Effects of Carotid Endarterectomy or Stenting on Blood Pressure in the International Carotid Stenting Study (ICSS)

Aysun Altinbas, MD; Ale Algra, MD, PhD; Martin M. Brown, MD, FRCP; Roland L. Featherstone, PhD; L. Jaap Kappelle, MD, PhD; Gert Jan de Borst, MD, PhD; Willem P.Th.M. Mali, MD, PhD; H. Bart van der Worp, MD, PhD

Background and Purpose—Arterial hypotension is more frequently observed early after carotid artery stenting (CAS) than after carotid endarterectomy (CEA), but their long-term effects on blood pressure (BP) are unclear. We compared the effects of CAS and CEA on BP up to 1 year after treatment in the International Carotid Stenting Study.

Methods—Patients with symptomatic carotid stenosis were randomly allocated to CAS or CEA. Systolic and diastolic BP were recorded at baseline, at discharge, and at 1, 6, and 12 months. Antihypertensive medication use was recorded. A per-protocol analysis was performed. Patients with missing BP records were excluded. Between-group BP changes were compared and adjusted for baseline covariates with linear regression. Within-group BP changes were compared with the paired t test.

Results—CAS (N=587) and CEA (N=637) were both associated with a decrease in BP at discharge, which was greater after CAS (mean decrease in systolic BP between groups, 10.3 mm Hg; 95% CI, 7.3–13.3; P<0.0001; in diastolic BP, 4.1 mm Hg; 95% CI, 2.4–5.7; P<0.0001). During follow-up, BP changes were not different between groups. Adjustment for differences in baseline characteristics did not change the results. Fewer patients undergoing CAS used antihypertensive medication during follow-up than patients undergoing CEA (relative risk at 12 months, 0.91; 95% CI, 0.85–0.97; P=0.0073).

Conclusions—CAS leads to a larger early decrease in BP than CEA, but this effect does not persist over time. CAS may lessen the requirement for antihypertensive medication more than CEA.

Clinical Trial Registration—URL: www.controlled-trials.com. Unique identifier: ISRCTN25337470.

(Stroke. 2011;42:3491-3496.)

Key Words: angioplasty and stenting ▪ blood pressure ▪ carotid endarterectomy ▪ follow-up ▪ symptomatic carotid stenosis

A rterial hypotension is a frequent complication after carotid artery stenting (CAS) and has been attributed to manipulation of the carotid sinus and baroreceptor dysfunction.1–3 The arterial baroreceptors are stretch receptors located in the carotid sinuses and play a key role in short-term adjustments of blood pressure.4 In case series of CAS, hypotension or hemodynamic depression has been observed in up to half of cases.1,2,5 Hypertension and the related cerebral hyperperfusion syndrome are well-known complications after carotid endarterectomy (CEA).6 However, previous studies have reported varying degrees of hypotension in the early postoperative period after CEA as well.7–9 The long-term effects of CAS and CEA on blood pressure (BP) are unclear. Systolic BP (SBP) remained lower than at baseline after CEA but not after endovascular treatment up to 6 months follow-up in 1 small trial.10 However, an older study found no BP-lowering effect of CEA.11

We hypothesized that lower BPs would persist longer after CAS than after CEA and that this would affect the use of antihypertensive drugs. Therefore, we compared the change in BP after CAS and CEA up to 12 months of follow-up from baseline and compared the use of antihypertensive drugs between these groups during follow-up.

Methods

Subjects

All patients in this study were participants in the International Carotid Stenting Study (ICSS, ISRCTN25337470). ICSS is an...
international, randomized controlled trial comparing the risks, benefits, and cost-effectiveness of CAS and CEA in patients with a recently symptomatic carotid artery stenosis >50%. Patient criteria, randomization, and the results of an interim safety analysis have been described elsewhere. Patients were followed up at 30 days after treatment and at 6 and 12 months and each subsequent year after randomization. BPs were recorded according to center policy at randomization, at discharge after treatment, and at 1, 6, and 12 months follow-up between the 2 treatment groups and for the use of any antithrombotic medication or a statin during follow-up visits. Patients with missing BP records were excluded from the analysis.

