Ischemic Complications after Carotid Artery Stenting Associated with Stent Cell Design: Closed-cell versus Open-cell Stents

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Objective: The influence of stent cell design on cerebral embolism after carotid artery stenting (CAS) is not well understood. The purpose of this study was to evaluate the influence of stent cell design on the incidence of periprocedural cerebral embolism in tailored CAS.

Materials and Methods: A total of 114 symptomatic and asymptomatic cases of carotid artery stenosis were treated with CAS. The stent type included closed-cell stent and open-cell stent (48 closed-cell and 66 open-cell stents). Procedural, imaging, and clinical outcomes were retrospectively assessed and compared between the closed-cell stent group and the open-cell stent group.

Results: Periprocedural neurological complications were not significantly different between the two groups (p = 0.4). The presence of new ischemic lesions and number of new ischemic lesions on post procedural examination were not significantly different between the two groups (p = 0.32, p = 0.4).

Conclusion: Stent selection according to the morphological and clinical characteristics is thought to be important to reduce periprocedural ischemic complications.

Keywords: complication, carotid artery stenosis, carotid artery stenting, stent cell design

Introduction

Carotid endarterectomy (CEA) is an effective treatment for the prevention of stroke in patients with significant carotid artery stenosis.1-5) Recent developments in neuro-interventional techniques and devices have led to carotid artery stenting (CAS) being a viable option in CEA.

Recent data from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) demonstrated similar outcomes and safety for both CAS and CEA.6) However, cerebral ischemic complications occurred more frequently among patients undergoing CAS compared with CEA (4.1% vs 2.3%).

Embolic protection devices (EPDs) have been developed to prevent intraprocedural embolism. Recent interest has focused on the effects of EPDs in preventing intraprocedural embolism.7,8) Safety of tailored CAS using individually selected EPDs and stent types based on morphological and clinical characteristics has been recognized.9) Our definition of tailored CAS is to select proper EPDs, stent types and access route including trans femoral artery approach, trans brachial artery approach and direct carotid artery approach according to morphological characteristics and patients’ neurological characteristics. Logically, closed-cell stent designs cover a greater percentage of the vascular wall within the stented region, and may better contain the fractured and dilated plaque during CAS compared with open-cell stent designs.10,11) However, the effects of stent
Materials and Methods

We retrospectively analyzed the medical records of patients who underwent CAS for symptomatic and asymptomatic carotid artery stenosis at our institution from April 2010 to June 2015. During this period, 121 cases were treated with CAS. The indications of CAS were carotid artery stenosis ≥50% in symptomatic patients and ≥80% in asymptomatic patients. A total of seven cases were excluded; four cases underwent acute CAS because of progressing stroke, and three cases used two different types of stents. Finally, 114 cases were included in this study. Clinical, procedural, and imaging outcomes were assessed and compared.

Morphological characteristics of the carotid artery lesion were evaluated on DSA, MR plaque imaging, 3D-CTA, and carotid duplex ultrasound. The degree of stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Vulnerable plaque was defined as high intensity area in the plaque compared with the sternocleidomastoid muscle detected by magnetic resonance (MR) plaque imaging or echo luent plaque detected by carotid duplex ultrasound. Pseudo-occlusion of the internal carotid artery (ICA) was defined according to the following criteria reported by Hirata et al.: severe ICA stenosis with a collapsed distal ICA, back filling of the ipsilateral carotid siphon via the ophthalmic artery in the early arterial phase, and delayed antegrade flow of the patent ICA in the late arterial phase. Existence of coronary artery stenosis or occlusion was examined before the CAS procedure in all cases. The coronary artery disease (CAD) was treated prior to the CAS if the lesion was judged to be under necessity of treatment by cardiologist. In symptomatic cases, CAS procedure was performed more than 3–4 w after symptom onset. Type of stents included closed-cell stent, Carotid Wallstent Monorail (Boston Scientific, Natick, MA, USA) and open-cell stent, Precise (Cordis Corporation, Miami, Lakes, FL, USA; and Protégé, ev3 Inc., Plymouth, MN, USA). Stent selection was at operator’s discretion according to the background characteristics. EPDs included distal filter protection, distal balloon protection, proximal protection as flow reversal technique, and a combination of distal and proximal protection. Vasopressor was administrated intravenously to maintain adequate cerebral perfusion when systolic blood pressure (sBP) was decreased under 80 mmHg and sustained after CAS procedure. Postprocedural diffusion weighted image (DWI) was performed within 72 hrs after the CAS procedure in all cases. DWI was evaluated for the presence of new ischemic lesions in the ipsilateral hemisphere compared with DWI before the CAS procedure.

