Periprocedural Hemodynamic Depression Is Associated With a Higher Number of New Ischemic Brain Lesions After Stenting in the International Carotid Stenting Study-MRI Substudy

Aysun Altinbas, MD; Ale Algra, MD, PhD; Leo H. Bonati, MD, PhD; Martin M. Brown, MD, FRCP; L. Jaap Kappelle, MD, PhD; Gert Jan de Borst, MD, PhD; Jeroen Hendrikse, MD, PhD; Ingeborg van der Tweel, PhD; H. Bart van der Worp, MD, PhD; on behalf of the ICSS Investigators

**Background and Purpose**—Carotid artery stenting (CAS) is associated with a higher risk of both hemodynamic depression and new ischemic brain lesions on diffusion-weighted imaging than carotid endarterectomy (CEA). We assessed whether the occurrence of hemodynamic depression is associated with these lesions in patients with symptomatic carotid stenosis treated by CAS or CEA in the randomized International Carotid Stenting Study (ICSS)-MRI substudy.

**Methods**—The number and total volume of new ischemic lesions on diffusion-weighted imaging 1 to 3 days after CAS or CEA was measured in the ICSS-MRI substudy. Hemodynamic depression was defined as periprocedural bradycardia, asystole, or hypotension requiring treatment. The number of new ischemic lesions was the primary outcome measure. We calculated risk ratios and 95% confidence intervals per treatment with Poisson regression comparing the number of lesions in patients with or without hemodynamic depression.

**Results**—A total of 229 patients were included (122 allocated CAS; 107 CEA). After CAS, patients with hemodynamic depression had a mean of 13 new diffusion-weighted imaging lesions, compared with a mean of 4 in those without hemodynamic depression (risk ratio, 3.36; 95% confidence interval, 1.73–6.50). The number of lesions after CEA was too small for reliable analysis. Lesion volumes did not differ between patients with or without hemodynamic depression.

**Conclusions**—In patients treated by CAS, periprocedural hemodynamic depression is associated with an excess of new ischemic lesions on diffusion-weighted imaging. The findings support the hypothesis that hypoperfusion increases the susceptibility of the brain to embolism.

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

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Key Words: angioplasty ■ bradycardia ■ carotid stenosis ■ endarterectomy, carotid ■ hypotension ■ stents

In patients with symptomatic carotid artery stenosis, carotid artery stenting (CAS) is associated with a higher risk of periprocedural stroke than carotid endarterectomy (CEA).1 Patients treated by CAS also more frequently have new ischemic lesions on post-treatment MRI scans with diffusion-weighted imaging (DWI).2 The cause of the higher risk of new cerebral ischemia early after CAS compared with CEA is uncertain.

Emboli from the carotid artery plaque during stent deployment or arterial dissection is generally held responsible for the majority of new ischemic lesions during carotid revascularization. During CAS and CEA, cerebral microembolic signals are often detected with transcranial Doppler.3 A high frequency of these signals has been associated with a higher risk of stroke,4 but the majority of the underlying emboli do not lead to cerebral ischemia.5 It has been proposed that under circumstances of a normal cerebral perfusion, most of these emboli are cleared by the cerebral circulation and that hypoperfusion increases the risk of a focal ischemic lesion.6 This is supported by a study that showed that patients with impaired perfusion in the hemisphere ipsilateral to the carotid artery stenosis before stenting had more ischemic lesions...
on DWI after the intervention than patients with a normal perfusion.7

Both CAS and CEA may be accompanied by periproce-
dural hemodynamic depression or other cardiovascular symp-
toms.8 In the International Carotid Stenting Study (ICSS),9
severe arterial hypotension, bradycardia, or asystole occurred
twice as often in patients treated by CAS than by CEA.10 Such
hemodynamic depression may lead to a temporary reduction
in cerebral perfusion.11,12

We hypothesized that hemodynamic depression during
CAS or CEA will impair the washout of emboli during revas-
cularization and will therefore be associated with a higher risk
of new DWI lesions on MRI performed soon after revascular-
ization. Therefore, we compared the number and volume of
new DWI lesions after CAS or CEA in patients who experi-
enced hemodynamic depression with the number and volume
of lesions in those without hemodynamic depression.

