

## Japan Carotid Atherosclerosis Study: JCAS

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### Abstract

The recent randomized trials, North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial, and Asymptomatic Carotid Atherosclerosis Study, have demonstrated the effectiveness of carotid endarterectomy to reduce the incidence of cerebral infarction in patients with symptomatic and asymptomatic high-grade carotid artery stenosis. However, no studies on Japanese patients have been done until now, and recent progress in endovascular stent treatment has been made. The present prospective, multicenter (not randomized) trial, the Japan Carotid Atherosclerosis Study, has started to analyze present practice and propose treatment guidelines for Japanese patients. Here, the protocol and early results of 565 patients registered until the end of January 2004 are presented.

### Background and Purpose

The recent randomized trials, North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial, and Asymptomatic Carotid Atherosclerosis Study, have demonstrated the effectiveness of the addition of carotid endarterectomy (CEA) to aggressive medical management to reduce the incidence of cerebral infarction in patients with symptomatic and asymptomatic high-grade carotid artery stenosis. However, no absolute significance of CEA has not been identified in the results of meta-analysis studies such as the Coklarn Review except for symptomatic stenosis of more than 70%. Endovascular treatment (carotid artery stenting: CAS) is also performed widely in this field. All these data are from North America and Europe, and no studies of Japanese patients have been done. Previous reports have identified some important clinical features in Japanese differing from Caucasians as follows: absolutely low incidence, 4000–5000 proposed CEA/CAS cases per year; incidences of high cervical lesion and intracranial tandem lesions are higher; most procedures and peri- and postoperative management of CEA/CAS are performed by neurosurgeons, and the results are superior compared to randomized studies, and others.

The present prospective, multicenter trial, the Japan Carotid Atherosclerosis Study (JCAS), has started to analyze present practice and propose treatment guidelines for Japanese patients. This study is not a randomized trial, because treatment of carotid artery stenosis is now performed based on the previously identified guidelines, so randomization without sufficient evidence is not acceptable.

### Design and Organization

Seventy-eight clinical centers with experience of more than 20 cases of CEA and/or CAS were chosen from the results of our preliminary study during 2000–2001. All centers obtained institutional review board approval of the study protocol. Patient accessibility and willingness to be followed for 5 years and valid informed consent were confirmed. Based on this study, simple and wide inclusion criteria

were established. All participants with internal carotid artery (ICA) stenosis of more than 50% identified by conventional angiography, magnetic resonance angiography, three-dimensional computed tomography angiography, and ultrasound sonography were included without exclusion criteria. Patients received medical treatment or surgical intervention (CEA or CAS) according to decisions made at each institute.

### Protocol Design

Details of the patients and protocols including preoperative conditions and postoperative results were registered to the center office of this study (Department of Neurosurgery, Toyama Medical and Pharmaceutical University). Registration was started from January 1, 2003. Clinical results were followed and gathered during 5 years after treatment. Deficits resolving within 24 hours were classified as a transient ischemic attack (TIA), and deficits persisting longer than 24 hours as stroke. All cases of stroke or death occurring within 30 days after treatment were included as end points to reflect the operative morbidity and mortality. The following subjects were included in the protocol.

#### Protocol 1: Patient condition

*Patient condition:* Age, sex, past history (cerebral infarction, coronary artery disease, arteriosclerosis obliterans, hypertension, diabetes mellitus, hypercholesterolemia, cigarette and alcohol consumption), symptoms (asymptomatic, ocular symptom, TIA, minor or major stroke), date of onset and treatment beginning, and modified Rankin Scale before treatment.

*Carotid lesion and atheromatous plaque:* Diagnosis method, degree and length of stenosis, location of the distal site of the ICA lesion, plaque ulceration and calcification, collateral circulation, contralateral ICA lesion, intracranial tandem lesion, cerebral blood flow, findings of ultrasound sonography, and preoperative medical treatment.