CAS procedure

All patients received statin at least 14d before the procedure and dual antiplatelet therapy with aspirin and clopidogrel, aspirin and cilostazol, or clopidogrel and cilostazol at least 7d before the procedure. All CAS procedures were performed under local anesthesia and intravenous sedation. Under adequate systemic heparin administration, pre dilatation, stent placement, and post dilatation if necessary were performed using EPDs. CAS technique including most appropriate EPD and stent type was at operator’s discretion according to the morphological and clinical characteristics. For tight, vulnerable, or thrombus-containing plaque, proximal protection was preferentially used. Our stent selection strategy was as follows: Closed-cell stent is suitable for cases of vulnerable plaque and straight lesions. Open-cell stent is suitable for cases of tortuous lesions and fibrous or calcified lesions. The diameter of the stent was 1–2 mm larger than the diameter of carotid artery lumen proximally to the stenosis. Atropine was administered before pre dilatation in all cases. Following CAS, dual antiplatelet therapy was continued for at least three months, and argatroban was administrated intravenously at operator’s discretion.

Clinical, imaging and procedural assessment

We compared base line characteristics of the patients, intraprocedural usage of EPDs, periprocedural neurological complications, and new ischemic lesions detected on postprocedural DWI between the closed-cell stent group and the open-cell stent group. All patients underwent pre- and postoperative neurological evaluations by specialized neurovascular physicians. Neurological complications were defined as transient ischemic attack (TIA), stroke, and death within 30d after CAS. TIA was defined as a neurological symptom disappeared within 24 hrs without cerebral intolerance due to balloon protection. Stroke including any minor or major stroke, was defined as a neurological deficit that persisted for >24 hrs. Intraprocedural
ischemic complication due to sustained cerebral intolerance was diagnosed by DWI examination and excluded from intraprocedural symptomatic embolic complication. Death was defined as any death related to neurovascular causes.

### Statistical analysis

Univariate analysis was used to compare the two stent groups. Fisher’s exact test was used to analyze category comparisons. Mann–Whitney U test and standard t-test were used to compare continuous variables as appropriate. Statistical significance was defined as p < 0.05. Statistical analyses were performed using R 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). This study was approved by Institutional Review Board of Kyoto Second Red Cross Hospital.

### Results

The patients included 99 men and 15 women with a mean age of 74.8 yrs (range 55–87). CAS was performed in 80 symptomatic cases (70.2%) and 34 asymptomatic cases (29.8%). EPDs were used in all cases. Closed-cell stents were used in 48 cases (42.1%). Open-cell stents were used in 66 cases (57.9%) including Precise (n = 47) and Protégé (n = 19) stent types. Baseline characteristics of the patients and morphological characteristics of the lesions were summarized and compared in Table 1. Nine cases (7.9%) had a pseudo-occlusion of the carotid artery and three cases (2.6%) had a severe calcification of the carotid artery. There were no significant differences with respect to age, sex, diabetes mellitus, dyslipidemia, and CAD between the two groups. Hypertension was significantly more frequent in the closed-cell stent group compared with the open-cell stent group (95.8% vs 75.8%; p = 0.007). There were no significant differences in the morphological characteristics of the lesions between the two groups. However, symptomatic cases were more frequent in the closed-cell stent group compared with the open-cell stent group. Proximal protection was more frequently used in the open-cell stent group compared with closed-cell stent group, however, EPDs used in CAS procedures were not significantly different between the two groups (Table 2). The outcomes of CAS procedures are summarized and compared in Table 3. Intraprocedural symptomatic embolic complications occurred in one case (2.1%) in the closed-cell stent group, and two cases (3.0%) in the open-cell stent group (p = 1). In the postoperative period, minor stroke of slight facial

