, S. Haller, A.L. Jacob, E. Kirsch, P.A. Lyrer, E.-W. Radue, P. Stierli, M. Wasner, S.G. Wetzel; Erasmus Medical Centre, Rotterdam, ...
Figure. Association between baseline variables and number of acute diffusion-weighted imaging lesions in the stenting group (blue) and in the endarterectomy group (red). Dots and horizontal lines are adjusted risk ratios (RR) and 95% confidence intervals (CIs) in the negative binomial regression model, calculated for each baseline variable, adjusted for interval between treatment and post-treatment MRI scan. RRs >1 (dots right of the vertical line) signify a higher lesion count in the comparative level (left in parentheses) than in the baseline level (right in parentheses) of the variables. Statistically significant P values (P<0.05) are in bold font. ARWMC indicates age-related white matter changes; and TIA, transient ischemic attack.

Acknowledgments
Dr Rostamzadeh wrote the article; Dr Zumbrunn performed statistical analysis. Drs Bonati and Jongen analyzed all scans. Dr Nederkoorn, S. Macdonald, Dr Lyrer, and Dr Kappelle contributed to data acquisition. Drs Bonati, Mali, Brown, van der Worp, and Engelster designed the International Carotid Stenting Study (ICSS)-MRI substudy and analyzed the scans in case of disagreement between the primary raters. Dr Brown is the chief investigator of ICSS. Dr Bonati conceived and supervised the present analysis. All authors reviewed the article and revised it critically for important intellectual content.

Sources of Funding
International Carotid Stenting Study (ICSS) was funded by grants from the Medical Research Council, the Stroke Association, Sanofi-Synthelabo, and the European Union. Funding for MRI scans done as part of the ICSS-MRI study was provided by grants from the Mach-Gaensslen Foundation, Switzerland, the Dutch Heart Foundation, and the Stroke Association, United Kingdom. Dr Bonati was supported by grants from the Swiss National Science Foundation.
Disclosures

S. Macdonald holds consultancy agreements with C.R. Bard and W.L. Gore. Dr van der Worp has received speaker’s fees from Servier, GlaxoSmithKline, and Sanofi-Aventis, and has served as a consultant to Bristol-Myers Squibb. Dr Engelbert has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim, Pfizer Inc, Sanofi-Aventis, and Shire plc; he has served on scientific advisory boards for Bayer and Boehringer Ingelheim and on the editorial board of Stroke. Dr Bonati has received funding for travel and served on scientific advisory boards for Bayer. The other authors report no conflicts.

References

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Stroke. published online December 24, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2013/12/23/STROKEAHA.113.003605

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### Supplemental Material

#### Study population

<table>
<thead>
<tr>
<th>Patients participating in the ICSS-MRI substudy (n=231)</th>
<th>*Patients not participating in the ICSS-MRI substudy (n=148)</th>
</tr>
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<tbody>
<tr>
<td>Pre- and early post-treatment MRI done</td>
<td>Additional 1-month follow-up MRI done</td>
</tr>
<tr>
<td>N patients included n (%)</td>
<td>231</td>
</tr>
<tr>
<td>Endarterectomy</td>
<td>107 (46%)</td>
</tr>
<tr>
<td>Stenting</td>
<td>124 (54%)</td>
</tr>
<tr>
<td>Age (years) median (IQR)</td>
<td>71.2 (63.7 - 76.9)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>163 (71%)</td>
</tr>
<tr>
<td>Vascular risk factors n (%)</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>159 (69%)</td>
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<tr>
<td>Diabetes</td>
<td>48 (21%)</td>
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<tr>
<td>Hyperlipidaemia</td>
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<tr>
<td>Smoking</td>
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<td>Peripheral artery disease</td>
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<tr>
<td>Coronary heart disease</td>
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<td>Qualifying event type n (%)</td>
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<tr>
<td>Retinal or TIA</td>
<td>137 (59%)</td>
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<tr>
<td>Hemispheric stroke</td>
<td>94 (41%)</td>
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<tr>
<td>Degree of stenosis n (%)</td>
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</tr>
<tr>
<td>Moderate</td>
<td>25 (11%)</td>
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<tr>
<td>Severe</td>
<td>206 (89%)</td>
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<tr>
<td>Contralateral severe stenosis or occlusion n (%)</td>
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<tr>
<td>Systolic blood pressure median (IQR)</td>
<td>158.5 (140.0-174.5)</td>
</tr>
<tr>
<td>Delay to treatment (days) median (IQR)</td>
<td>41.0 (17.0 - 82.5)</td>
</tr>
</tbody>
</table>

*Supplementary table I: Characteristics of patients included in the analyses of acute and persisting lesions. *Characteristics of patients not participating in the ICSS-MRI substudy at the seven substudy centres. DWI, diffusion-weighted imaging; IQR, interquartile range; MRI, magnetic resonance imaging; TIA, transient ischaemic attack.*