Study Approval
ICSS was approved by local ethics committees for non-UK centers and by the Northwest Multicenter Research Committee in the United Kingdom. Each patient provided written informed consent.

Outcome Measures
The primary outcome measure of the present study was the changes in SBP and diastolic BP (DBP) between baseline and follow-up. The use of antihypertensive medication during follow-up was a secondary outcome measure.

Statistical Analysis
A per-protocol analysis was performed for the primary and secondary outcome measures. Because of the explanatory character of this study, analysis was restricted to the patients who received the allocated treatment as their first and only treatment; thus, patients with an abandoned treatment were excluded from the analyses.

Results
Figure 1 illustrates the flow of the 1713 enrolled patients in ICSS and provides reasons for exclusion from analysis. The present study population consists of the 766 patients undergoing CAS and 819 patients undergoing CEA with a single initiated and completed intervention.
Baseline Characteristics
Baseline SBP and DBP did not differ between the 2 groups, and there was no difference in the percentage of patients with treated hypertension. Fewer patients randomized to CAS had a history of cardiac failure at randomization; there were no other differences in baseline characteristics between the groups (Table 1).

Follow-Up
The mean length of postprocedural hospitalization did not differ between both groups (CAS, 3.2 days; CEA, 3.6 days; mean difference [MD], 0.4 days; 95% CI, −0.3 to 1.2; \( P = 0.272 \)). Patients without follow-up BP measurement at 1 month were 2.6 years older (95% CI, 0.5–4.6; \( P = 0.015 \)) and had 1.4 times more often a transient ischemic attack as a presenting symptom (95% CI, 1.1–1.8; \( P = 0.017 \)). The patients who did not have a follow-up BP measurement at 12 months were 2.7 years older (95% CI, 1.4–4.1; \( P < 0.0001 \)), had lower baseline SBP (−5.2 mm Hg; 95% CI, −9.1 to −1.3; \( P = 0.008 \)), and had 1.47 times more often a history of myocardial infarction (95% CI, 1.12–1.95; \( P = 0.006 \)). The baseline characteristics between patients undergoing CAS and patients undergoing CEA who were not seen for follow-up examination did not differ at 1 month, but patients undergoing CAS who did not have BP measurements at 12 months had 0.87 times less often treated hypertension at baseline (95% CI, 0.75–1.00; \( P = 0.047 \)).

BP Changes in Primary and Secondary Outcomes
SBPs and DBPs at baseline and during follow-up in both groups are shown in Figure 2. At discharge after treatment, the decrease in SBP and DBP was larger in the CAS group than after CEA (MD in SBP between groups, −1.1002; 95% CI, −2.5 to −0.7, \( P = 0.008 \); MD in DBP between groups: −1.1; 95% CI, −2.4 to −0.9, \( P < 0.0001 \)). In both groups, DBP decreased significantly between baseline and discharge after treatment. There were no differences between the groups at subsequent follow-up visits up to 12 months after randomization (Table 2). The differences between BP changes after CAS or CEA did not alter substantively after adjustment for age, sex, and history of cardiac failure. At 1 month from randomization, DBP was approximately 1 mm Hg higher than at baseline after each of the procedures, but this change was only significant after CAS. At 6 months, SBP was slightly lower than at baseline in both groups (MD SBP CAS, −2.5; 95% CI, −4.7 to −0.4, \( P = 0.022 \), MD SBP CEA, −3.0; 95% CI, −5.0 to −0.9, \( P = 0.005 \)), but at 12 months only in patients treated with CEA (MD SBP, −4.4; 95% CI, −6.5 to −2.2; \( P < 0.0001 \)). There were no differences between SBP at baseline and after 12 months follow-up in patients treated with CAS. Significantly fewer patients undergoing CAS were using antihypertensive medication than patients treated with CEA at all the follow-up appointments up to 1 year after randomization (Table 3). The numbers of patients treated with any antithrombotic medication or a statin during follow-up were similar between the 2 groups with the exception of a slightly less frequent use of any antithrombotic treatment in patients treated with CEA at 6 months (Supplemental Table I; http://stroke.ahajournals.org).
BP Changes in Patients With Treated Hypertension at Baseline

In a sensitivity analysis of patients with treated hypertension at baseline, the difference between both groups stayed evident for the decrease in BP at discharge (MDs between CAS and CEA in SBP, −9.2 mm Hg, 95% CI, −12.8 to −5.6, P<0.0001; DBP, −3.8, 95% CI, −5.8 to −1.9, P=0.0001). The differences between the changes between CAS and CEA during follow-up were largely of the same magnitude as in the overall analysis.

