Selecting an Appropriate Surgical Treatment Instead of Carotid Artery Stenting Alone According to the Patient’s Risk Factors Contributes to Reduced Perioperative Complications in Patients with Internal Carotid Stenosis: A Single Institutional Retrospective Analysis

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Abstract
This retrospective study was aimed to compare the perioperative complications for internal carotid artery stenosis (ICS) in a Japanese single institute between the use of carotid artery stenting (CAS) alone or the use of an appropriate individualized treatment method allowing either carotid endarterectomy (CEA) or CAS based on patient risk factors. Based on the policy at our hospital, only CAS was performed on patients (n = 33) between January 2005 and November 2009. From December 2009 to December 2012, either CEA or CAS (tailored treatment) was selected for patients (n = 61) based on individual patient risk factors. CEA was considered the first-line treatment in all cases. In high-risk CEA cases, CAS was performed instead (n = 11), whereas in low-risk CEA cases, CEA was performed (n = 19). Further, in moderate-risk CEA cases based on own criteria, CAS was considered first, whereas for high-risk CAS cases, CEA was performed (n = 17). For low-risk CAS cases, CAS was performed (n = 9). Perioperative clinical complications (any stroke, myocardial infarction, or death within 30 days) were compared between both periods. Significantly reduced perioperative complications were observed during the tailored period (4/61 sites, 6.6%) as compared with the CAS period (8/33 sites, 24.2%) [Fisher’s exact test p = 0.022; odds ratio, 4.56 (CAS/tailored); 95% confidence interval, 1.26–16.5]. Selecting an appropriate individualized treatment method according to patient risk factors, as opposed to adhering to a single treatment approach such as CAS, may contribute to improved overall outcomes in patients with ICS.

Key words: carotid artery stenting, carotid endarterectomy, carotid stenosis

Introduction
Cervical internal carotid artery stenosis (ICS) is one of the common causes of ipsilateral ischemic stroke. Preventive treatment for ICS includes medical and surgical treatments, such as carotid endarterectomy (CEA) or carotid artery stenting (CAS).

Since 2005, the number of ICS cases treated by CAS has surpassed that treated by CEA in Japan. In 2008, CAS was included under the national insurance coverage in Japan, but only for patients with high-risk CEA. After publication of the Japanese guidelines citing high-risk CEA as an indication for CAS in 2009,1) the number of cases treated by CAS has further increased.

Randomized controlled trials (RCTs) comparing CEA and CAS in Europe and in the United States revealed that perioperative myocardial infarction (MI) was more frequent with CEA than CAS.2–6) In contrast, Japanese lifestyle and the ease to access medical services may contribute to lower cardiovascular events in Japan than in Europe or in the United States.7–9) Therefore, it is important to establish an optimal treatment strategy specialized in ICS in Japan. A recent retrospective study on CAS in Japan reported an improvement in therapeutic outcomes.10) However, the number of cases registered in this study accounted only for approximately 10%
of all cases treated by CAS during the study period, and thus likely represented a high selection bias. Furthermore, the treatment results of CEA were not analyzed in the study. Hence, studies comparing the outcomes of different treatment strategies using either CEA or CAS are needed.

In recent years, the outcome of CEA/CAS/medical treatment for iCS has improved. However, no criteria has been developed for the classification of CEA/CAS patients as “high-risk” individuals. In this study, we conducted a retrospective comparative investigation of all patients with ICS who were treated with either CEA or CAS. Because of the policy at our institute, CAS alone was performed for all patients between January 2005 and November 2009, whereas from December 2009 to December 2012, either CEA or CAS (tailored treatment) was selected based on individual patient risk factors. Here, we examined whether the perioperative complications were reduced with tailored treatment based on the concept of risk categorization as compared with treatment with CAS alone.

**Methods**

We conducted a retrospective study of 94 patients with ICS who underwent consecutive surgeries (CEA or CAS) performed by the same operator (CEA: K.S. and CAS: A.K.) at our hospital between January 2005 and December 2012. Our study population consisted of patients with ICS who underwent either CAS or CEA (≥ 50% stenosis in symptomatic patients and ≥ 60% stenosis in asymptomatic patients). The period between January 2005 and November 2009 is considered the “CAS period” because all the patients with ICS (n = 33) underwent CAS as the treatment method. Meanwhile, the period between December 2009 and December 2012 is considered the “tailored period” since the patients with ICS (n = 61) underwent either CEA or CAS in the treatment of this condition.