Methods

Subjects
All patients in this study were participants in the ICSS-MRI sub-
study; a prospective multicenter substudy in 7 centers within ICSS
(ISRCTN25337470).13 ICSS is an international, randomized con-
trolled trial comparing the risks and benefits of CAS versus CEA in
patients with recently symptomatic carotid artery stenosis 50%.
The design of both studies, patient eligibility criteria, the results of an
interim safety analysis of ICSS, and the main results of the MRI sub-
study have been reported previously.1,9

Study Approval
ICSS (ISRCTN25337470) and the MRI substudy were approved by
local ethics committees for non-UK centers and by the Northwest
Multicentre Research Committee in the United Kingdom. All patients
provided written informed consent.

Stenting and Surgery Procedures
The ICSS study protocol prescribed that all patients should receive the
best medical care throughout the entire study period. The combina-
tion of aspirin and clopidogrel was recommended to cover stenting
procedures. Intraprocedural heparin was mandatory at a dose deter-
mined by the operator. Approved cerebral protection devices were
recommended for use during stenting, when it was feasible and safe
to deploy them, as well as the intravenous administration of atropine
or a similar agent just before balloon dilatation or stent placement.
Endarterectomy procedures included the use of local or general anes-
thesia and shunts or patches as determined by the operating surgeon.15

Data Collection and Definitions of Hemodynamic
Events
At study inclusion, data were collected on the patients’ present-
ing symptoms, demographic characteristics, and cardiovascular risk fac-
tors. Hemodynamic depression was defined as the occurrence during
or soon after revascularization of ≥1 of the physiologically related
symptoms of bradycardia (defined as a heart rate of ≤40 bpm), asysto-
tole, or hypotension requiring treatment.10 In ICSS, no fixed cutoff
blood pressure value was set to define hypotension requiring treat-
ment. Treatment of any hemodynamic complication was at the discre-
ton of the treating physician. Investigators were asked to complete
the forms as soon as possible after the revascularization procedure,
but it was not mandatory to provide information on the exact tim-
ing and duration of hemodynamic changes after revascularization.
Therefore, hemodynamic depression could occur at any time between
the start of the intervention and discharge.

Imaging
MRI scans at field strengths of 1.5 T or 3.0 T were performed 1 to
7 days before treatment (pretreatment MRI) and 1 to 3 days after
(1.5-T scanners (CAS, n=7; CEA, n=16) and 165 were stud-
ied with 1.5-T scanners (CAS, n=7; CEA, n=78). Prettreatment
and post-treatment scans included DWI sequences. On each scan,
the number and volume of hyperintense lesions on DWI was mea-
sured. New periprocedural ischemic brain lesions were defined as
hyperintense DWI lesions on post-treatment MRI that were not pres-
ent on pretreatment MRI. In each patient, the total number of
new DWI lesions (lesion count) and the total lesion volume were
assessed. White matter lesions, or age-related white matter changes
(ARWMCs), are correlates of small vessel disease on imaging of
brain parenchyma.14 Quantification of these lesions was done on
the pretreatment fluid-attenuated inversion recovery sequences
with the ARWMC scale.15

Outcome Measures
The primary outcome measure of the present study was the total
count of new hyperintense DWI lesions on the post-treatment scan
that were not present on the pretreatment scan. The total volume of
these lesions was a secondary outcome measure.

Statistical Analysis
For this study, we performed a per-protocol analysis including only
patients who completed the allocated treatment as their first and only
ipsilateral treatment. Patients who received the alternative revascular-
zation procedure (crossovers) or received no revascularization were
therefore excluded from the analyses.

Because of the differences in the occurrence of hemodynamic de-
pression and in the risk of new ischemic lesions between CAS and
CEA, we performed all analyses separately for each of the 2 treat-
ment groups. We compared the number of new DWI lesions between
patients with or without hemodynamic depression with Poisson regre-
sion and calculated crude risk ratios (RRs) with corresponding
95% confidence intervals (CIs). To accommodate the large variance
in the lesion count data, we adapted the scale parameter of the Poisson
model. We adjusted crude RR estimates for the 5 largest imbalances
in baseline characteristics per treatment. In a post hoc analysis, we
also adjusted for the use of a cerebral protection device or atropine
during stenting.

