Low Stroke Rate of Carotid Stenosis Under the Guideline-Oriented Medical Treatment Compared With Surgical Treatment

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SUMMARY

Medical treatment for asymptomatic carotid artery stenosis (ACAS) has advanced recently. The outcomes of medical treatment and surgical treatment were evaluated to clarify the optimal treatment for ACAS.

Patients with ACAS of ≥ 50% luminal narrowing underwent serial follow-up carotid artery ultrasonography for one year or more at the Center for Cardiovascular Disease Prevention between November 2006 and October 2013. The incidence of cardiovascular events (stroke, myocardial infarction, cardiovascular death) was examined in 64 patients (medical treatment group), and in 47 patients (surgical group) who underwent surgical treatment (carotid endarterectomy or carotid artery stenting) during this same period at the Department of Neurosurgery.

Annual cardiovascular event rate was 0.91% (2/219 person-year) in the group of guideline-oriented medical treatment with an annual check-up for disease management and 5.6% (6/107 person-year) in the surgical group (log-rank P = 0.027; HR in the medical treatment group, 0.19 [medical treatment/surgical]; 95% confidence interval [CI], 0.028 to 0.87). Annual stroke event rate was 0.46% (1/219 person-year) in the medical treatment group and 4.7% (5/107 person-year) in the surgical group (log-rank P = 0.016; HR in the medical treatment group, 0.11 [medical treatment/surgical]; 95% CI, 0.0057 to 0.70). Multivariate logistic analysis showed that the surgical group was an independent variable associated with cardiovascular events (P = 0.049).

Annual cardiovascular and stroke event rates were low in patients receiving medical treatment for ACAS and better than surgical treatment. The present study shows that medical treatment is an important option for ACAS. (Int Heart J 2016; 57: 80-86)

Key words: Asymptomatic, Carotid artery stenting, Carotid endarterectomy

Carotid endarterectomy (CEA) is considered to be superior to medical treatment for asymptomatic carotid artery stenosis (ACAS) based on randomized controlled trials (RCTs) which have generally included patients enrolled for more than 10 years.1-3 Recently, the indications for surgical treatment using CEA or carotid artery stenting (CAS) in patients with ACAS have become controversial due to advances in medical treatment based on large studies conducted in Europe and the United States.4-15 The clinical outcomes of medical treatment for ACAS remain largely unclear, and actual CEA outcomes may be worse than those reported in RCTs.16 The incidence of cardiovascular events is lower in Japan than in Europe and the United States.17 Outcomes of medical treatment for ACAS have not been evaluated in Japan. Consequently, the Japanese guidelines on the indications for surgical treatment have been created based on data from Europe and the United States.

The present study investigated the outcomes after guideline-oriented medical treatment for ACAS in Japan for comparison with surgical treatment, to clarify the optimal treatment for ACAS in the clinical context.18

METHODS

Patient population and data sources: A total of 2,313 registered patients underwent carotid artery ultrasonography at the Center for Cardiovascular Disease Prevention, Kitasato University East Hospital between November 2006 and October 2013. Of these, 67 consecutive patients with ACAS, defined as more than 50% stenosis on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) index, underwent serial follow-up examinations for one year or more.18 Three patients who underwent elective CEA were excluded, so the incidence of cardiovascular events (stroke, myocardial infarction [MI], cardiovascular death) was examined in 64 patients who received guideline-oriented medical treatment (medical treatment group),18 and in 47 patients who underwent surgical
treatment (surgical group) during this same period at the Department of Neurosurgery, Kitasato University Hospital (Figure 1). After treatment in the surgical group, carotid artery lesions were managed by neurosurgeons, whereas other diseases were mainly managed by each patient's primary physician. The baseline clinical characteristics were compared between the medical treatment group and the surgical group. Patients in the medical treatment group were observed from the day of treatment until the day of the cardiovascular event or the final examination day. Patients in the surgical group were observed from the day of treatment until the day of the cardiovascular event or the final examination day. The observation period was 9-103 months (median, 41 months) in the medical treatment group, and 0-70 months (median, 26 months) in the surgical group.