Before the patients received CEA or CAS, stress myocardial scintigraphy, coronary computed tomography angiography, or coronary angiography was generally performed in the department of cardiology. Thereafter, percutaneous coronary intervention (PCI) was performed when indicated, and subsequently, either CEA or CAS was performed. No patients who received PCI experienced a stroke before CEA or CAS. The perioperative complications in this study were evaluated by any stroke, MI, or death within 30 days after CEA or CAS. Stroke was defined as relevant clinical features that have caused by fresh ischemic events (infarction or transient ischemic attack) or intracerebral hemorrhage. MI was defined by the symptoms (chest pain or discomfort) accompanied by a ST change on the electrocardiogram and/or elevation of enzyme. The institutional review board approved this study, and the requirement for informed consent was waived.

**I. Criteria for treatment selection during the tailored period (Fig. 1)**

CEA was considered as the first-line treatment during the tailored period and was performed in the majority of low-risk CEA cases (n = 19). Meanwhile, CAS was performed for the high-risk CEA cases (n = 11), regardless of the CAS risk categorization, and for 3 of the low-risk CEA cases, despite the CAS risk profile, because of the patients’ preference.

In the moderate-risk CEA cases, CAS was considered as the first-line treatment. CAS was performed for all the low-risk CAS cases (n = 9) and based on the patients’ preference, for 2 of the 19 high-risk CAS cases. CEA was performed for the remaining 17 cases.

**II. CEA/CAS risk classification**

Patients were classified into risk categories based on the following criteria:

1. High-risk CEA patients were defined as those in whom general anesthesia was considered risky (i.e., severe pulmonary disease and left ventricular ejection fraction of < 30%) and
those with contralateral laryngeal nerve palsy, previous neck surgery or a history of radiation to the neck.

2. Moderate-risk CEA patients were defined as those with lesions located higher than the second cervical vertebra, contralateral internal carotid artery occlusion, a possible history of Swan-Ganz catheterization. We classified these patients into the moderate-risk CEA group rather than the high-risk CEA group because the risk of complications in the former group can be reduced with several techniques, such as surgical maneuvers to expose the distal ICA for higher lesions, the routine use of the intraluminal-shunt not only for cases with contralateral internal carotid artery occlusion, and careful exposure of a lesion using microsurgical technique to reduce scar formation in carotid sheaths with a possible history of Swan-Ganz catheterization.

3. High-risk CAS patients were defined as those with aortic valve stenosis, unfavorable access route, impaired renal function (dialysis), complete circumferential calcification of the lesion, or unstable plaques on T1-weighted black-blood magnetic resonance imaging (MRI) (signal intensity ratio ≥ 1.25).

III. Therapeutic procedure

CAS: CAS was performed under local anesthesia for all patients, and the technical success rate of stent placement was 100%. During the CAS period, distal protection devices consisted of the Angioguard XP (Cordis, Miami, Florida, USA, n = 21), PercuSurge Guardwire (Medtronic, Santa Rosa, California, USA, n = 8), and MintCatch (Medtronic, n = 2). However, no distal protection device was used in two of the cases. Precise stents (Cordis) were used in 24 cases, Wall RP stents (Boston Scientific, Natick, Massachusetts, USA) in 5 cases, Protege stents (Covidien, Plymouth, Massachusetts, USA) in 3 cases, and Xpert stents (Abbott Vascular, Abbott Park, Illinois, USA) in 1 case. During the CAS period, CAS was performed with unapproved multi-devices until March 2008 because the procedure had not been approved. From April 2008 onwards, CAS was performed in all cases with Angioguard XP and Precise stents, which were the only approved devices in Japan. During the tailored period, the distal protection devices consisted of FilterWire EZ (Boston Scientific, n = 19), Angioguard XP (n = 5), and Spider (ev3 Endovascular, Plymouth, Massachusetts, USA, n = 1). The stents consisted of Wall stent (Boston Scientific, n = 20) or Precise (n = 5). During the tailored period, Angioguard XP, which is less effective in preventing distal embolism from plaques, was replaced with FilterWire EZ and Spider, which were more effective, after the latter devices that were approved for National Health Insurance reimbursement. Antiplatelet treatment was initiated several days before CAS and was continued postoperatively. However, the type, number, and dose of these agents were left to the discretion of the physician. Intraoperative heparinization was performed based on the anticoagulation time, which was usually set to > 300 s (or double the control value) before the procedure. Pre- or post-dilation using a balloon was performed, if needed.

