INTERVENTIONAL RADIOLOGY
Official journal of the Japanese Society of Interventional Radiology and Asia Pacific Society of Cardiovascular and Interventional Radiology

REVIEW

Current Status of Carotid Artery Stenting

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Abstract:
In 2008, carotid artery stenting was formally approved in Japan. Since then, more than fourteen years have already passed. Much evidence concerning carotid artery stenting has already been published, and several new devices are available. Thus, indications and procedures for carotid artery stenting have changed. In this review, I describe the current status of carotid artery stenting by literature review with particular focus on the evidence regarding its effectiveness and safety, history with the transition of devices in Japan, and complications related to carotid artery stenting procedures. A recent topic (a new category of subtype of carotid stenosis) is also mentioned briefly.

Keywords:
carotid artery stenting (CAS), evidence of CAS, Japanese history of CAS

Interventional Radiology 2024; 9(3): 122-126
https://doi.org/10.22575/interventionalradiology.2022-0020
https://ir-journal.jp/

Background

In 2008, when CAS (carotid artery stenting) was formally approved in Japan. Over 14 years later, new evidence about CAS has been published in Japan, European countries, and the United States, and several new devices have become available. As a result, CAS indications and procedures have changed. So in this review, I describe the current status of CAS by literature review with particular focus on the evidence regarding its effectiveness and safety, history with the transition of devices in Japan, and complications related to CAS procedures. In addition, I mention a recent topic (a new category of subtype of carotid stenosis).

Evidence Regarding CAS Effectiveness and Safety

In 2004, the SAPPIHRE study, a randomized control trial (RCT) of CAS and Carotid endarterectomy (CEA) among CEA high-risk patients, showed CAS was not inferior to CEA [1]. According to this evidence, CAS was approved for only CEA high-risk patients. However, as RCT for CAS in standard risk patients undergoing CEA, Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) was conducted in 2006 to compare stenting with endarterectomy in patients with symptomatic carotid stenosis of at least 60% [2]. This study was interrupted during the study because the periprocedural stroke rate was much higher in CAS (9.6%) than in CEA (3.9%). This study showed CAS was inferior to CEA. The cause of the high stroke rate in the CAS group was speculated that the embolic protection device (EPD) in CAS procedure was not mandatory and operator skill also was not high enough compared with the SAPPHIRE study. However, FU data of EVA-3S suggested that CAS was as effective as CEA for the middle-term prevention of ipsilateral stroke. The safety of CAS needed to be improved before it could be used as an alternative to CAS in patients with symptomatic carotid stenosis at that time [3].

In 2010, International Carotid Stenting Study (ICSS), which was conducted as RCT for symptomatic stenosis in standard risk patients for CEA in Europe, also showed primary endpoints (stroke, MI, death) were inferior in CAS (8.5%) than in CEA (5.2%) [4].

In addition, a sub-analysis of ICSS documented DWI-positive rate was higher in CAS using an embolic protection device (EPD) (73%) than in CEA (17%) [5].

However, in the same year, an RCT Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) study for symptomatic and asymptomatic carotid stenosis in patients with standard risk for CEA was conducted. It showed the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly between the

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Received: May 11, 2022, Accepted: July 28, 2022, Advance Publication by J-STAGE: February 9, 2023

groups undergoing CAS and CEA. Periprocedural MI was higher in CEA (2.3%) than in CAS (1.1%). Periprocedural stroke was higher in CAS (4.1%) than in CEA (2.3%). Ipsilateral stroke rate in follow-up data showed there were no significant differences between the CAS group (2.0%) and the CEA group (2.4%) [6].

Therefore, the CREST study concluded that among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing CAS and the group undergoing CEA. Both CEA operators and interventionists in this study were highly skilled physicians. In particular, interventionists were certified after a satisfactory evaluation of their endovascular experience, carotid stenting results, hands-on training, and a lead-in training phase [7].

According to the result of the CREST study, American Heart Association changed the classification of recommendation as follows: CAS was classified as Class I like CEA in symptomatic stenosis. As for asymptomatic stenosis, CAS was classified as Class IIb, unlike CEA, which was classified as IIa.

The Asymptomatic Carotid Trial (ACT) I, an RCT, compared the outcomes of CEA versus CAS with EPD in patients with asymptomatic severe carotid artery stenosis at standard risk for surgical complications [8]. Among previous RCTs between CEA and CAS, for the first time ACT I showed there was no significant difference between the two groups regarding periprocedural stroke. Not only stroke but also MI didn't differ between the two groups. Ipsilateral stroke rate in 5 years follow-up data showed no significant differences between the CAS group (2.2%) and the CEA group (2.7%).

On the other hand, the SPACE 2 study regarding asymptomatic patients did not show CEA and CAS were superior to the best medical treatment. Because of slow patient recruitment, this study was prematurely terminated in 513 patients [9].

