Evidence for Management of Carotid Artery Stenosis

Kazumichi YOSHIDA¹ and Susumu MIYAMOTO¹

¹Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Kyoto

Abstract

In this review, we presented the evidence concerning carotid artery stenosis treatment in symptomatic stenosis and asymptomatic stenosis separately, and discussed the future challenges. The validity of carotid endarterectomy (CEA) to treat moderate or greater degree of symptomatic carotid artery stenosis appears to be established. Due to the additional option of carotid artery stenting (CAS), it is necessary to comprehensively determine whether CEA or CAS is more appropriate for each individual patient. Moreover, since there are rapid advancements in devices for CAS and improvements in treatment outcomes, continual learning of the latest treatment method is essential. For asymptomatic stenosis, due to improvements in the outcomes with best medical treatment (BMT), it is essential to re-evaluate the use of invasive CEA/CAS. Continual verification of the latest randomized clinical trial that compares CEA, CAS, and BMT, and establishment of a diagnostic method that can accurately extract the group of patients who have the highest future risk of developing ischemia, are desired.

Key words: carotid artery stenosis, evidence, carotid endarterectomy, carotid artery stenting, best medical treatment

Introduction

In Western countries, carotid artery stenosis accounts for approximately 20–30% of the cases of cerebral infarction.¹ In Japan, the number of patients with carotid artery stenosis is predicted to increase rapidly in the future due to the Westernization of the diet and changes in lifestyle habits. Further, with the population rapidly aging, it is growing increasingly more important to improve care and treatment for carotid artery stenosis in order to extend healthy lifespans and reduce medical costs.

The efficacy of carotid endarterectomy (CEA) in preventing strokes secondary to both symptomatic and asymptomatic carotid artery stenosis was established through multiple large-scale clinical trials published from the 1990s onwards. Carotid artery stenting (CAS), which is a less invasive revascularization technique, has been performed as an alternative to CEA since the late 1990s; multiple randomized clinical trials (RCTs) reported the equivalent efficacy of CAS compared to CEA, resulting in an increase in the number of CAS performed. Furthermore, the current multifaceted medical prophylaxis has markedly improved the outcomes of cerebral infarction since a previously reported comparison with CEA.² Since rapid progress has been made in various methods to treat carotid artery stenosis, it is necessary to continually assess appropriate treatment strategies based on the latest evidence.

Prognosis and treatment strategies differ greatly between symptomatic and asymptomatic stenosis cases; hence, in this article, we reviewed the evidence for each strategy separately, and present an overview of the latest international guidelines as well as a discussion of future challenges.

Symptomatic Stenosis

I. CEA for the treatment of symptomatic stenosis

Several large-scale clinical trials have compared the efficacy of CEA and medical treatments for the prevention of recurrence of symptomatic stenosis. Notable examples of such trials include the North American Symptomatic Carotid Endarterectomy Trial (NASCET),³,⁴ the European Carotid Surgery Trial (ECST),⁵ and the Veterans Affairs Cooperative Studies Program 309 Trial (Table 1).⁶

II. NASCET³,⁴

This was a Class I study conducted in North America on 2,885 patients with carotid artery stenosis who had symptoms of transient ischemic attack (TIA) or nondisabling stroke. Patients were randomized to

Received October 19, 2014; Accepted January 9, 2015
| Trial          | Published year | Inclusion criteria                                                                 | Treatment arm                  | Participants | Main conclusions                                                                 |
|---------------|----------------|------------------------------------------------------------------------------------|-------------------------------|--------------|----------------------------------------------------------------------------------|
| NASCET        | 1991, 1998     | Symptomatic > 30% stenosis                                                        | CEA + BMT, BMT                | 2,885        | Significant benefit for CEA in 70–99% stenosis (NNt: 6)                             |
|               |                |                                                                                    |                               |              | Significant but small benefit for CEA in 50–69% stenosis (NNt: 15.4)              |
| ECST          | 1991, 1998     | Any degree of symptomatic stenosis                                                | CEA + BMT, BMT                | 3,024        | Significant benefit for CEA in 70–99% stenosis                                    |
| ACAS          | 1995           | Asymptomatic ≥ 60% stenosis                                                       | CEA + BMT, BMT                | 1,662        | Significant benefit for CEA (NNt: 17)                                             |
| ACST          | 2004, 2010     | Asymptomatic ≥ 60% stenosis                                                       | immediate CEA, deferred CEA   | 3,120        | Significant benefit for CEA (NNt: 19)                                             |
| SAPPHIRE      | 2004, 2008     | > 50% symptomatic or > 80% asymptomatic stenosis and high risk for CEA            | CEA + BMT, CAS + BMT          | 334          | CAS was not inferior to CEA in a high surgical-risk population                     |
| EVA-3S        | 2006           | Symptomatic > 60% stenosis                                                        | CEA + BMT, CAS + BMT          | 527          | CAS has a significantly higher incidence of the primary endpoint of stroke or death within 30 days of treatment |
| SPACE         | 2006           | Symptomatic ≥ 70% stenosis                                                        | CEA + BMT, CAS + BMT          | 1,200        | The trial did not prove the noninferiority of CAS to CEA                           |
| CREST         | 2010           | ≥ 50% on angiography, ≥ 70% on US, CTA, and MRA symptomatic stenosis or ≥ 60% on angiography, ≥ 70% on US, ≥ 80% on CTA or MRA asymptomatic stenosis | CEA + BMT, CAS + BMT          | 2,502        | CAS was not inferior to CEA in a low surgical-risk population                      |
| ICSS          | 2010 (an interim analysis) | Symptomatic > 50% stenosis                                                        | CEA + BMT, CAS + BMT          | 1,713        | CEA should remain the treatment of choice for patients suitable for surgery       |
|               |                |                                                                                    |                               |              | Completion of long-term follow-up is needed to establish the efficacy of CAS       |
| CREST-2       | on going       | Asymptomatic ≥ 70% stenosis on US and one confirmatory study (CTA or MRA)          | BMT, CEA + BMT, CAS + BMT     | 2,400 (target)|                                                                                  |
| ACST-2        | on going       | Asymptomatic stenosis in which intervention is thought to be needed               | CEA + BMT, CAS + BMT          | 5,000 (target)|                                                                                  |
| SPACE-2       | on going       | Asymptomatic ≥ 70% stenosis on US                                                  | BMT, CEA + BMT, CAS + BMT     | 3,500 (target)|                                                                                  |
| AMTEC         | on going       | Asymptomatic 70–79% stenosis on US or 60–79% stenosis on CTA/MRA                  | CEA + BMT, BMT                | 400 (target) |                                                                                  |