Discussion

The present study shows that both CAS and CEA are associated with a decrease in BP in the first days after treatment and that this decrease is larger after CAS than after CEA. The difference in BP between CAS and CEA disappeared at 1 month after treatment and was not seen during follow-up up to 1 year after randomization. Patients in both groups had slightly lower SBP at 12 months than at baseline, but the difference was only significant in the patients undergoing CEA. However, patients treated with CAS used antihypertensive drugs less frequently during the complete period of follow-up, whereas there were no major differences in the use of any antithrombotic medication or statins.

In observational studies, early postprocedural decreases in BP have been observed after both CEA7–9,11 and CAS.1,3,14–16 Controlled but nonrandomized studies have suggested that arterial hypotension is a more frequent complication after CAS than after CEA.17,18 In the randomized Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe

Table 2. Change in Blood Pressures From Baseline to Follow-Up

<table>
<thead>
<tr>
<th>No. (CAS, CEA)</th>
<th>SBP† (587–637)</th>
<th>DBP† (586–637)</th>
<th>SBP† (612–656)</th>
<th>DBP† (612–655)</th>
<th>SBP† (567–601)</th>
<th>DBP† (567–601)</th>
<th>SBP† (567–606)</th>
<th>DBP† (566–605)</th>
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<tr>
<td></td>
<td>−19.1</td>
<td>−9.0</td>
<td>−0.4</td>
<td>1.1</td>
<td>−2.5</td>
<td>−0.9</td>
<td>−2.1</td>
<td>−0.5</td>
</tr>
<tr>
<td></td>
<td>−21.3 to −16.9</td>
<td>−10.2 to −7.9</td>
<td>−2.4 to 1.7</td>
<td>0.0 to 2.1</td>
<td>−4.7 to −0.4</td>
<td>−2.1 to 0.2</td>
<td>−4.3 to 0.2</td>
<td>−1.7 to 0.6</td>
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<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.734</td>
<td>0.048</td>
<td>0.022</td>
<td>0.106</td>
<td>0.077</td>
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<td></td>
<td>−8.8</td>
<td>−5.0</td>
<td>−1.6</td>
<td>0.8</td>
<td>−3.0</td>
<td>−0.3</td>
<td>−4.4</td>
<td>−0.7</td>
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<td></td>
<td>−10.9 to −6.8</td>
<td>−6.1 to −3.8</td>
<td>−3.4 to 0.2</td>
<td>−0.2 to 1.9</td>
<td>−5.0 to −0.9</td>
<td>−1.4 to 0.9</td>
<td>−6.5 to −2.2</td>
<td>−1.9 to 0.4</td>
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<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.084</td>
<td>0.117</td>
<td>0.005</td>
<td>0.632</td>
<td>&lt;0.0001</td>
<td>0.208</td>
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<td></td>
<td>−10.3 (−13.3 to −7.3)</td>
<td>−4.1 (−5.7 to −2.4)</td>
<td>1.3 (−1.5 to 4.0)</td>
<td>0.2 (−1.3 to 1.7)</td>
<td>0.4 (−2.5 to 3.4)</td>
<td>0.7 (−2.3 to 1.0)</td>
<td>2.3 (−0.8 to 5.4)</td>
<td>0.2 (−1.4 to 1.8)</td>
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<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.370</td>
<td>0.775</td>
<td>0.772</td>
<td>0.430</td>
<td>0.147</td>
<td>0.793</td>
</tr>
</tbody>
</table>

Baseline measurement is at randomization. Negative within-group scores mean a decrease from baseline. Numbers represent patients with blood pressure records both at baseline and at follow-up.

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; MD, mean difference between CAS and CEA; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

*Effect estimates remained essentially the same after adjustment for age, sex, and cardiac failure.