#### Protocol 2: Treatment and results

*CEA:* Anesthesia, shunt, patch, complications

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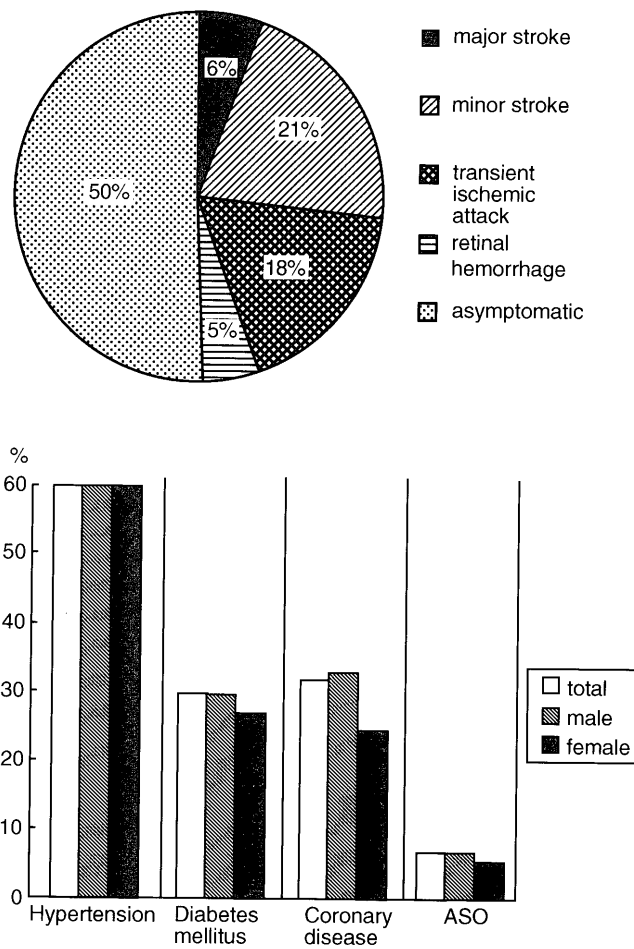


Fig. 1 Clinical characteristics of 565 patients with greater than 50% stenosis of the internal carotid artery registered by the end of January 2004 (490 males and 75 females, mean age  $69.8 \pm 7.4$  years). The upper graph shows symptoms before treatment. The lower graph shows the complication rates of hypertension, diabetes mellitus, coronary disease, and arteriosclerosis obliterans (ASO). No sex difference was observed in the incidence of these diseases.

(cerebral infarction, hyperperfusion syndrome, intracranial hemorrhage, wound hematoma, cranial nerve paresis), and modified Rankin Scale 1 month later.

**CAS:** Device, kink of carotid artery, methods and timing of distal protection, postoperative stenosis rate, complications (cerebral infarction, hyperperfusion syndrome, intracranial hemorrhage), bradycardia and hypotension, and modified Rankin Scale 1 month later.

**Medical treatment:** Type and dose of medical treatment.

**Protocol 3: Follow up**

Modified Rankin Scale and occurrence and character of recurrent stroke, degree of stenosis, and type and dose of medical treatment.

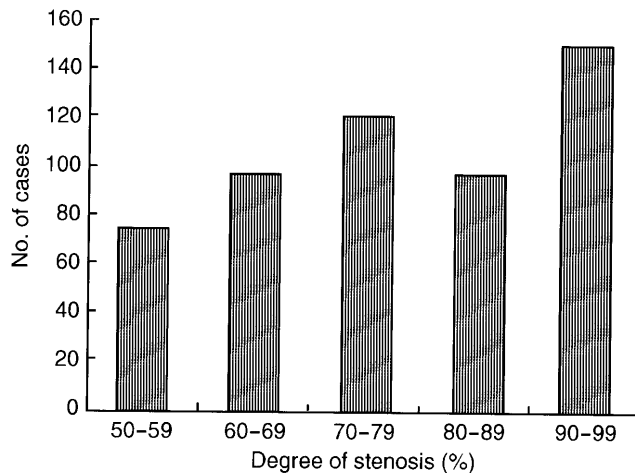


Fig. 2 Number of cases and degree of stenosis in the 565 patients. Sixty-eight percent of patients had 70-99% stenosis, 35% had ulceration, and 30% had calcification.

**Preliminary Results**

Until the end of January 2004, 565 patients, 490 males (87%) and 75 females (13%) aged 52 to 89 years (mean 69.8 years), had been registered. Two hundred eighty-two patients (approximately 50%) had neurological symptoms: cerebral stroke (27%), TIA (18%), and ocular symptoms (5%). Sixty percent had hypertension, 30% had diabetes mellitus, and 30% had previous coronary disease. No sex difference was observed in the incidence of these diseases (Fig. 1). Sixty-eight percent of patients had 70-99% stenosis, 35% had ulceration, and 30% had calcification (Fig. 2). The distal site of the ICA stenosis was located from upper C-2 to middle C-5 vertebrae (average C-3 vertebra), and 50% of patients had contralateral ICA stenosis (41%) or occlusion (9%).