ACAS: Asymptomatic Carotid Atherosclerosis Study, ACST: Asymptomatic Carotid Surgery Trial, AMTEC: Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis, BMT: best medical therapy, CAS: carotid artery stenting, CEA: carotid endarterectomy, CREST: Carotid Revascularization Endarterectomy versus Stenting Trial, CTA: computed tomography angiography, ECST: European Carotid Surgery Trial, EVA-3S: Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis, ICSS: International Carotid Stenting Study, MRA: magnetic resonance angiography, NASCET: North American Symmetric Carotid Endarterectomy Trial, NNt: number needed to treat, SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy, SPACE: Stent-Protected Angioplasty versus Carotid Endarterectomy, US: ultrasonography.
receive best medical treatment (BMT) or BMT plus CEa. In the report published in 1991, “symptomatic” stenosis was defined as onset of symptoms within the previous 4 months, and patients were divided into three groups depending on the degree of stenosis (< 30%, 30–69%, and 70–99%). In a report from 1998, in which symptomatic stenosis was defined as onset of symptoms within the previous 6 months, subjects with moderate or lesser degree of stenosis (50–69%, < 50%) were analyzed. The summarized results of these two reports were as follows. In patients in whom the surgical risk was considered to be ≤ 6%, the 2-year incidence of ipsilateral stroke in patients with high-grade stenosis of 70–99% was significantly lower in the CEA group than the BMT group (9% vs. 26%, P < 0.001). The absolute risk reduction (ARR) was 17.0% and the number needed to treat (NNT) was 6. In a comparison of cases with moderate stenosis of 50–69%, patients in the CEA group had a significantly lower 5-year incidence of ipsilateral stroke as compared to the BMT group (15.7% vs. 22.2%, ARR: 6.5%, NNT: 15.4, P = 0.045).

III. ECST

In this Class I study conducted in Europe, 3,024 patients with carotid artery stenosis who were within 6 months of the onset of TIA, nondisabling stroke, or retinal ischemia were assigned to BMT or BMT plus CEa groups. In patients with high-grade stenosis of 70–99%, the collective incidence of perioperative complications and ipsilateral stroke was significantly lower in the CEa group compared to the BMT group (6.8% vs. 20.6%, P < 0.0001). Compared to the results of NASCET, CEA showed a higher efficacy in patients with greater stenosis in this study, indicating a slight difference between the two studies. However, this difference is a result of the difference between NASCET and ECST in the method of measuring stenosis, since when ECST data were re-analyzed using the NASCET method of stenosis measurement, the results of the two studies closely resembled each other.

IV. Veteran Affairs Cooperative Studies Program 309 Trial

This randomized trial was conducted in the United States, and assigned 189 male patients with ≥ 50% stenosis within 4 months of onset of symptoms into BMT or CEa + BMT groups. During a mean follow-up period of 11.9 months, the efficacy of CEA in preventing recurrence was shown with an ARR of 11.7% (P = 0.011). However, due to the earlier publication of the results of the NASCET study, this study was discontinued.

V. Pooled analysis

Based on the above three clinical trials, Rothwell et al. conducted a pooled analysis of 6,092 patients with 35,000 patient-years of follow-up, which is believed to be the most reliable data demonstrating the efficacy of CEA in symptomatic carotid artery stenosis. Since the definition of symptomatic stenosis and method of stenosis measurement differs according to the trial, this pooled analysis was conducted according to the criteria in NASCET. The overall operative mortality was 1.1% and the operative risk of stroke or death was 7.1%, operative risks being independent of the degree of stenosis.