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**Table 1** Baseline characteristics and morphological characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Closed-cell stent</th>
<th>Open-cell stent</th>
<th>Test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) - (years)</td>
<td>74.4 (6.1)</td>
<td>59.3 (6.9)</td>
<td>t-test</td>
<td>0.045</td>
</tr>
<tr>
<td>Man, n (%)</td>
<td>56 (91.3%)</td>
<td>49 (94.3%)</td>
<td>Fisher</td>
<td>0.49</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>28 (45.8%)</td>
<td>14 (7.6%)</td>
<td>Fisher</td>
<td>0.004</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>31 (51.6%)</td>
<td>16 (21.6%)</td>
<td>Fisher</td>
<td>0.007</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>42 (68.3%)</td>
<td>28 (35.4%)</td>
<td>Fisher</td>
<td>0.002</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>21 (33.3%)</td>
<td>13 (23.7%)</td>
<td>Fisher</td>
<td>0.34</td>
</tr>
<tr>
<td>Left, n (%)</td>
<td>24 (40.0%)</td>
<td>18 (30.8%)</td>
<td>Fisher</td>
<td>0.26</td>
</tr>
<tr>
<td>Lesion length, median (mm)</td>
<td>19 (10–29.5)</td>
<td>16 (10–25)</td>
<td>Mann–Whitney</td>
<td>0.01</td>
</tr>
<tr>
<td>PreCAS stenosis rate, median (IQR)</td>
<td>75 (10–87.4)</td>
<td>75 (10–87.4)</td>
<td>Mann–Whitney</td>
<td>0.83</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
<td>9 (14.6%)</td>
<td>3 (5.6%)</td>
<td>Fisher</td>
<td>0.04</td>
</tr>
<tr>
<td>Pseudo-occlusion, n (%)</td>
<td>3 (5.1%)</td>
<td>1 (1.4%)</td>
<td>Fisher</td>
<td>0.06</td>
</tr>
<tr>
<td>Calcification, n (%)</td>
<td>2 (3.3%)</td>
<td>0 (0%)</td>
<td>Fisher</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; DM: diabetes mellitus; HT: hypertension; IQR: interquartile range; SD: standard deviation
palsy occurred in one case of the open-cell stent group due to in-stent plaque protrusion detected by carotid duplex ultrasound on the next day of CAS procedure. The symptom was disappeared within 30d after the procedure. Major stroke of severe hemiparesis occurred in one case of the open-cell stent group due to acute instent thrombosis three days after CAS procedure. The symptom had continued at 30d after the procedure. In contrast, TIA and death did not occur in either group. Totally, stroke occurred within 30d in five cases (4.4%). Stroke occurred in one case (2.1%) in the closed-cell stent group, and in four cases (6.1%) in the open-cell stent group. Periprocedural neurological complications occurred more often in the open-cell stent group, but there was no significant difference between the two groups (p = 0.4). New ischemic lesions detected on postprocedural DWI were observed in 14 cases (29.2%) in the closed-cell stent group, and in 26 cases (39.4%) in the open-cell stent group, and there was not significantly different between the two groups (p = 0.32). Number of new ischemic lesions detected on postprocedural DWI was not also significantly different between the two groups (p = 0.53).

### Discussion

The major ischemic events are not related with hemodynamic compromise, but the artery to artery embolism in patients with carotid artery stenosis.11) Cerebral embolic event is one of the most frequent complications of CAS. CEA procedure removes the source of embolic event, and is the gold standard for preventing stroke in patients with significant carotid artery stenosis.14,15) The CAS procedure opens the stenotic lesion and prevent embolic event through scaffolding of the plaque by the stent strut against the carotid arterial wall.11) Thus, after the CAS procedure, only the struts of the stent can protect from postprocedural neurological events.16–18) It is possible that carotid artery lesion often release embolic materials after CAS procedure.6,19) Flexibility and scaffolding are the main key characteristics of stent design.20) Closed-cell stents are rigid and less flexible, and difficult to deploy in tortuous vessels. However, closed-cell stents can potentially lower the plaque protrusion and embolization because of maximal scaffolding to the carotid artery lesion. Open-cell stents conform to tortuous vessel; however, there are increased risks of plaque protrusion through the deployed stent strut. Moreover, apices of the open-cell strut may have a risk of penetration and rupture of the plaque.

### Table 2
Comparison of EPDs used in CAS procedure between closed-cell stent and open-cell stent groups

<table>
<thead>
<tr>
<th>Procedure Protection</th>
<th>Total n = 114</th>
<th>Closed-cell stent n = 48</th>
<th>Open-cell stent n = 66</th>
<th>Test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal protection, n (%)</td>
<td>43 (37.7%)</td>
<td>15 (31.3%)</td>
<td>28 (42.4%)</td>
<td>Fisher</td>
<td>0.25</td>
</tr>
<tr>
<td>Distal protection (filter or balloon), n (%)</td>
<td>71 (62.3%)</td>
<td>33 (68.8%)</td>
<td>38 (57.6%)</td>
<td>Fisher</td>
<td>0.09</td>
</tr>
</tbody>
</table>