Among these 565 patients, 204 underwent CEA (36%) and 177 underwent CAS (31%). More CEAs than CASs were performed in the symptomatic group, and almost the same in the asymptomatic group (Fig. 3). All CEAs were done under general anesthesia, with shunting and patching in 60% and 2%, respectively. Ninety-eight percent of CASs were done with the distal protection technique. Morbidity and mortality during one month after surgical treatment were 2.5% (5 cases) for CEA and 3.4% (6 cases) for CAS. Three cases of persistent ischemic cerebral symptoms, one case of hemorrhagic stroke due to hyperperfusion syndrome, and one case of fatal cardiac failure occurred after CEA. Four cases of persistent ischemic symptoms due to distal embolism, one case of hemorrhagic stroke, and one case of cardiac complication occurred after CAS. In addition, 10 patients (4.9%) with CEA and seven (4.0%) with CAS had temporary complications including TIAs (CEA/CAS), wound hematoma and cranial nerve paresis (CEA), and long-standing hypotension and bradycardia (CAS). These temporary complications resolved and symptoms disappeared during the following month (Table 1). In the medical treatment group, only one patient with 95%

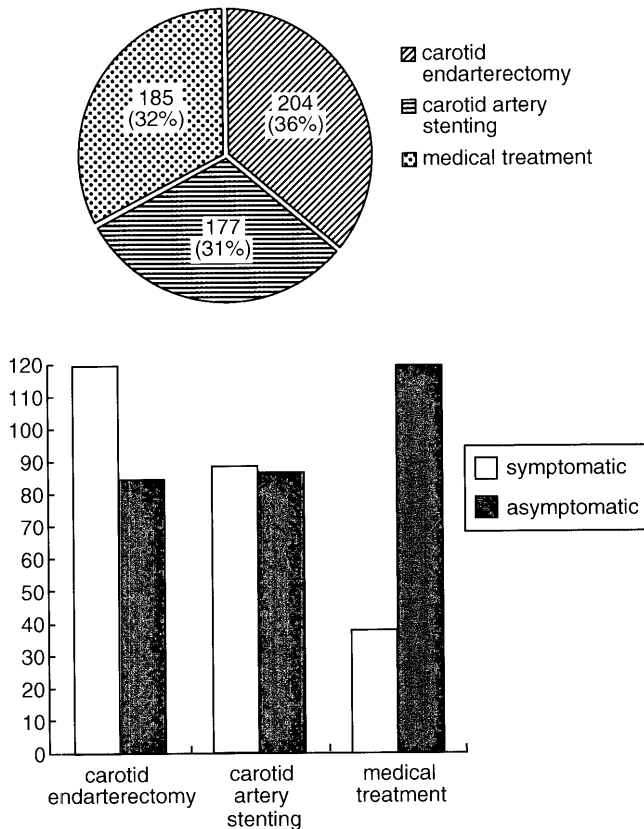


Fig. 3 Treatment in the 565 patients.

Table 1 Perioperative complications within one month after surgical treatment

|                          | CEA        | CAS       |
|--------------------------|------------|-----------|
| No. of patients          | 204        | 177       |
| Total complications      | 15 (7.4%)  | 13 (7.3%) |
| Mortality/morbidity      | 5 (2.5%)   | 6 (3.4%)  |
| Mortality                | 1 (0.5%)*  | 0 (0%)    |
| Morbidity                | 4 (2.0%)   | 6 (3.4%)  |
| ischemic complication    | 3          | 4         |
| hemorrhagic complication | 1          | 1         |
| others                   | 0          | 1         |
| Temporary                | 10 (4.9%)* | 7 (4.0%)* |

\*Cause of death: myocardial infarction. \*TIA, headache due to hyperperfusion, cranial nerve paresis. \*\*TIA, long-lasting bradycardia and hypotension. CAS: carotid artery stenting, CEA: carotid endarterectomy.

stenosis had repeated TIAs and was treated by CEA. No cerebral stroke or TIA was observed in the other patients.

**Conclusion**

Although the JCAS is now ongoing and suffers from some weak points and limitations as a cohort study, the presented data approximately shows the present status of treatment of high-grade ICA stenosis in Japan. This study has investigated various topics including indications, technique, and perioperative management of CEA and CAS. In particular, hyperperfusion syndrome, coronary disease due to calcified atheromatous plaque, and best medical treatment are important in this field. In addition, medical insurance recognition of the carotid stent must be considered as more important. The JCAS members will continue this study and hope to propose adequate treatment guideline for Japanese patients with carotid artery stenosis.

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**Appendix: Members of Japan Carotid Atherosclerosis Study**

This study is supported by a Research Grant for Cardiovascular Disease from the Ministry of Health, Labour and Welfare. The members include the following: Shunro Endo, Akira Ogawa (Iwate Medical University, Morioka, Iwate), Nobuyuki Sakai (Kobe Central City Hospital, Kobe, Hyogo), Takeshi Shima (Chugoku Rosai Hospital, Kure, Hiroshima), Waro Taki (Mie University, Tsu, Mie), Kimihiko Kichikawa (Nara Medical University, Kashihara, Nara), Kazuo Yamada (Nagoya City University, Nagoya, Aichi), Shinji Nagahiro (Tokushima University, Tokushima), Izumi Nagata (Nagasaki University, Nagasaki), Yasushi Okada (Kyushu National Medical Center, Fukuoka), Kazuyuki Nagatsuka (National Cardiovascular Center, Suita, Osaka), Junjiro Kobayashi (National Cardiovascular Center, Suita, Osaka).