CEA: All patients were operated on under general anesthesia induced by intravenous fentanyl (2–4 μg/kg), propofol (1–2 mg/kg), and vecuronium (0.1 mg/kg) or rocuronium (0.6–1 mg/kg) and maintained by the administration of remifentanil (0.15–0.3 μg/kg per min), vecuronium, or rocuronium and 1.5–2.0% inspired sevoflurane. All patients were artificially ventilated with an air-oxygen mixture (inspired fraction of oxygen, approximately 0.30). Intermittently drawn arterial blood samples were subjected to gas analysis to ensure normoventilation. Routine monitoring during anesthesia included standard electrocardiography, placement of an intra-arterial catheter for direct arterial blood pressure measurements, pulse oximetry, and capnography. Throughout the procedure, the blood pressure was kept stable in a range of ± 20% of the preoperative level by adjusting the depth of anesthesia or, if needed, by intravenous administration of a vasodilator or a vasoconstrictor. A bolus of heparin (100 U/kg) was injected before internal carotid artery clamping. We used an intraluminal shunt in all procedures. Postoperatively, the systolic arterial blood pressure of all patients was kept between 100 mm Hg and 140 mm Hg for 1 day by intravenous administration of antihypertensive drugs under continuous sedation with propofol.

IV. Statistical analysis

Differences in the characteristics between treatment groups (e.g., CAS period vs. tailored period) were evaluated by the Student’s t-test for continuous variables (age and degree of stenosis) and the chi-square test (sex, hypertension, hyperlipidemia, statin use, diabetes mellitus, smoking, ischemic heart disease, and symptomatic stenosis) or Fisher’s exact test (peripheral artery disease and antiplatelet agent use) for absolute categorical variables. Differences with a p-value of < 0.05 were considered statistically significant. All statistical analyses were conducted using JMP software (JMP 10, SAS Institute Inc., Cary, North Carolina, USA).
Results

No significant differences were observed in the baseline characteristics except for the number of antiplatelet agents of patients between the CAS period and the tailored period (Table 1). However, significantly reduced perioperative complications (stroke, MI, or death within 30 days) were observed in the tailored period compared with the CAS period (4/61 sites (6.6%) vs. 8/33 sites (24.2%); Fisher’s exact $p = 0.022$, odds ratio = 4.56 (CAS/tailored); 95% confidence interval = 1.26–16.5, Table 2). No significant differences were observed in the outcomes between CEA and CAS during the tailored period (Fisher's exact $p = 0.296$), or in the CAS outcomes between the CAS period and the tailored period (Fisher's exact $p = 0.320$).

The eight complications caused by CAS during the CAS period were five embolic infarctions, one MI, and two deaths. One patient developed cardiogenic cerebral embolism at 4 days after CEA during the tailored period (Table 2). All three patients who developed complications caused by CAS during the tailored period were high-risk CAS patients, and two of these patients were both high-risk CEA and high-risk CAS patients (Fig. 1). CAS resulted in ipsilateral intracerebral hemorrhage in one patient and embolic infarction in the other patient (Fig. 1). The third patient was a case of moderate-risk CEA and underwent CAS because of personal preference; this patient experienced embolic infarction (Case 2) (Fig. 1).

Representative Cases

I. Case 1: A CAS case with high-risk CEA and high-risk CAS status

A 74-year-old man was referred to our hospital because of a transient ischemic attack with right iCS (Fig. 2A). PCI was not possible to perform, and the patient had a high-risk CEA status according to the classification system used in this study. On T1 black-blood MRI, the plaque was observable as a high-intensity area suggestive of intra-plaque hemorrhage (Fig. 2B). Meanwhile, computed tomography angiography (CTA) revealed atherosclerosis obliterans (ASO) of the femoral artery and right subclavian...
artery stenosis, also leading to his classification as a high-risk CAS patient (Fig. 2C). CAS was performed by direct puncture in the right common carotid artery because of his high-risk CEA status (Fig. 2D). The right side of his neck got swollen 1 hour after removing the guiding sheath (Fig. 2E). An emergency operation was performed after tracheal intubation. Bleeding at the puncture point of the guiding sheath was detected and stopped (Fig. 2F, G). Despite these complications, he was discharged without neurological deficits.