The 5-year ARR with CEA was 4.6% in those with 50–69% stenosis and 16% in those with a high degree of stenosis of ≥ 70%, excluding near-occlusion, demonstrating the efficacy of CEA. In near-occlusion cases, the 5-year ARR was 1.7% (P = 0.9), indicating a low efficacy of CEA in such patients. CEA was not beneficial in mild stenosis of 30–49%, and was concluded to be harmful when performed for < 30% stenosis.

VI. CAS for the treatment of symptomatic stenosis

No large-scale clinical studies have directly compared treatment outcomes between CAS and BMT, although the efficacy of CAS to treat carotid artery stenosis has been previously verified through comparisons between CEA and CAS. Table 1 shows the major large-scale clinical trials that compared the outcomes between CEA and CAS. There are three clinical trials that included symptomatic stenosis alone, namely: Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and International Carotid Stenting Study (ICSS). However, all three trials failed to prove the equivalent efficacy of CAS to CEA. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study and Carotid Revascularization Endarterectomy versus Stent Trial (CREST) included patients with both symptomatic and asymptomatic stenosis, integrated acute myocardial infarction (MI) into the items of primary endpoint and standardized the devices for CAS. SAPPHIRE and CREST finally proved the noninferiority of CAS compared to CEA, which resulted in the widespread use of CAS at the present time (Table 1).

VII. EVA-3S

This RCT was conducted in 30 centers in France and included 527 patients with symptomatic internal carotid artery stenosis (stenosis of at least 60%
Evidence for Carotid Artery Disease

according to NASCET) who were at a low risk of complications associated with CEA. Five types of stents and seven types of embolic protection devices were used. During the study, the safety committee recommended using protection devices, and the rate of its usage was ultimately 91.9%. The incidence of stroke or death was 3.9% for CEA and 9.6% for CAS [relative risk (RR); 2.5, \( P = 0.01 \)] after 30 days, and 6.1% for CEA and 11.7% for CAS (RR: 1.9, \( P = 0.02 \)) after 6 months. This study not only failed to prove the noninferiority of CAS compared to CEA, but also demonstrated a significant inferiority of CAS compared to CEA. The trial was discontinued at the time of the 6-month follow-up due to safety reasons.

This trial was criticized for the method used for selection of surgeons for CAS, since these surgeons were less experienced, and for the fact that the high usage rate of procedurally-complicated protection devices by inexperienced surgeons may have led to an increased incidence of perioperative complications.\(^{13}\) However, regarding the latter criticism, the perioperative complications rate (cerebral infarction or death) was 7.9% when protection devices were used and 25% when they were not used, indicating that outcomes were better with the use of protection devices.\(^{16}\)

VIII. SPACE\(^{11}\)

The SPACE trial was an RCT conducted in 35 centers in 3 countries (Germany, Switzerland, and Austria), and included 1,200 patients with symptomatic internal carotid artery stenosis who were at low risk of complications associated with CEA (stenosis of at least 50% according to NASCET or at least 70% according to ECST). Although the trial was originally planned to include 2,500 patients, enrollment was discontinued at 1,200 patients due to lack of funding. Three types of stents and five types of protection devices were used. While the primary endpoint, which was the rate of ipsilateral ischemic stroke or death until 30 days after the procedure, was 6.34% in the CEA group and 6.84% in the CAS group (\( P = 0.09 \)), the CEA group demonstrated better outcomes than the CAS group in six out of eight evaluation items. Hence, this trial failed to prove the noninferiority of CAS.

The issues with this study were the high rate of perioperative complications and the low rate of protection device usage (27% usage).\(^{17}\) The incidence of any stroke or death within 30 days after the procedure was 6.51% in the CEA group and 7.68% in the CAS group, both of which exceeded the allowable perioperative complication rate (6%) for CEA in the treatment of symptomatic internal carotid artery stenosis.

IX. ICSS\(^{12}\)

In this RCT, 1,713 patients with symptomatic carotid artery stenosis of \( \geq 50\% \) were enrolled and assigned to CEA (858 patients) or CAS groups (855 patients). In the 120 days after randomization, the CAS group had significantly greater incidences of stroke, death, or MI [72 events vs. 44 events; hazard ratio (HR) 1.69, 1.16–2.45], any stroke (65 vs. 35 events; HR 1.92, 1.27–2.89), and all-cause death (19 vs. 7 events; HR 2.76, 1.16–6.56) compared to the CEA group.