CAS: carotid artery stenting; EPDs: embolic protection devices

### Table 3
Comparison of the outcomes between closed-cell stent and open-cell stent groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total n = 114</th>
<th>Closed-cell stent n = 48</th>
<th>Open-cell stent n = 66</th>
<th>Test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAE(&lt;30days), n (%)</td>
<td>5 (4.4%)</td>
<td>1 (2.1%)</td>
<td>4 (6.1%)</td>
<td>Fisher</td>
<td>0.4</td>
</tr>
<tr>
<td>TIA(&lt;30days), n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>Fisher</td>
<td>NA</td>
</tr>
<tr>
<td>Stroke(&lt;30days), n (%)</td>
<td>5 (4.4%)</td>
<td>1 (2.1%)</td>
<td>4 (6.1%)</td>
<td>Fisher</td>
<td>0.4</td>
</tr>
<tr>
<td>Death(&lt;30days), n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>Fisher</td>
<td>NA</td>
</tr>
<tr>
<td>Intraprocedural embolization, n (%)</td>
<td>3 (2.6%)</td>
<td>1 (2.1%)</td>
<td>2 (3.0%)</td>
<td>Fisher</td>
<td>1</td>
</tr>
<tr>
<td>New DWI high lesion, n (%)</td>
<td>40 (35.1%)</td>
<td>14 (29.2%)</td>
<td>26 (39.4%)</td>
<td>Fisher</td>
<td>0.32</td>
</tr>
<tr>
<td>Number of new lesions on DWI: 0</td>
<td>74</td>
<td>34</td>
<td>40</td>
<td>Fisher</td>
<td>0.53</td>
</tr>
<tr>
<td>Number of new lesions on DWI: 1–5</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>Fisher</td>
<td>NA</td>
</tr>
<tr>
<td>Number of new lesions on DWI: ≥6</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>Fisher</td>
<td>1</td>
</tr>
</tbody>
</table>

MAE: major adverse event; TIA: transient ischemic attack
greater percentage of the vascular wall within a stented region, and that closed-cell stents have an intrinsically greater potential to scaffold and support fractured plaque and support the movement of thrombogenic material away from the moving blood pool compared with open-cell stent. In addition, greater complexity of hematologic factors may contribute to the superiority of closed-cell stent designs. Indeed, increased platelet activation after coronary stent placement has previously been reported. In that report, platelet activation was greater during the 30d following implantation of open-cell stents compared with closed-cell stents. Gurbel et al. compared platelet activation after implantation of heparin-coated and uncoated coronary stents of the same design in a prospective randomized pilot trial. The authors reported that platelet activation was attenuated early after the placement of heparin-coated stents compared with uncoated stents.

Timaran et al. conducted a randomized clinical trial, and concluded that cerebral embolization, as detected by transcranial Doppler and DWI, occurs at a similar rate after CAS with open-cell and closed-cell stents. Park et al. reported that the occurrence of new lesions on DWI was strongly associated with open-cell stents, and all postprocedural embolic events (TIA and stroke) occurred in the closed-cell stent group. Stagnant flow in the residual ulcer or gap may have caused clinically significant embolism and stroke in the closed-cell stent group.

In our study, there were no significant differences in morphological characteristics of the lesion and EPDs used in CAS procedures between the two groups. New ischemic lesions, detected on postprocedural DWI, were not significantly different between the two stent groups. Periprocedural neurological complications tended to occur more often in the open-cell stent group, but this was not significant compared with the closed-cell stent group. We used two kinds of open-cell stents. Ischemia occurred in one case of 47 Precise stent group (2.1%) and in three cases of 19 Protégé stent group (15.8%). The plaque at bending portion of carotid artery tended to be destructed more frequently by Protégé stent strut. This tendency may be due to the difference of stent strut arrangement or the difference of stent strut behavior to the plaque. Now we use Precise stent when we select open-cell stent for CAS. Therefore, this study revealed the equal postprocedural outcome especially between Precise stent group and Carotid Wallstent group, with respect to cerebral ischemic complication. We chose the type of stent according to the morphological characteristics of the lesion, and our decisions concerning stent selection may have influenced the results in our tailored CAS series. Preoperative evaluation of the morphological characteristics of the lesion, recognition of the particularity of carotid stents, appropriate stent selection, and administration of adequate antiplatelet agents are thought to be important in reducing periprocedural ischemic complications.

There are some limitations of the current study. First, this study was a retrospective non-randomized study and the number of ischemic complication case was small. Second, we did not evaluate plaque volume. Moreover, pressure of pre- and postdilatation, stent profile, deliverability, shortening, or radial force factors were not evaluated or compared. These factors may influence cerebral embolic complications. Finally, we were unable to examine platelet aggregation in all patients. Poor response to antiplatelet drugs could be a risk factor of cerebral embolic complications. For further evaluation, a prospective randomized study involving a greater number of patients may be needed in the future to properly assess our results.

Conclusion

The data generated by the current study revealed that in tailored CAS, the difference of the postprocedural ischemic complication rate was not significantly different between both types of stents. Large sample size retrospective analyses, or prospective randomized trials comparing different stent cell designs should be conducted to confirm the results of this study.

Disclosure Statement

The authors declare no conflict of interest (COI). All authors who are the member of The Japan Neurosurgical Society (JNS) have registered self-reported COI Disclosure Statement Forms online through the website for JNS members.

References

3) European Carotid Surgery Trialists’ Collaborative Group: Randomised trial of endarterectomy for recently symptomatic