†Measurement in mm Hg.

Figure 2. Graph demonstrating means and 95% CIs of systolic and diastolic blood pressures during the study period in both treatment groups. BP indicates blood pressure; CAS, carotid artery stenting; CEA, carotid endarterectomy; D, discharge; DBP, diastolic blood pressure; R, randomization; SBP, systolic blood pressure; CI, confidence interval.
Carotid Stenosis (EVA-3S) trial of CAS versus CEA in patients with symptomatic carotid artery stenosis, bradycardia or hypotension was observed during the first 30 days of treatment in 11 (4.2%) of the 261 patients treated with CAS and in none of the 259 patients treated with CEA.19 None of the other recent randomized trials of CAS versus CEA reported on early BP changes.12,20,21

Arterial hypotension during or after CAS has been explained by the stretching of the carotid sinus baroreceptors by the stent.5 CEA impairs BP homeostasis through ipsilateral carotid baroreceptor denervation. Some drugs used in the perioperative period such as opioids affect cardiovascular function by attenuation of sympathetic afferent and efferent activity, direct central or peripheral vagal stimulation, and direct and indirect effects on the myocardium and vascular smooth muscle.22

The effects of CEA and endovascular treatment on BP during a longer period of follow-up have been compared in a single-center substudy of the randomized Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) and in the EVA-3S trial.10 Of the 55 patients randomized to endovascular treatment in CAVATAS, 31 received percutaneous transluminal angioplasty alone and 24 were treated by stenting. At 6 months follow-up, SBP was 4.9 mm Hg lower compared with baseline in surgically treated patients, whereas there was a nonsignificant decrease of 1.9 mm Hg in patients treated with percutaneous transluminal angioplasty or stenting. In the EVA-3S trial, no statistically significant differences between patients treated with CEA and those treated with CAS were found in SBP and the use of antihypertensive drugs at 1 and 4 years follow-up. At 1 year, 82% of the patients randomized to stenting used antihypertensive medication as compared with 87% of the patients randomized to CEA.23 This difference may have missed statistical significance because of the smaller group sizes than in our study. In a substudy of the randomized North American Symptomatic Carotid Endarterectomy Trial (NASCET), no difference in SBP at 2 years was observed between patients treated with CEA and patients who received best medical care alone.24

More stringent BP control could further reduce the long-term risk of stroke in patients treated with CAS or CEA. Randomized trials have shown that the use of antihypertensive medication reduces the risk of recurrent stroke after stroke or transient ischemic attack.25 Guidelines for the prevention of stroke in patients with transient ischemic attack or stroke therefore recommend the use of antihypertensive medication for the large majority of patients.26,27 We consider overall BP control in ICSS unsatisfactory, because the majority of patients had SBPs above target levels in guidelines current at the time (Figure 2). The use of any antihypertensive medication at 1 year was just 67% of patients after CAS and 74% after CEA. This could be seen as indicating a reduced requirement for antihypertensive medication after CAS. However, the data also indicate considerable undertreatment of hypertension in both arms. In ICSS, medical care during follow-up was at the discretion of the treating physician, and at 1 year, this is most likely to have been the patient’s general practitioner.

Our study has limitations. First, there was no predefined BP measurement protocol in ICSS. However, we do not expect this to have a large effect on our findings, because we calculated BP difference scores per patient and because BP measurements were done according to the same policy in each center for patients treated with CAS or CEA. Second, no records were kept why BP measurements were missing, which could have caused selection bias. However, baseline characteristics of patients excluded from the analyses because of missing data did not differ greatly from those of the included patients. Excluded patients were older, which could have caused an underestimation of BP changes. In the present study, BP changes between baseline and follow-up at 1, 6, and 12 months were similar between CAS and CEA. The interpretation of this finding is hampered by the substantially more frequent use of any antihypertensive drug in patients treated with CEA despite a similar frequency of treated hypertension at baseline. In addition, no records were kept of the type of antihypertensive medication and dosages in both groups. It appears plausible that because of the larger early BP reduction after CAS than after CEA, antihypertensive medication was stopped and not resumed more frequently after CAS than after CEA. The absence of a difference in BP between CAS and CEA during follow-up after discharge despite lower use of antihypertensive medication suggests that CAS may have a long-term hypotensive effect compared with CEA. The analysis of data from further follow-up in ICSS beyond 1 year, which will be available after completion of the trial, may provide further insights into this effect.