Patients were registered at the Center for Cardiovascular Disease Prevention as cases of ischemic heart disease, valvular disease, arrhythmia, cardiomyopathy, heart failure, and hypertension. The Center performs routine ultrasonography for screening and follow-up examinations for ACAS approximately once a year, and manages risk factors and provides health guidance to patients. The Center is independent of the neurosurgical department, and physicians in the Center recommended medical treatment as the first choice to patients, even to those with ACAS. On the other hand, either CEA or CAS is recommended to patients with carotid artery stenosis of ≥ 50% in symptomatic patients or ≥ 60% stenosis in patients with ACAS at the neurosurgical department. ACAS is classified as moderate (50–69%) or severe (70–99%) on the basis of the rate of stenosis on the NASCET index. Peak systolic flow velocity (PSV) of 125 cm/s or 75% area stenosis corresponds to 50% on the NASCET index, and PSV of 200 cm/s or 84% area stenosis corresponds to 70% on the NASCET index.20-22 Bilateral lesions were observed in 9 patients in the medical treatment group. The higher stenosis is reported for bilateral lesions. All patients with ACAS who underwent CEA were treated by the same surgeon (K.S.) and CAS was performed by a board-certified surgeon of the Japanese Society of Neuroendovascular Therapy.

Stroke was defined as clinical features caused by fresh ischemic events (infarction or transient ischemic attack) or intracerebral hemorrhage. MI was defined as symptoms (chest pain or discomfort) accompanied by ST change on electrocardiography and/or elevation of myocardial enzyme levels. Cardiovascular death was defined as death caused by MI, heart failure, pulmonary embolism, lower limb gangrene, ruptured abdominal aortic aneurysm, mesenteric artery thrombosis, and renal failure. Diabetes mellitus (DM) was defined as self-reported type 2 diabetes, use of glucose lowering agents, or glycated hemoglobin A1 (HbA1c) > 7.0%.

The Ethics Committee of our hospital approved this study, and the requirement for written informed consent was waived to avoid patient enrolment bias (B14-191).

**Statistical analyses:** The incidence of cardiovascular events or stroke of the open cohort was calculated as person-years. Cox regression was used to analyze the hazard ratio (HR) for cardiovascular or stroke events. The cardiovascular or stroke event-free curves were created using the Kaplan-Meier method. Differences in clinical characteristics between the medical treatment and surgical groups were evaluated by Student’s t-test for continuous variables (age, blood pressure, body mass index, total cholesterol, low-density lipoprotein, high-density lipoprotein [HDL], triglycerides, HbA1c, fasting glucose, serum creatinine, and estimated glomerular filtration rate [eGFR]) and Fisher’s exact test for absolute categorical variables (sex, blood pressure-lowering agent use, statin use, DM, current smoking, ever smoking, current drinker, atrial fibrillation, antiplatelet agent use, antithrombotic agent use, stroke prior to 6 months, coronary artery disease, peripheral artery disease, abdominal aortic aneurysm, and degree of carotid artery stenosis). Multivariate logistic analysis was conducted with cardiovascular events as the dependent variable and medical treatment or surgical group as the independent variable, where adjustments were made using the propensity scores for other factors. The propensity scores obtained for cardiovascular or stroke events included the following 12 variables: age, sex, blood pressure-lowering agent use, statin use, HbA1c, current smoker, current drinker, antithrombotic agent use, antiplatelet agent use, stroke prior to 6 months, coronary artery disease, and degree of carotid stenosis. 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, NC).

**Results**

The prevalence of ACAS in the Center for Cardiovascular Disease Prevention was 2.9% (67/2313 patients). The baseline characteristics of the patients are shown in Table I. Compared with the surgical group, the patients in the medical treatment group were more likely to be older, with a higher prevalence of coronary artery disease, antihypertensive drug use, DM, ever smoked, and lower eGFR. Missing data in the medical treatment group were eGFR in 3 patients and HDL in 3 patients; and in the surgical group, HbA1c value was unavailable in 1 patient. These missing data points were excluded from our data analyses. Patients with missing data had no cardiovascular events.