For log-transformed DWI total lesion volumes, we calculated
mean differences with corresponding 95% CIs between the patients
with and without hemodynamic depression with linear regression and
adjusted for imbalances in baseline characteristics.

Results

Baseline Characteristics
There were 231 patients included in the ICSS-MRI substudy.2
Two CAS patients with missing information on hemody-
namic complications were excluded from the current analy-
ses. Therefore, this study included a total of 229 patients, of
whom 122 were treated by CAS and 107 by CEA. Fifteen
patients (12%) treated by CAS and 9 (8%) treated by CEA
had hemodynamic depression requiring treatment. Baseline
characteristics of the patients are shown in Table 1. In patients
treated by CAS, relevant baseline differences in the patients
with and those without hemodynamic depression comprised
baseline ARWMC score, sex, smoking history, the index isch-
emic event, and a history of multiple ischemic events before
randomization. In patients treated by CEA, these were base-
line ARWMC score, age, sex, smoking history, and systolic
blood pressure at randomization.

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The mean patient stay was 3.5 days in the hospital after the intervention, without differences according to treatment or the occurrence of hemodynamic depression (data not shown). In 44 (36%) CAS procedures, a cerebral protection device was used. In 12 (10%) CAS patients, information on the use of cerebral protection devices was missing. Hemodynamic depression occurred in 6 (14%) CAS patients treated with such a device and in 9 (14%) CAS patients treated without cerebral protection (RR, 1.0; 95% CI, 0.4–2.6). Atropine was administered during stenting in 75 (61%) CAS patients; information on atropine use was not available in 21 (17%) patients. Thirteen (17%) patients treated with atropine had periprocedural hemodynamic depression and 2 (8%) patients not treated with atropine (RR, 2.3; 95% CI, 0.5–9.3).

### Table 1. Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>CAS (n=122)</th>
<th>CEA (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD+ (n=15)</td>
<td>HD– (n=107)</td>
</tr>
<tr>
<td>Age, y</td>
<td>70 (8.7)</td>
<td>70 (9.4)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>13 (87%)</td>
<td>72 (67%)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>10 (67%)</td>
<td>73 (68%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>159 (24)</td>
<td>156 (26)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>84 (11)</td>
<td>82 (13)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (13%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4 (27%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1 (7%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (7%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Diabetes mellitus type II</td>
<td>2 (13%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1 (7%)</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 (20%)</td>
<td>35 (36%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>8 (53%)</td>
<td>40 (41%)</td>
</tr>
<tr>
<td>Treated hyperlipidemia</td>
<td>9 (60%)</td>
<td>68 (64%)</td>
</tr>
<tr>
<td>Degree of symptomatic carotid stenosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%–69%</td>
<td>1 (7%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>70%–99%</td>
<td>14 (93%)</td>
<td>93 (87%)</td>
</tr>
<tr>
<td>Degree of contralateral stenosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>9 (60%)</td>
<td>70 (65%)</td>
</tr>
<tr>
<td>50%–69%</td>
<td>1 (7%)</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>70%–99%</td>
<td>3 (20%)</td>
<td>20 (19%)</td>
</tr>
<tr>
<td>Occluded</td>
<td>2 (13%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>ARWMCs at baseline</td>
<td>4.7 (5.1)</td>
<td>5.5 (4.7)</td>
</tr>
<tr>
<td>Most recent ipsilateral event†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>4 (27%)</td>
<td>19 (18%)</td>
</tr>
<tr>
<td>Transient ischemic event</td>
<td>4 (27%)</td>
<td>37 (35%)</td>
</tr>
<tr>
<td>Ischemic hemispheric stroke</td>
<td>5 (33%)</td>
<td>48 (45%)</td>
</tr>
<tr>
<td>Retinal infarction</td>
<td>2 (13%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Multiple events before randomization</td>
<td>6 (40%)</td>
<td>49 (50%)</td>
</tr>
<tr>
<td>Stroke before index event</td>
<td>1 (7%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Modified Rankin score at randomization</td>
<td>0–2‡</td>
<td>14 (93%)</td>
</tr>
</tbody>
</table>

Data are number (%) or mean (SD). ARWMCs indicates age-related white matter changes; CABG, coronary artery bypass grafting; CAS, carotid artery stenting; CEA, carotid endarterectomy; HD, hemodynamic depression (hypotension requiring treatment, severe bradycardia, and asystole); and mRS, modified Rankin scale.