II. Case 2: A CAS case with moderate-risk CEA and high-risk CAS status

A 79-year-old man had been monitored at another hospital because of right-sided iCS (Fig. 3A) and was referred to our hospital after experiencing repeated transient ischemic attacks. We recommended CEA because his plaque both extended to the level of the second cervical vertebral body (Fig. 3B) and artery stenosis, also leading to his classification as a high-risk CAS patient (Fig. 2C). CAS was performed by direct puncture in the right common carotid artery because of his high-risk CEA status (Fig. 2D). The right side of his neck got swollen 1 hour after removing the guiding sheath (Fig. 2E). An emergency operation was performed after tracheal intubation. Bleeding at the puncture point of the guiding sheath was detected and stopped (Fig. 2F, G). Despite these complications, he was discharged without neurological deficits.

Fig. 2 Case 1. A: Preoperative angiogram of the right carotid artery, lateral view, showing severe stenosis of the internal carotid artery. B: The plaque on a T1-black-blood magnetic resonance image showed a high-intensity signal. C: Computed tomography (CT) angiogram showing right subclavian artery stenosis. D: Postoperative angiogram, lateral view, showing carotid artery stenting performed by the direct puncture approach using the right common carotid artery. E: Preoperative photograph showing swelling of the right side of neck, 1 hour after removal of the guiding sheath. F: Intraoperative photograph showing bleeding at the puncture point of the guiding sheath. G: Postoperative CT scan showing subcutaneous swelling on the right side of the neck.

Fig. 3 Case 2. A: Preoperative angiogram of right carotid artery, lateral view, showing severe stenosis of internal carotid artery. B: Computed tomography angiogram showing the plaque extended to the level of the second cervical vertebral body. C: The plaque showed a high-intensity signal on a T1-black-blood magnetic resonance image (MRI). D: Postoperative angiogram, lateral view, showing carotid artery stenting being performed. E: Postoperative diffusion-weighted MRI of the head showing a high-intensity lesion in the territory of the right middle cerebral artery.
was unstable (Fig. 3C) and also the patient had an unfavorable access route as a result of ASO. However, the patient requested CAS instead. Therefore, we performed CAS through his right brachial artery (Fig. 3D). He experienced left hemiparesis after CAS, and diffusion-weighted MRI of the head showed a high-intensity lesion in the territory of the right middle cerebral artery (Fig. 3E).

**Discussion**

In recent years, the outcome of CEA/CAS/medical treatment for ICS has improved. To date, no standardized criteria has been established for the classification of CEA/CAS patients as “high-risk” individuals. For example, older patients were included in the high-risk CEA group in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. On the other hand, older patients showed a better outcome with CEA compared with CAS in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). So, the selection of treatment can depend on the operator’s skill, geographic location, and era.

In this study, we compared perioperative complications (stroke, MI, or death within 30 days) over two separate periods: (i) the CAS period, during which the treatment consisted of CAS alone and (ii) the tailored period, during which CEA and CAS treatment were selected on the basis of our own criteria. Compared with the CAS period, significant reduced perioperative complications were observed during the tailored period. These findings suggest that selecting an appropriate individualized treatment method according to patient risk factors, instead of adhering to a single treatment approach will likely contribute to improved overall outcomes in all patients with ICS.

The incidence of MI is low among Japanese patients with atherosclerosis or multiple risk factors. This indicates that the incidence rate is non-uniform globally, as the incidence of atherosclerotic/thrombotic diseases is higher in Europe and in the United States. In addition, previous epidemiological studies have shown that the risk of developing MI increased in Japanese patients who immigrated to Hawaii or California; thus, the low rate of cardiovascular events in Japan may be attributed to lifestyle choices and the existing healthcare system (such as the national insurance system), and not necessarily to genetic factors. In RCTs comparing CEA and CAS in Europe and in the United States, MI was often included among the primary endpoints. In addition, the CREST did not reveal any significant differences between CEA and CAS in terms of primary endpoints (perioperative stroke, MI, death, or ipsilateral stroke within 4 years). However, the rates of perioperative stroke (p = 0.01) and perioperative stroke or death (p = 0.005) were significantly frequent with CAS. Perioperative MI was significantly more frequent with CEA (p = 0.03), and it influenced the results pertaining to the primary endpoints. In the CREST, approximately 45% patients in the CEA and CAS groups had a history of cardiac disease, and approximately 20% had undergone coronary artery bypass grafting; however, only electrocardiography, echocardiography, and enzyme levels were considered to be essential for preoperative cardiac assessment. In contrast, before performing CEA or CAS in our institute, we consulted the department of cardiology, and subsequently, if needed, PCI was performed before conducting CEA or CAS. It might have also contributed to the good outcomes without patients developing MI caused by CEA.