The issues with this trial are that, in the CAS group, the surgeons were less experienced resulting in poor treatment outcomes, and that use of protection devices was not required (72% usage).\(^{18}\)

X. SAPPHIRE\(^{19}\)

This RCT was conducted at 29 centers primarily in North America, and investigated 334 patients who were at a high risk of complications associated with CEA. Included patients with symptomatic carotid artery stenosis were required to have stenosis of at least 50%, while patients with asymptomatic carotid artery stenosis were required to have stenosis of at least 80%. The trial was limited to surgeons who had complication rates of less than 6%. Use of self-expanding stents and a filter-type protection device (Angioguard or Angioguard XP, Cordis Corp., Miami, Florida, USA) was mandatory. Primary endpoints were the 1-year incidence of major cardiovascular events (death, cerebral infarction, or MI) within 30 days after the procedure, and ipsilateral cerebral infarction or death between 31 days and 1 year after the procedure), which was significantly lower in the CAS group (12.2% vs. 20.1%, \( P = 0.048 \)), proving its noninferiority to CEA (\( P = 0.004 \)). Significant differences in treatment outcomes between the two groups were also not observed on 3-year follow-up.\(^{19}\)

The results of this trial have greatly contributed to the widespread use of CAS as it is at the present day.\(^{20}\) However, the following criticisms have been pointed out: (1) the prevalence of significant coronary artery disease in the study patients was extremely high, at 85%; (2) approximately 70% of the patients in both groups had asymptomatic stenosis; and (3) there was a problem with the definition of perioperative MI [creatine kinase at least twice the normal level with positive mass band (MB) fraction] and the diagnostic threshold of MI was too low.

XI. CREST\(^{14}\)

CREST is an RCT conducted in the United States and Canada in 2,502 patients at a low risk of complications associated with CEA. The trial included patients with symptomatic stenosis of \( \geq 50\% \) and
asymptomatic stenosis of ≥ 60%. For both CEA and CAS, strict criteria for the technical proficiency of operators were established. In addition, the protocol specified the use of a specific device for CAS and also required the use of protection devices (Acculink for stent and Accunet system, Abbott Laboratories, Abbott Park, Illinois, USA). The primary composite endpoints were perioperative stroke, death, and MI, and ipsilateral stroke within 4 years of randomization. There was no significant difference in the estimated 4-year incidence rates of primary endpoints between CAS and CEA groups, proving the noninferiority of CAS compared to CEA [7.2% and 6.8%, respectively; HR for CAS, 1.11; 95% confidence interval (CI), 0.81–1.51; P = 0.51]. Additionally, there were no significant differences specific to symptomatic status or gender in terms of the primary endpoints.

However, when only the perioperative endpoint was compared, the incidences of stroke (4.1% vs. 2.3%, P = 0.01) and death (0.7% vs. 0.3%, P = 0.18) were greater in the CAS group, and incidence of MI (1.1% vs. 2.3%, P = 0.03) was greater in the CEA group.

Based on the CREST trial results, the US guidelines were revised in 2011. These guidelines recommend CAS at a high level as an alternative to CEA for treating internal carotid artery stenosis in patients at a low (or traditional) risk of complications associated with CEA, and consequently, the usage of CAS is becoming more widespread.

The following are the primary flaws pointed out in CREST: (1) The study initially included patients with only symptomatic internal carotid artery stenosis. However, due to a lag in recruitment, the study began enrolling patients with asymptomatic stenosis at a later point. By the end of the enrollment, approximately 47% of patients in each of the groups (CAS and CEA) had asymptomatic stenosis. Since the treatment outcomes greatly differ between symptomatic and asymptomatic stenosis, the inclusion of these two forms of stenosis considerably decreased the power and significance of the CREST results. (2) This study included MIs as a primary endpoint. Specifically, CREST defined MI as an increase in creatine kinase MB or troponin levels to at least twice the upper limit of normal, in addition to changes in the electrocardiogram (ECG) readings that are indicative of chest pain or myocardial ischemia, including asymptomatic MI. Another flaw in the study design was that it included stroke [a condition that clearly affects quality of life (QOL)] and minor MI (a condition that minimally affects QOL) at the same level. (3) There are discrepancies between the initial report of CREST and the results of subgroup analysis.

In terms of the presence of symptoms, stroke, and death rate for all patients (symptomatic and asymptomatic) in the CAS group was approximately twice that in the CEA group (HR: 1.90; P = 0.005), and perioperative stroke and death rates among symptomatic patients in the CAS group were also approximately twice those in the CEA group (HR: 1.89; P = 0.02). In terms of gender-specific differences, perioperative stroke risk in women was ≥ 2.5 times greater in the CAS group compared to the CEA group (HR: 2.63; P = 0.013). In terms of age-specific differences, perioperative event risk was greater with increasing age, while in terms of the primary endpoint, the risk of events in the CAS group was approximately twice that in the CEA group for patients 70 years and older (HR: 2.04; 95% CI: 1.48–2.82).

**Asymptomatic Stenosis**

**I. CEA for the treatment of asymptomatic stenosis**

The two large-scale Class I RCTs that compared efficacy of CEA and medical treatment for asymptomatic stenosis are the Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST). Both trials proved the superior efficacy of CEA over BMT in asymptomatic internal carotid artery stenosis of ≥ 60%. However, because the absolute benefit of CEA is small and the treatment outcomes with BMT have markedly improved since the time both these trials were conducted, it is necessary to re-evaluate the use of CEA for asymptomatic stenosis at the present time. As a matter of fact, the clinical guidelines of the United States updated in 2014 concluded that the harms of screening for asymptomatic carotid stenosis outweigh the benefits and recommends against the screening carotid ultrasonography in the general adult populations (Table 1).