*Degree of stenosis measured by North American Symptomatic Carotid Endarterectomy Trial (NASCET) method at randomization center.

†If 2 events were reported on the same day, the more serious was counted (stroke > retinal infarction > transient ischemic attack > amaurosis fugax).

‡Some Rankin scores of ≥3 were caused by nonstroke disability.
**DWI Lesions**

In both patient groups, there was no difference in the proportion of patients with ≥1 new DWI lesion between patients who had hemodynamic depression compared with those without hemodynamic depression (Tables 2 and 3). After CAS, patients with hemodynamic depression had a mean of 13 new DWI lesions versus a mean of 4 in those without hemodynamic depression (RR, 3.36; 95% CI, 1.73 to 6.50). Adjustments for the potentially confounding baseline factors (ARWMC score, sex, smoking history, the index ischemic event, and history of multiple ischemic events) had no major influence on the crude effect estimate (Tables 2 and 3). The occurrence of hemodynamic depression had no effect on lesion count after CEA (RR, 0.71; 95% CI, 0.13 to 3.86; Tables 2 and 3). This did not change after adjustment for the baseline ARWMC score, age, sex, smoking history, or systolic blood pressure. Most patients had their postprocedural MRI within 1 day of the intervention. Table I in the online-only Data Supplement shows the distribution of lesions in patients with or without hemodynamic depression based on the timing of the postprocedural scan. Post hoc adjustments for the use of a cerebral protection device or atropine during stenting did not affect the outcomes (Tables 2 and 3).

For both CAS and CEA, there were no differences in total DWI lesion volume between patients with hemodynamic depression and those without hemodynamic depression after log transformation. The mean differences did not change essentially after adjustment (Tables 2 and 3). Table II in the online-only Data Supplement shows the data of the combined treatment groups.

**Discussion**

We found that in patients who were treated by CAS, the occurrence of periprocedural hemodynamic depression was associated with a >3 times higher number of new ischemic brain lesions on DWI compared with patients without this complication. This effect was not observed in patients who had hemodynamic depression after CEA.

Our finding of an increased occurrence of new ischemic lesions on DWI in patients with hemodynamic depression after CAS is in line with previous observations in uncontrolled studies, in which periprocedural hemodynamic depression was associated with increased rates of stroke or death after CAS. However, this association has not been found in every study.

In the current study, 12% of the patients treated by CAS had periprocedural hemodynamic depression requiring treatment, whereas uncontrolled series of patients treated by CAS have reported frequencies of arterial hypotension or hemodynamic depression ranging from 19% to 51%. This difference may be explained by ascertainment bias because the assessment of hemodynamic depression was a primary aim of some of the observational studies but not of ICSS. In addition, definitions for hypotension or hemodynamic depression as a composite measure differed between ICSS and the observational studies. Most of the observational studies defined arterial hypotension as a drop in systolic blood pressure below a fixed value, or as a specific absolute fall in blood pressure, whereas in ICSS, hypotension was only reported if this required treatment. We therefore could have missed less severe episodes of hypotension.

In ICSS, hemodynamic depression requiring treatment occurred in 13.8% of the patients treated by CAS and in 7.2% of the patients treated by CEA. In the ICSS-MRI substudy, 35% of the patients treated by CAS and 9% of those treated by CEA had ≥2 new ischemic lesions on DWI. Because the number of patients with ≥2 new DWI lesions after CAS was substantially higher than the number with hemodynamic depression requiring treatment, it is clear that the difference in the risk of hemodynamic depression requiring treatment between CAS and CEA is not the only determinant of the difference in the occurrence of new ischemic lesions between the 2 treatments. However, smaller reductions in blood pressure that did not require treatment were not reported in ICSS, and it is possible that these may have contributed to the development of new lesions in some patients not fulfilling our definition of hemodynamic depression. Our assumption that in