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### Disclosures
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References
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### Supplemental table. Treatment with antithrombotic medication or statin during follow-up

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<tr>
<th>N (CAS, CEA)</th>
<th>CAS</th>
<th>CEA</th>
<th>RR</th>
<th>95% CI</th>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Antithrombotic medication (722-770)</td>
<td>705 (98%)</td>
<td>745 (97%)</td>
<td>1.01</td>
<td>0.99 to 1.03</td>
<td>0.295</td>
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<tr>
<td><strong>6 Months follow-up</strong></td>
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<tr>
<td>Antithrombotic medication (672-722)</td>
<td>660 (98%)</td>
<td>692 (96%)</td>
<td>1.03</td>
<td>1.01 to 1.04</td>
<td>0.009</td>
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<tr>
<td><strong>12 Months follow-up</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic medication (661-720)</td>
<td>632 (96%)</td>
<td>687 (95%)</td>
<td>1.00</td>
<td>0.98 to 1.03</td>
<td>0.860</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>N (CAS, CEA)</th>
<th>CAS</th>
<th>CEA</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td><strong>1 Month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin/lipid lowering medication (722-770)</td>
<td>556 (77%)</td>
<td>619 (80%)</td>
<td>0.96</td>
<td>0.91 to 1.01</td>
<td>0.112</td>
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<tr>
<td><strong>6 Months follow-up</strong></td>
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<tr>
<td>Statin/lipid lowering medication (672-722)</td>
<td>531 (79%)</td>
<td>595 (79%)</td>
<td>0.96</td>
<td>0.91 to 1.01</td>
<td>0.110</td>
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<tr>
<td><strong>12 Months follow-up</strong></td>
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<tr>
<td>Statin/lipid lowering medication (661-720)</td>
<td>537 (81%)</td>
<td>601 (84%)</td>
<td>0.97</td>
<td>0.93 to 1.02</td>
<td>0.278</td>
</tr>
</tbody>
</table>

Data are numbers (%). CAS, carotid artery stenting; CEA, carotid endarterectomy; RR, risk ratio.
Abstract 15

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(Stroke. 2011;42:3491-3496.)

Key Words: angioplasty and stenting, blood pressure, carotid endarterectomy, follow-up, symptomatic carotid stenosis

Table 2. Change in Blood Pressures From Baseline to Follow-Up

<table>
<thead>
<tr>
<th>No. (CAS, CEA)</th>
<th>Change discharge baseline</th>
<th>Change 1-mo follow-up baseline</th>
<th>Change 6-mo follow-up baseline</th>
<th>Change 12-mo follow-up baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (567-637)</td>
<td>−19.1</td>
<td>−0.4</td>
<td>−2.5</td>
<td>−0.9</td>
</tr>
<tr>
<td>DBP (567-637)</td>
<td>−9.1</td>
<td>−2.0</td>
<td>−0.3</td>
<td>−2.1</td>
</tr>
<tr>
<td>SBP (612-656)</td>
<td>−0.4</td>
<td>−2.4</td>
<td>0.74</td>
<td>−4.7</td>
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<td>DBP (612-655)</td>
<td>−0.1</td>
<td>0.0</td>
<td>0.04</td>
<td>0.2</td>
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<td>SBP (657-601)</td>
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<td>SBP (656-605)</td>
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<td>DBP (656-605)</td>
<td>−0.5</td>
<td>−2.0</td>
<td>0.077</td>
<td>0.632</td>
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</table>

Baseline measurement is at randomization. Negative within-group scores mean a decrease from baseline. Numbers represent patients with blood pressure records both at baseline and at follow-up.

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; DBP, diastolic blood pressure; MD, mean difference between CAS and CEA; SBP, systolic blood pressure.

Clinical Trial Registration: URL: www.controlled-trials.com. Unique identifier: ISRCTN25337470.