**II. ACAS**

In this RCT, conducted in North America in 1,662 patients with 60–99% stenosis, patients were randomly assigned to BMT or BMT + CEA groups. After a median follow-up of 2.7 years, the 5-year ARR over 5 years with CEA was estimated to be 5.9%, and the study was stopped upon recommendation from the Data Safety and Monitoring Board. The 5-year projected rate of ipsilateral stroke was 11.0% in the BMT group and 5.1% in the BMT + CEA group (53% relative risk reduction, P = 0.004). However, the efficacy of CEA in major ipsilateral stroke alone (defined as a Glasgow Coma scale score of 2 or higher) was not proven (6.0% for BMT vs. 3.4% in BMT + CEA, P = 0.12). This study included the requirement to keep
Evidence for Carotid Artery Disease

III. ACST\textsuperscript{27}

This RCT was conducted in 126 hospitals in 30 countries primarily in Europe. The 3,120 patients enrolled in this study had $\geq 60\%$ stenosis that was asymptomatic for at least 6 months, and were randomly assigned to immediate CEA (1,560 patients) or indefinite deferral of CEA groups (1,560 patients). The net 5-year risks of all strokes and death were 6.4\% (immediate CEA group) vs. 11.8\% (deferred CEA group), indicating a significantly lower risk with immediate CEA (net gain: 5.4\%; 95\% CI, 3.0–7.8, \textit{P} < 0.0001). Sub-analysis showed that, in terms of age, the benefit of CEA was greater in patients who were $\leq$ 74 years old, and in terms of gender, CEA was shown to be beneficial in both men and women. Moreover, there were no significant differences in treatment outcomes between patients who were never symptomatic and patients who were symptomatic more than 6 months previously. The 10-year long-term outcomes were also revealed,\textsuperscript{29} and the analysis concluded that the efficacy of CEA in treating $\geq 60\%$ asymptomatic carotid artery stenosis was proven in treatment facilities that can maintain the rate of perioperative complications at less than 3\%.

Advancements in Medical Treatment

Specific data, such as those from RCTs on medical treatment for internal carotid artery stenosis, do not exist. However, there is strong indirect evidence that indicates that lifestyle habit improvements, antiplatelet therapy, targeted blood pressure lowering, and intensive medical therapy with drugs such as statins to reduce the risk of atherosclerosis are all effective in suppressing the onset of stroke in patients with internal carotid artery stenosis. For example, the efficacy of statins has been demonstrated in a sub-analysis of the SPARCL trial, which showed that atorvastatin administration after stroke or TIA in patients diagnosed with carotid artery stenosis reduced the rate of carotid revascularization by about 50\% compared to placebo.\textsuperscript{30} The improvement over time in the outcomes of best medical treatment has also been indicated in a meta-regression analysis,\textsuperscript{31} which showed that, in the past 30 years, the annual risk of ipsilateral stroke with medical treatment of asymptomatic carotid artery stenosis has decreased from about 2.5\% to less than 1\%. Considering the fact that the incidence of stroke with CEA in the ACAS is 1.5\% per year\textsuperscript{20} at the present time, it is necessary to more carefully investigate the use of CEA for asymptomatic carotid artery stenosis and to conduct clinical studies that clarify treatment outcomes using the latest BMT in asymptomatic carotid artery stenosis.

2011 Guidelines for the Management of Carotid Stenosis

In 2011, multiple carotid artery stenosis treatment guidelines were announced primarily in Europe and in the United States. The three notable guidelines that discuss the topic of distinguishing between CEA and CAS are the American College of Cardiology/American Heart Association (ACC/AHA) guidelines,\textsuperscript{31} the updated Society for Vascular Surgery (SVS) guidelines,\textsuperscript{32} and the European Society of Cardiology (ESC) guidelines.\textsuperscript{33} In addition, the two guidelines concerning the indications for CAS are the Australasian Guidelines\textsuperscript{34} and the UK National Institute for Health and Clinical Excellence (NICE) Guidelines (available at: http://www.nice.org.uk/nicemedia/live/13026/54241/54241.pdf). NICE guidelines concern only the role of CAS in asymptomatic carotid stenosis.

These guidelines were published around the same time, based on the results of the aforementioned large-scale RCTs on carotid artery stenosis; however, there are some differences between the guidelines, especially regarding the nuances of the recommendation of CAS.\textsuperscript{30} A revision in the Japanese Guidelines for the Management of Stroke 2009 is planned in 2015, and its content is of high interest. In the light of the fact that there are racial differences in the natural history of atherosclerotic disease and the anatomical level of carotid bifurcation, large clinical trials with Japanese patients will be required in the future to establish Japanese quality treatment guidelines for carotid artery stenosis.