From this recent evidence, the 2021 European Stroke Organization stated that based on moderate evidence level, CEA is recommended for patients with ≥60-99% asymptomatic carotid stenosis, considered a high-risk lesion of stroke despite best medical treatment alone. CEA is recommended for patients with 70%-99% symptomatic stenosis based on moderate evidence level. It is suggested for patients with 50%-69% symptomatic stenosis. Based on strong evidence, CEA should be performed for patients with ≥50%-99% symptomatic stenosis, ideally within two weeks after symptoms like the retinal or cerebral ischemic event. On the other hand, regarding CAS based on low-level evidence, CAS may be considered only for patients < 70 years old with symptomatic ≥50%-99% carotid stenosis.

In Europe, unlike in the United States, particularly for asymptomatic patients, CAS is not yet recommended as CEA because of a lack of European evidence. CREST 2 study has been undergoing since 2014. This study is RCT between CAS, CEA, and the best medical treatment for asymptomatic carotid stenosis. The result will be shown in October 2022. This study result really will have a great impact on treatment guidelines for patients with asymptomatic stenosis.

The History of CAS and Transition CAS Devices in Japan

In Japan, cardiologists (Nobuyoshi and Yokoi) performed the first CAS in 1996. Then in 1997, neurosurgeons Taki and Sakai performed the first CAS. After that in 1999, as for radiologist, Kichikawa, Nakagawa and author performed first CAS.

Before CAS was formally approved, several types of peripheral vascular stents, such as the Smarter stent (Cardinal Health Inc, Dublin, OH, USA) and Wallstent (Boston Scientific Corporation) were used with distal protection balloons (Nabi balloon, KANEKA MEDIX CORP, Osaka, Japan; PercuSurge™, Medtronic Vascular, Santa Rosa, CA, USA) or a filter wire (Mitchcatch, IR medical, Japan).

When CAS was approved in Japan in 2008 for EPD, only Angioguard™XP/RX (Cardinal Health Inc) was available. Only the Precise stent (Cardinal Health Inc) could be used then.

In 2010, FilterWire EZ™ (Boston Scientific Corporation), a filter protection device, and PercuSurge™ (Medtronic, Vascular), a balloon protection device, were approved for EPD. In 2012, Spider FX™ (Medtronic, Vascular) was a filter protection device and MO.MA™ Ultra (Medtronic, Vascular) is a proximal protection device.

Regarding stents, in 2010, Carotid WallStent™ (Boston Scientific Corporation), a closed-cell design, was approved. In 2012, Protégé™ (Medtronic, Vascular), an open cell design, was approved.

Nowadays, the CAS devices that can be used in Japan are similar to those in European countries. In addition, in 2020, the Casper stent (Terumo Co., Tokyo, Japan), a micromesh stent expected to prevent plaque protrusion, was approved. As the clinical trial for government approval of Casper stent in patients at either high or normal risk for CEA was conducted in Japan [10], the indication for CAS was expanded for not only CEA high-risk patients but also conventional risk patients when Casper stent is used.

Procedure-related Complications

Periprocedural ischemic stroke

Although it was considered to be that EPD might prevent ischemic stroke during CAS, Kotsugi et al. [11] reported EPD could not prevent ischemic stroke, and plaque protrusion (PP) was strongly associated with ischemic stroke. It was reported that the incidence of PP was 2.6%, and risk factors of PP reported the use of open cell stent and unstable plaque. Avoiding PP is necessary to reduce ischemic stroke during CAS; therefore, a smaller stent cell size is required. Myouchin et al. [12] reported CAS using two conventional closed-cell stents for all patients with carotid

stenosis with unstable plague. No PP and postprocedural ischemia were observed in patients who underwent CAS using the closed-cell stent-in-stent technique.

On the other hand, micromesh stents, whose smaller stent cell sizes than conventional stents, have already been developed and available for clinical use.

Micromesh stents may have developed to prevent PP. Micromesh stents have been expected to prevent PP and reduce ischemic stroke during CAS. Several studies with micromesh stents showed that the periprocedural ischemic stroke rate was much lower than in previous studies using conventional stents. At the moment, the following three micromesh stents are available in the world Roadsaver or Casper (Terumo Co., Tokyo, Japan), C-guard (Inspire MD, Boston, MA, USA), and Gore® Carotid Stent (GCS; W.L. Gore & Associates, Inc., Flagstaff, AZ, USA). In C-guard (Inspire MD), among 106 CAS procedures, the ipsilateral stroke rate was only one minor stroke (0.9%) [13]. In Roadsaver among 100 CAS procedures, minor stroke occurred in 1 patient (1%) [14], regarding Gore® Carotid Stent (GCS; W.L. Gore & Associates, Inc.) among 265 CAS procedures, minor stroke occurred in three patients (1.1%) [15]. Ipsilateral stroke rate using micromesh stents was the lowest among previous studies using conventional stents. In addition, several studies with one-year follow-up data also showed favorable results. Regarding Roadsaver or Caser, ipsilateral stroke, restenosis, and retreatment were 4.2%, 7.5%, and 2.1%, respectively [16]. Concerning C-guard, ipsilateral stroke rate, restenosis rate, and retreatment was 0%, 0.2%, 0.2% [17] respectively. In Carotid Gore, the ipsilateral stroke rate and retreatment were 1.2% and 1.2%, respectively [15].