| Table 2. Hemodynamic Depression and New Ischemic Brain Lesions (Lesion Count) |
|---------------------------------|----------------|----------------|----------------|
|                                | CAS (n=122)    | CEA (n=107)    |                |
|                                | HD+ (n=15)     | HD− (n=107)    | RR (95% CI)    |
| At least 1 new DWI lesion       | 8 (53%)        | 52 (49%)       | 1.10 (0.66–1.83) |
| Count DWI lesions, mean (SD)    | 13 (30)        | 4 (10)         | 3.36 (1.73–6.50) |
| Adjustment                      |                |                | 0.71 (0.13–3.86) |
| ARWMCs                          | ...            | ...            | 0.82 (0.15–4.40) |
| Age                             | ...            | ...            | 0.76 (0.14–4.14) |
| Sex                             | ...            | ...            | 0.71 (0.13–3.87) |
| Smoking (present and past)      | ...            | ...            | 0.83 (0.15–4.63) |
| Ipsilateral index event         | ...            | ...            | ...            |
| Multiple events before index event | ...        | ...            | 1.08 (0.22–5.32) |
| SBP                             | ...            | ...            | ...            |
| Cerebral protection device use   | ...            | ...            | ...            |
| Atropine use                    | ...            | ...            | ...            |

**ARWMCs indicates age-related white matter changes; CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; DWI, diffusion-weighted imaging; HD, hemodynamic depression (hypotension requiring treatment, severe bradycardia, and asystole); RR, risk ratio; and SBP, systolic blood pressure.**
ICSS reductions in blood pressure after CAS did occur more frequently than reported is supported by the fact that at discharge, systolic blood pressures were 10 mm Hg lower after CAS than after CEA. Moreover, in the present study, hemodynamic depression remained strongly associated with an increased number of new ischemic lesions after adjustments for potentially confounding baseline factors.

The main source for periprocedural ischemia after CEA or CAS is thromboembolism. Our findings are consistent with the hypothesis that hypoperfusion increases the susceptibility of the brain to infarction from emboli by impairing washout of emboli from the cerebral circulation. Hemodynamic depression after carotid revascularization procedures occurs when carotid sinus stimulation leads to bradycardia, by affecting the sinus and atrioventricular nodes, and to hypotension, by peripheral vasodilatation. In ICSS as a whole, we found no evidence that the increased rate of hemodynamic depression after CAS explained the excess of stroke and death within 30 days of CAS versus CEA. However, the number of clinical outcome events was relatively small. MRI increases the number of ischemic insults detected as a result of revascularization, increasing the sensitivity to differences between patients. Using ischemic lesions on DWI as a surrogate marker for ischemic stroke after carotid revascularization, we have now been able to correlate hemodynamic depression with postprocedural cerebral ischemia.

Our study suggests that prevention of severe hypotension and bradycardia might reduce the number of new DWI lesions after CAS, but this can only be tested in a new randomized trial. It has been proposed that in case of hemodynamic depression after stenting, patients should be treated with intravenous fluids, atropine and α-agonists, and that any oral antihypertensive medication should be discontinued. However, treatment options may vary based on patient characteristics and on the severity of hemodynamic symptoms.

In contrast to patients treated by CAS, we found no evidence that hemodynamic depression was associated with a higher number of new ischemic lesions in patients treated by CEA. However, the number of new ischemic lesions in patients treated by CEA was very low, and we therefore lacked statistical power to detect any association. Total lesion volumes did not differ between patients with or without hemodynamic depression; however, our data suggest that the individual lesions were smaller in patients who had hemodynamic depression.