**Incidence of cardiovascular events:** The annual cardiovascular event rate was 0.91% (2/219 person-year) in the medical treatment group and 5.6% (6/107 person-year) in the surgical group (log-rank P = 0.027; HR in the medical treatment group, 0.19...
The annual stroke event rate was 0.46% (1/219 person-year) in the medical treatment group and 4.7% (5/107 person-year) in the surgical group (log-rank $P = 0.016$; HR in the medical treatment group, 0.11 [medical treatment/surgical]; 95% CI, 0.0057 to 0.70; Figure 2B). Multivariate logistic analysis showed that the surgical group was an independent variable associated with cardiovascular events ($P = 0.049$). The propensity scores for other factors were not significantly correlated ($P = 0.83$). No event was observed in 3 patients (all with unilateral lesions) in the surgical group (all treated with CEA) during the observation periods at the Center for Cardiovascular Disease Prevention.

### Discussion

**Major new findings:** The principal new finding of the present study is that the latest medical treatment for ACAS in Japanese people has good outcomes. Furthermore, the annual cardiovascular and stroke event rates of the medical treatment group were lower than those of the surgical group in clinical practice. **Possible mechanism:** Previous RCTs have included various ethnic and regional origins of the patients, and used older and unstandardized medical treatments. In contrast, the present study included only patients from Japan where cardiovascular events are less common than in Europe and the United States. That is, all patients led the Japanese lifestyle with ease of access to medical services. All patients received medical treatment followed by thorough guidance regarding smoking cessation and medicine intake. At the Center for Cardiovascular Disease Prevention, Japanese guideline-oriented health guidance and comprehensive risk management are provided by a specialized physician, and many patients had a history of coronary artery disease manifesting as chest pain and shortness of breath, suggesting that the patients in the facility were highly motivated for secondary prevention. Consequently, the present patients achieved good outcomes, and the prevalence of ACAS was lower compared to previous studies.

One-quarter of stroke patients are reported to discontinue...
1 or more of their prescribed regimen of secondary prevention medications within 3 months of hospitalization for acute stroke. Furthermore, if outpatients with stable coronary artery disease discontinue preventive treatment, the risk for recurrent cardiovascular events, including stroke, is doubled. Medication adherence is considered to be very important in clinical practice, and the present study reiterates the importance of good patient guidance.

**Previous medical treatments for ACAS:** The most common cause of ischemic stroke is cardiogenic embolism, whereas approximately 10% of ischemic strokes are caused by carotid artery stenosis. Medical treatments are continuously improving, and the recent annual stroke rate in patients with ACAS has dropped to approximately 0.3-3%. Medical treatment is now believed to yield the best outcomes for patients with ACAS. Therefore, we believe that the time has come to re-examine the indications of surgical treatment for ACAS.

**What is the optimal medical treatment?** The optimal medical treatment for ACAS has not yet been defined, but probably includes administration of statins, antiplatelet drugs, and management of smoking, hypercholesterolemia, DM, and hypertension. The Reduction of Atherothrombosis for Continued Health (REACH) Registry indicates the current rate of patients who smoke 5 or more cigarettes per day is 15.3%, and Japan is second worst after Eastern Europe with 17%, suggesting that...
smoking cessation guidance remains inadequate. The SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) clinical trial of intracranial arterial stenosis published in 2011 found that aspirin, clopidogrel for 90 days, and management of risk factors (blood pressure, low-density lipoprotein cholesterol, DM, non-HDL cholesterol, smoking, excess weight, insufficient exercise) combined with a lifestyle modification program formed an aggressive medical therapy for patients with transient ischemic attack or nondisabling stroke. A cohort study of an urban general population in Japan in 1994 conducted carotid artery ultrasonography on 682 men and 763 women aged 50 to 79 years, and revealed that the incidence of carotid artery stenosis with an area stenosis of 25% to 50% was 6.5% in men and 3.0% in women; and the incidence of ACAS with an area stenosis of more than 50% was 7.9% in men and 1.3% in women.

Carotid artery ultrasonography in 152 consecutive patients hospitalized for acute coronary syndrome found that 52% of patients had carotid artery stenosis in at least one site; < 30% stenosis (NASCET index) in 43%, 30% to 60% stenosis in 6%, and high-grade stenosis (> 60%) in 2.6%. The presence of carotid artery stenosis was associated with age, DM, hypertension, and coronary atherosclerosis. Multivariate analysis revealed that age and DM were independent factors associated with ACAS.