I. Symptomatic carotid stenosis

The updated SVS and Australasian guidelines recommend CAS only in patients with symptomatic carotid stenosis who are at a high risk of complications associated with CEA. Specifically, the high risk factors for CEA include tracheal stoma, prior ipsilateral neck surgery, external beam radiotherapy, prior cranial nerve injury, lesions that extend proximal to the clavicle or distal to the C2 vertebral body, severe uncorrectable coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease. The ESC guidelines also state that CAS is recommended as an alternative to CEA only in the group at a high risk of complications associated with CEA or at high-volume centers where the perioperative risk of CAS is $< 6\%$. 

Neurol Med Chir (Tokyo) 55, March, 2015
In contrast to the three guidelines described above, the ACC/AHA guidelines recommend CAS at a high level (Class I with Level of Evidence B), stating that “CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention.”

II. Asymptomatic carotid stenosis

The ACC/AHA guidelines recommend CAS at Class IIb Level of Evidence B, stating that “CAS might be considered as an option for asymptomatic carotid stenosis.” The ESC guidelines also recommend CAS at a relatively high level of Class IIb, albeit with the condition that the procedure is performed at high-volume centers with documented stroke and death rates of < 3%. In contrast, the updated SVS and Australasian guidelines state that, at the present time, there is not enough evidence to recommend CAS for asymptomatic stenosis, and the NICE guidelines state that the “evidence on efficacy is inadequate in quantity.” Therefore, CAS should only be used after special arrangements with clinical governance, consent, and audit, or for research at the present time, and CAS to treat asymptomatic stenosis is severely restricted.

Future Directions

I. Symptomatic stenosis

The efficacy of CEA has been established in symptomatic patients with moderate and greater stenosis, and the efficacy of CAS has also been proven in multiple RCTs through its noninferiority compared to CEA, leading to an increasing trend in the number of CAS performed. In contrast, there are no RCTs at the present time that include only symptomatic stenosis and demonstrate the noninferiority of CAS compared to CEA, and there are also differences in treatments between guidelines published by several different international groups, reflecting the controversy regarding the efficacy of CAS.

In terms of CAS, due to the rapid advancements in devices and techniques and to appropriate patient selection due to the awareness of patients who are at a high risk of complications associated with CAS, its treatment outcomes have markedly improved compared to the results of various RCTs conducted in the past, which were the basis of the current guidelines. Another advantage of CAS over CEA is that operator experience has less influence on the outcome, which contributes to the recent increasing popularity of CAS. For this reason, it is essential to continually verify the efficacy of CAS through the latest RCTs in the future.

II. Asymptomatic stenosis

Ongoing RCTs: Treatment outcomes with BMT in patients with asymptomatic stenosis have markedly improved in the past 30 years. Consequently, treatment outcomes greatly differ between current and past RCTs, which were the basis of current guidelines. Consequently, the use of invasive CEA/CAS to treat asymptomatic stenosis should be re-evaluated at the present time. Continual validation through RCTs is therefore necessary when selecting the appropriate treatment for asymptomatic stenosis. Currently, there are several ongoing RCTs of asymptomatic stenosis, including Carotid Revascularization Endarterectomy versus Stent Trial 2 (CREST-2), the Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis versus Endarterectomy (SPACE-2) study, the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis (AMTEC), and Asymptomatic Carotid Surgery Trial-2 (ACST-2). The primary endpoint is stroke and death in first 30 days and ipsilateral stroke thereafter up to 4 years. SPACE-2 was originally a three-arm study that compares treatment outcomes among BMT, BMT + CEA, and BMT + CAS. Due to low recruitment rates, however, the protocol was changed in 2012 to split the three-arm trial into two separate two-arm clinical trials. The primary aim of the new study design is to compare CEA/CAS with BMT on a superiority level: SPACE-2A (CEA + BMT vs. BMT) and SPACE2-B (CAS + BMT vs. BMT). The sample size is 1,636 for each group and the primary efficacy endpoint is the cumulative rate of any kind of stroke or death from any cause within 30 days, plus ipsilateral ischemic stroke within 5 years of follow-up. The AMTEC study is a two-arm study that compares BMT and BMT + CEA in patients with a high degree of stenosis (70–79%). The primary outcomes of this study are nonfatal stroke, nonfatal MI, and death during follow-up of up to 5 years. ACST-2 is an RCT that studies patients who require revascularization but are not at a high risk of complications associated with either CEA or CAS, and is designed to fit in easily with normal clinical practice. The target enrollment of this study is 5,000 patients, and the main outcomes will be 30-day MI, stroke, and death, and 5-year stroke rates. Furthermore, sub-analysis related to procedural and stroke-related healthcare costs and QOL is also planned.

Identification of asymptomatic patients at higher risk for stroke: While it is termed “symptomatic
Evidence for Carotid Artery Disease

stenois," symptoms of cerebral infarction occur after a period of asymptomatic stenosis, and not all cases of asymptomatic stenosis can be definitely prevented with BMT. One of the major future challenges is to identify the group of patients who have a high risk of development of symptoms from among those with asymptomatic stenosis, in other words, to diagnose the group of patients who are more likely to benefit from CEA/CAS, and to accurately stratify asymptomatic stenosis based on the risk of cerebral infarction.