Strengths of this study are the prospective assessment of hemodynamic depression and of new ischemic lesions on DWI, in addition to its relatively large sample size. A limitation is the lack of direct periprocedural cerebral perfusion measures. We therefore cannot confirm that hemodynamic depression resulted in compromised cerebral perfusion. Second, in ICSS, it was not mandatory to report the exact timing of periprocedural hemodynamic complications, although the investigators were asked to complete the form as soon as possible after the procedure. It is therefore possible that these could have occurred at any time between the start of the revascularization and discharge. However, based on observations in uncontrolled series, we expect that the majority of hemodynamic events would have occurred during or immediately after CAS or CEA. For this reason, most if not all MRI scans will have been performed after the development of hemodynamic depression. Moreover, we do not have data on the duration of hemodynamic depression; therefore, we cannot refute the possibility that duration of hemodynamic compromise influences the amount of new ischemic lesions. In the ICSS-MRI substudy, the interval to the postprocedural MRI was longer after CEA than after CAS: median 1 day (interquartile range, 1–2) and 1 (interquartile range, 1–1), respectively, P=0.008. And we could therefore have missed additional new ischemic lesions after CAS. Finally, apart from the severity of the stenosis, we do not have information on plaque characteristics.

### Conclusions

In patients treated by CAS, hemodynamic depression was associated with a higher number of new ischemic lesions on...
postprocedural DWI MRI. This finding suggests that avoidance of periprocedural hypotension and bradycardia may reduce the risk of DWI lesions occurring during CAS.

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Disclosures

None.

References

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SUPPLEMENTAL MATERIAL
**SUPPLEMENTAL TABLE I**

**Supplemental Table I.** Timing of new lesions between patients with or without hemodynamic depression

<table>
<thead>
<tr>
<th></th>
<th>HD+</th>
<th>HD-</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N total</td>
<td>229</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=205</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Postprocedural MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At same day or day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 lesion</td>
<td>8 (40%)</td>
<td>50 (34%)</td>
<td>1.18 (0.66-2.10)</td>
</tr>
<tr>
<td>≥ 2 lesions</td>
<td>5 (25%)</td>
<td>31 (21%)</td>
<td>1.19 (0.52-2.69)</td>
</tr>
<tr>
<td><strong>Total 167 (73%)</strong></td>
<td>20</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>After day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 lesion</td>
<td>3 (75%)</td>
<td>17 (29%)</td>
<td>2.56 (1.28-5.12)</td>
</tr>
<tr>
<td>≥ 2 lesions</td>
<td>3 (75%)</td>
<td>12 (21%)</td>
<td>3.63 (1.70-7.73)</td>
</tr>
<tr>
<td><strong>Total 62 (27%)</strong></td>
<td>4</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HD, hemodynamic depression; RR, risk ratio.
<table>
<thead>
<tr>
<th></th>
<th>HD+ N=24</th>
<th>HD- N=205</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any new DWI lesion (yes/no)</strong></td>
<td>11 (46%)</td>
<td>67 (33%)</td>
<td>1.40 (0.87-2.26)</td>
</tr>
<tr>
<td><strong>Count DWI lesions Mean (SD)</strong></td>
<td>8.46 (24.4)</td>
<td>2.36 (7.4)</td>
<td>3.58 (2.07-6.22)</td>
</tr>
<tr>
<td><strong>Adjustment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARWMC</td>
<td>3.71 (2.14-6.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>4.02 (2.36-6.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>3.41 (1.96-5.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (present and past)</td>
<td>3.82 (2.21-6.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral index event</td>
<td>3.63 (2.10-6.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple events before index event</td>
<td>3.37 (1.94-5.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>3.54 (2.03-6.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>3.10 (1.87-5.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median volume (Q1-Q3)</strong></td>
<td>0 (0.00-0.26)</td>
<td>0 (0.00-0.05)</td>
<td>0.40 (-0.04-0.84)</td>
</tr>
<tr>
<td><strong>Adjustment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARWMC</td>
<td>0.43 (-0.00-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.42 (-0.01-0.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.39 (-0.05-0.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (present and past)</td>
<td>0.43 (-0.01-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral index event</td>
<td>0.41 (-0.03-0.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple events before index event</td>
<td>0.40 (-0.06-0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.41 (-0.03-0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>0.36 (-0.07-0.79)</td>
<td></td>
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</tr>
</tbody>
</table>

ARWMC indicates age-related white matter changes; CAS, carotid artery stenting; CEA, carotid endarterectomy; HD, hemodynamic depression (hypotension requiring treatment, severe bradycardia, and asystole); MD, mean difference; Q1-Q3, interquartile range; RR, risk ratio; SBP, systolic blood pressure. *mean difference after log transformation; a positive difference indicates larger volumes with HD+.