The ipsilateral stroke and retreatment rates in Roadsaver or Casper seemed higher than in others. In a Japanese study using the Casper stent, the treatment result was better than the European one. Ipsilateral stroke rate within 30 days and within 1 year, retreatment rate was 1.4%, 0%, and 2.1%, respectively [10].

Casper stent has been available since 2020 in Japan. Therefore Casper stent will be used more than conventional stents.

Ischemic Lesion on DWI after CAS

The ischemic lesion positive rate on DWI in CAS is considered much higher than in CEA [18]. It was considered that asymptomatic new ischemic lesions might lead to long-term clinical complications like cognitive decline and dementia [19]. So reducing ischemic lesions as less as possible is needed in CAS. Furthermore, the recurrent TIA or stroke rate after CAS is significantly higher in the group with DWI-positive lesions than in the group without DWI-positive lesions [20]. Therefore, it is recommended to reduce ischemic lesions to prevent recurrent stroke. It was already reported stent design [21], plaque morphology [22], and prestatin therapy [23] were associated with an ischemic lesion on DWI after CAS. So, selecting devices and statin therapy are also important to reduce ischemic lesions.

Hyperperfusion Syndrome (HPS)

HPS, including intracranial hemorrhage, is a serious complication after CEA or CAS. The incidence of HPS was reported as 0.2%-18.9%. However, HPS seemed to be lower in CAS than in CEA. HPS and intracranial hemorrhage incidence in CAS were 1.1% and 0.7%, respectively [24]. Although strict control of blood pressure may help prevent life-threatening hemorrhage, it doesn't seem easy to prevent HPS completely.

Yoshimura et al. [25] reported that staged angioplasty for carotid artery stenosis followed by delayed CAS (SAP) could effectively prevent HPS among eighteen patients at high-risk of postprocedure HPS. In the conventional carotid artery stenting group, 5 of 9 patients (56%) showed HPS just after CAS, and status epilepticus was observed in 1 patient (11%) due to HPS. In the SAP group, none of the 8 patients were found, and postprocedure HP phenomenon or HP syndrome occurred in only one patient who required stent placement during the first stage owing to a wall dissection.

Murai S et al. [26] also described SAP in twenty-six patients with a high-risk for HPS. Although all patients had severe impairment of hemodynamic reserve was assessed by 123I-IMP SPECT with acetazolamide, HPS was not observed in any patients. Therefore SAP may become a way to prevent HPS after CAS.

Follow-up Result

Several studies have shown no differences between CAS and CEA regarding preventing stroke after treatment. In the CREST study, the ipsilateral stroke rate in 4 years follow-up, CAS and CEA was 2.0% and 2.4%, respectively [6].

In the ACT 1 study, in 5 years of follow-up, CAS and CEA were 2.7% and 2.2%, respectively [8]. Ten years of follow-up data from the CREST study showed no differences between CAS (6.9%) and CEA (5.6%) [27].

Concerning restenosis after CAS, it was considered that the restenosis rate was 2.27% to 8.3%. And Cilostazole was also recognized to be able to reduce restenosis after CAS [28]. Restenosis often occurs within 6 months after CAS [28,29]. However, it rarely becomes symptomatic, and the retreatment rate reported was 3.7% [29].

New Category of Subtype of Carotid Stenosis

Nearly occlusion with full collapse

It has been considered to be that carotid near occlusions (NO) shows a lower risk of stroke than other types of severe stenosis. Therefore NO should be treated with CEA. However, recently published evidence suggests a significant difference in stroke risk between NO with full and without full collapse. A prospective study was conducted to assess stroke

recurrence rate among 230 consecutive patients with symptomatic 50%-99% carotid stenosis, including near-occlusion by Johansson et al. [30]. They showed that the 90-day risk of recurrent stroke rate was significantly higher in symptomatic NO with full collapse (43%) group than in symptomatic NO without full collapse (0%) group or symptomatic 50%-99% carotid stenosis (18%) group. In addition, all recurrent stroke cases of NO with full collapse occurred within four weeks. Therefore, revascularization should be considered in patients with symptomatic NO with full collapse to prevent stroke. There were a few reports regarding CAS for NO with full collapse. Omoto et al. [31] reported CAS for NO with a full collapse in 18 cases. They described that CAS was successful in all cases, and no periprocedural ischemic complication was observed. They concluded only well-experienced physicians should perform CAS because highly technique was required to perform CAS for NO with full collapse.

Summary

The purpose of CAS is to prevent stroke. When a stroke during CAS occurs, it seems to put the cart before the horse. Therefore physician has to reduce stroke during CAS as less as possible.

Conflict of Interest: None

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