Promising imaging techniques for diagnosing high-risk patients include evaluation of plaque properties with ultrasonography or MRI, cerebrovascular reserve with transcranial Doppler (TCD) or nuclear medicine studies, asymptomatic silent microemboli with TCD, and asymptomatic cerebral infarction with CT or MRI. In particular, due to more profound understanding of the natural course of atherosclerosis resulting from advancements in vascular biology, plaque properties, in addition to the degree of stenosis, which is a conventional index of risk for cerebral infarction, have been shown to play an extremely important role in the development of symptoms. Histologically, plaques that are accompanied by conditions such as intraplaque hemorrhage, large lipid core, and thin fibrous cap are considered to be vulnerable plaques with a high risk of developing ischemia. On ultrasonography, echolucent plaques are considered to be more high risk than echogenic plaques. Due to significant advances in equipment and imaging techniques, it has become feasible to quite accurately diagnose plaque histology along with vulnerable plaques using MRI, and a prospective observational study in asymptomatic patients has also indicated the usefulness of MRI in diagnosing vulnerable plaques.

With consideration given to factors such as accuracy, convenience, and economic aspects, it is necessary to establish the most practical method of diagnosing unstable plaques in the future, and also to conduct an RCT to verify the safety and efficacy of CEA/CAS and BMT to treat asymptomatic stenosis based on this method.

Summary

The validity of CEA for symptomatic carotid moderate to high-grade stenosis appears to be established. Due to the additional option of CAS, it is necessary to comprehensively determine whether CEA or CAS is more appropriate for each individual patient. Moreover, since there are rapid advancements in devices for CAS and improvements in treatment outcomes, continual learning of the latest treatment method is essential.

Due to significant improvements in the outcomes with BMT, there is a need to re-evaluate the use of invasive CEA/CAS especially for asymptomatic stenosis. Continual verification of the latest RCT that compares CEA, CAS, and BMT, and establishment of a diagnostic method that can accurately extract the group of patients who have the highest future risk of developing ischemia, are desired.

A revision in the Japanese Guidelines for the Management of Stroke 2009 is planned in 2015, and its content is of high interest.

Conflicts of Interest Disclosure

None

References

1) White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, Sacco RL: Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. Circulation 111: 1327–1331, 2005
2) Abbott AL: Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 40: e573–e583, 2009
3) North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 325: 445–453, 1991
4) Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis, North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 339: 1415–1425, 1998
5) Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST) Lancet 351: 1379–1387, 1998
6) Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR: Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. JAMA 266: 3289–3294, 1991
7) Barnett HJ, Warlow CP: Carotid endarterectomy and the measurement of stenosis. Stroke 24: 1281–1284, 1993
8) Rothwell PM, Gutnikov SA, Warlow CP: European Carotid Surgery Trialist’s Collaboration: Reanalysis of the final results of the European Carotid Surgery Trial. Stroke 34: 514–523, 2003

Neurol Med Chir (Tokyo) 55, March, 2015
9) Rothwell PM, Eliasziw M, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists' Collaboration: Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 361: 107–116, 2003

10) Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lièvre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touzé E, Giroud M, Hosseini H, Pillet JC, Favrolo P, Neau JP, Ducrocq X; EVA-3S Investigators: Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 355: 1660–1671, 2006

11) SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Friedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stinglege R, Zeumer H; Hacke W: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368: 1239–1247, 2006

12) International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PJ, Macdonald S, Lyer PA, Hendriks JM, Collum C, Nederkoorn PJ, Brown MM: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 375: 985–997, 2010

13) Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Sneed DB, Cutlip DE, Firth BG, Ouriel K; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 351: 1493–1501, 2004

14) Brott TG, Hobson RW, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CRESt Investigators: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 363: 11–23, 2010

15) Forsting M: Shortcomings and promises of recent carotid-stenting trials. *Lancet Neurol* 6: 101–102, 2007

16) Mas JL, Chatellier G; EVA-3S investigators: Recent carotid stenting trials. *Lancet Neurol* 6: 295–296, 2007

17) Setacci C, Cremonesi A; SPACE and EVA-3S trials: the need of standards for carotid stenting. *Eur J Vasc Endovasc Surg* 33: 48–49, 2007

18) Veith FJ, Paraskevas KI: Influence and critique of CRESt and ICSS Trials. *Semin Vasc Surg* 24: 153–156, 2011

19) Gurun HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Ansel G, Strickman NE, Wang H, Cohen SA, Massaro JM, Cutlip DE; SAPPHIRE Investigators: Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 358: 1572–1579, 2008

20) Dumont TM, Rughani AI: National trends in carotid artery revascularization surgery. *J Neurosurg* 116: 1251–1257, 2012

21) Thomas DJ: Protected carotid artery stenting versus endarterectomy in high-risk patients reflections from SAPPHIRE. *Stroke* 36: 912–913, 2005

22) Paraskevas KI, Mikhaillidis DP, Liapis CD, Veith FJ: Critique of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): flaws in CREST and its interpretation. *Eur J Vasc Endovasc Surg* 45: 539–545, 2013

23) Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, Goldstein LB, Meschia JF, Ferguson RD, Moore WS, Howard G, Brott TG; CREST Investigators: Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 42: 675–680, 2011

24) Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD, Gonzales NR, Sheffet AJ, Voeks JH, Meschia JF, Brott TG; CREST investigators: Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol* 10: 530–537, 2011

25) Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh WC, Aronow HD, Eskandari MK, Sheffet AJ, Lal BK, Meschia JF, Brott TG; CREST Investigators: Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. *Stroke* 42: 3484–3490, 2011

26) Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 273: 1421–1428, 1995

27) Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group: Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 363: 1491–1502, 2004

28) LeFevre ML; U.S. Preventive Services Task Force: Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 161: 356–362, 2014

29) Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group: 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis.
(ACST-1): a multicentre randomised trial. *Lancet* 376: 1074-1084, 2010

30) Silleisen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, Messig M, Welch KM: Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investigators: Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 39: 3297-3302, 2008

31) Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ; American College of Cardiology; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American American College of Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery: 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Circulation* 124: e54-e130, 2011

32) Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery: Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg* 54: e1-e31, 2011

33) European Stroke Organisation, Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, Heras M, Kownator S, Minar E, Ostergren J, Poldermans D, Rambau V, Roffi M, Röther J, Sievert H, van Sambeek M, Zeller T; ESC Committee for Practice Guidelines: ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 32: 2851-2906, 2011

34) Carotid Stenting Guidelines Committee: an Inter-collegiate Committee of the RACP (ANZAN, CSANZ), RACS (ANZSVS) and RANZCR: Guidelines for patient selection and performance of carotid artery stenting. *Intern Med J* 41: 344-347, 2011

35) Paraskevas KI, Mikhailidis DP, Veith FJ: Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg* 55: 1504–1508, 2012

36) Chaturvedi S, Matsumura JS, Gray W, Xu C, Verta P; CAPTURE 2 Investigators and Executive Committee: Carotid artery stenting in octogenarians: periprocedural stroke risk predictor analysis from the multicenter Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) clinical trial. *Stroke* 41: 757–764, 2010

37) Safian RD: Carotid artery stenting and CABANA: implications for credentialing. *Catheter Cardiovasc Interv* 84: 1005–1006, 2014

38) Morales-Valero SF, Lanzino G: Asymptomatic carotid artery stenosis: time to rethink our therapeutic options? *Neurosurg Focus* 36: E2, 2014

39) Lal BK, Meschia JF, Brott TG: CREST-2: guiding treatments for asymptomatic carotid disease. *Endovascular Today* (September): 73–76, 2013

40) Reiff T, Stinele R, Eckstein HH, Fraedrich G, Jansen O, Mudra H, Mansmann U, Hacke W, Ringleb P; SPACE2-Study Group: Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy: SPACE2 - a three-arm randomised-controlled clinical trial. *Int J Stroke* 4: 294–299, 2009

41) Kolos I, Loukianov M, Dupik N, Boytsov S, Dee A: Optimal medical treatment versus carotid endarterectomy: the rationale and design of the Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis (AMTEC) study. *Int J Stroke* 2013 [Epub ahead of print]

42) Rudarakanchana N, Dialynas M, Halliday A: Asymptomatic Carotid Surgery Trial-2 (ACST-2): rationale for a randomised clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis. *Eur J Vasc Endovasc Surg* 36: 239–242, 2009

43) Reiff T, Eckstein HH, Amiri H, Hacke W, Ringleb PA; SPACE2-Study Group: Modification of SPACE-2 study design. *Int J Stroke* 9: E12–E13, 2014

44) Gupta A, Chazen JL, Hartman D, Delgado D, Anumula N, Shao H, Mazumdar M, Segal AZ, Kamel H, Leifer D, Sanelli PC: Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *Stroke* 43: 2884–2891, 2012

45) Markus HS, King A, Shipley M, Topkian R, Cullinane M, Reihill S, Bornstein NM, Schaafsma A: Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol* 9: 663–671, 2010

46) Kakko SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M, Geroulakos G, Nicolaides AN; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group: Silent embolic infarcts on
computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc Surg* 49: 902–909, 2009

47) Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, Tegos T, Geroulakos G, Labropoulos N, Dore CJ, Morris TP, Naylor R, Abbott AL: Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg* 52: 1486–1496. e5, 2010

48) Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, Dunning A, Mushlin AI, Sanelli PC: Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* 44: 3071–3077, 2013

49) Esposito-Bauer L, Saam T, Ghodrati I, Pelisek J, Heider P, Bauer M, Wolf P, Bockelbrink A, Feurer R, Sepp D, Winkler C, Zepper P, Boeckh-Behrens T, Riemenschneider M, Hemmer B, Poppert H: MRI plaque imaging detects carotid plaques with a high risk for future cerebrovascular events in asymptomatic patients. *PLoS ONE* 8: e67927, 2013

Address reprint requests to: Kazumichi Yoshida, MD, PhD, Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, Kyoto 606-8507, Japan. e-mail: kazuy@kuhp.kyoto-u.ac.jp