In the present study, the medical treatment group had a high mean age of 77 years, and most patients (73%) had a history of coronary artery disease. Although the Center for Cardiovascular Disease Prevention treats mainly high-risk patients, the prevalence of carotid artery stenosis was low at 2.9%, possibly due to successful guideline-oriented medical treatment including lifestyle guidance and comprehensive risk management.

Medical treatment for high-risk patients with ACAS: ACAS is likely to become symptomatic in some patients. Consequently, selection of patients with ACAS for surgical treatment is very important. Surgical treatment is required for progression of stenosis, especially rapid progression. Ipsilateral neurological events occurring in 17% of patients over ≥ 5 years were associated with rapid stenosis progression but not slow stenosis progression. The annual stroke rate was 1.92% with stenosis progression. In the present study, no cardiovascular events were observed in the 8 patients who experienced stenosis progression during the follow-up period. Magnetic resonance imaging, ultrasound, transcranial Doppler, and computed tomography of the head have revealed findings suggestive of unstable plaque. A number of imaging parameters may be predictive of increased risk of stroke, but none of these factors have been independently validated. Furthermore, a history of DM and contralateral symptoms was significantly and independently correlated with ipsilateral neurological events during medical treatment for ACAS. In patients with type 2 DM, use of pioglitazone for blood glucose management attenuates carotid plaque, so proactive blood glucose control is desirable in diabetic patients while considering the risk of hypoglycemic attacks. In the present study, the medical treatment group had low HbA1c levels.

Further clarification of predictive factors for symptomatic ACAS is an extremely important issue that needs to be addressed in the future.

Clinical implications: Cardiovascular events are considered to be less common in Japan than in Europe and the United States. In the REACH Registry, “enrollments from Japan” was an independent factor associated with a decrease in cardiovascular events, suggesting that the incidence of cardiovascular events differs among regions worldwide. Therefore, racial differences and residential areas should be taken into consideration in the natural course of ACAS. The present study included a population that was comprised entirely of Japanese people, which is reflected in the good results.

Permanent cranial nerve damage, lung embolism, pneumonia, and local hematoma requiring surgery are CEA complications that are not usually included as the endpoints of RCTs. CAS may cause complications at the puncture site, and stroke after preoperative angiography. For example, 1.2% of patients (5 of 414) suffered stroke after angiography, and 1 of these patients died in the Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. No RCT has directly compared medical treatment and CAS. Our present study suggests that the number of patients indicated for surgical treatment could be extremely limited in clinical practice, and good outcomes for medical treatment of ACAS in Japan require that the indications for surgical treatment need to be reexamined.

Study limitations: The limitations of this study are the small number of patients treated at a single institution, and the limited amount of clinical data.

In the present study, the medical treatment group included ≥ 50% stenosis, whereas the surgical group included ≥ 60% stenosis. The medical treatment group had a low rate of stenosis, which probably affected the difference in cardiovascular events. The onset of events in patients with ACAS is associated with the rate of stenosis, and vice versa. More recent reports have found no correlation between the rate of stenosis and symptoms, which we believe is due to advances in medical treatment.

The optimal medical treatment for ACAS has not been clarified, but may depend on differences in race, region, and time period. The treatment administered to the medical treatment group in the present study was not necessarily the best medical treatment. The present treatment is thought to be good for clinical practice, but improvement is always possible.

The outcomes of the surgical group in the present study were worse than the rates of perioperative stroke or death rate from RCTs. On the other hand, the RCT protocols did not allow further enrollment of patients by surgeons or institutions with unacceptably high morbidity or mortality during the trial. Consequently, CEA outcomes may be better in the RCTs than in clinical practice, and the present study may reflect actual clinical practice better than RCTs.

Conclusions: The annual cardiovascular and stroke event rates in patients who received medical treatment for ACAS were low at 0.91% and 0.46%, respectively, indicating that medical treatment is better than surgical treatment for patients with ACAS. The present study shows that medical treatment is an important option for ACAS, especially in Japan.
DISCLOSURE

Conflict of interests: The authors do not have any conflict of interests to declare.

REFERENCES