A tailored CAS regimen requires a non-invasive diagnostic work-up (ultrasoundography, CTA, and MRI plaque-imaging) to select the most appropriate embolic protection device (e.g., proximal-flow blockage/reversal in the carotid artery or distal-filter or occlusive balloon) and stent type (closed-cell or open-cell). The outcomes of the tailored CAS reported by Miyachi et al. were better compared with those conducted at our institute. A possible explanation for this difference is the limited number of patients in the present study compared with the substantial number of patients (> 8,000) used in the study by Miyachi et al., which accounted for 10% of all cases treated using CAS in Japan during the study period. Moreover, events that occurred at the time of diagnostic angiography were not reflected in the CAS in the study by Miyachi et al. At our institute, diagnostic angiography and CAS were performed together, and the outcomes of CAS may have been influenced by cerebral infarction occurring as a result of catheter manipulation at the time of diagnosis. Also, the present study enrolled all patients who underwent ICS treatment in our institute; hence, it may be more representative of real world.

Since high-risk cases for CEA and CAS cannot be easily identified at present, the CEA risk category in this study was set at moderate, in which CEA should be reconsidered and CAS should be withheld for patients who have factors often associated with high-risk CEA cases and those who are at high-risk for CAS complications. Moreover a limitation of this study is that verification analysis was not performed with regard to the adequacy of the CEA/CAS risk classifications. This analysis will need to be verified in future studies.
In previous RCTs, the treatment outcomes of CEA and CAS have improved, and importantly, CAS is often dependent on the progress of device advancement. **Angioguard XP** was used in four of the five patients who developed cerebral infarction in the CAS period and two patients who developed cerebral infarction in the tailored period. This trend is consistent with that reported by Miyachi et al. **During the tailored period, Angioguard XP** was replaced by FilterWire EZ and Spider, which are more effective than Angioguard XP in preventing distal embolism from plaques, after the latter devices were approved for National Health Insurance reimbursement. **Although remarkable advances have been made in devices for CAS, it is important for operators to be familiar with the device and understand their performance before use.**

Because the operator who performed CAS in this study is a board-certified operator from the Japanese Society of Neuroendovascular Therapy and not a low-volume operator, we do not believe that lack of skill affected the incidence of perioperative complications in the CAS cases. **Intraoperative transcranial Doppler (TCD), which was not used in this study, may be useful for preventing cerebral embolization during CAS.** When CAS is performed for patients with microembolic signals detected on TCD, the use of a reverse flow device may be additionally required. Moreover, in patients with cerebral embolization detected by preoperative TCD, CAS may be effective if it is performed after the plaques are stabilized with statins.

A limitation of this study is retrospective in nature and represented only single-institutional performance, and the amount of clinical data is limited. The total perioperative complication rate in the high- or moderate-risk CEA patients was 7.1% during the tailored period in this study. This rate is similar to the perioperative complication rate of CEA in high-risk CEA patients from the SAPPHIRE trial (9.9%). In the future, it will be necessary to improve the complication rate. In recent years, the outcome of medical treatment of ICS has improved as well. **In this study, all three patients who developed CAS complications during the tailored period were considered high-risk CAS patients (two high-risk CEA patients and one moderate-risk CEA patient), consistent with the improvement in outcomes.** At present, there is no evidence that the treatment outcomes of CEA and CAS are superior to those of medical treatment in high-risk CEA cases. Particularly in Japan, where the incidence of natural ischemic vascular events is low, medical treatment may also be considered in patients who appear to be at high-risk for both CEA and CAS.

## Conclusion

Selecting an appropriate individualized treatment method according to patient risk factors, instead of adhering to a single treatment approach, will likely contribute to improved overall outcomes in all patients with ICS.

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## Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors (except Hirotsugu Okamoto) are members of the Japan Neurosurgical Society (JNS), and have registered online Self-reported COI Disclosure Statements forms through the website for JNS members. This manuscript has no COI that should be disclosed.

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