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Review Article

Carotid Artery Stenting Using a Double-layer Micromesh Stent

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Carotid artery stenting (CAS) has recently emerged as a potential alternative to carotid endarterectomy (CEA) in Japan. However, one of its disadvantages is the higher incidence of ischemic complications than CEA, such as distal embolism during or after the procedure. Plaque protrusion (PP) through the stent strut after deployment of the stent has been suggested as one of the major causes of distal embolism, especially in patients with unstable plaques. The need for increased plaque coverage to reduce the risk of PP through the stent struts has led to the development of a double-layer micromesh stent (micromesh stent) system. This stent system has already been used clinically in European countries with good short- to medium-term follow-up results. Also clinical trials evaluating micromesh stents have been completed in Japan. Hence, usefulness of the micromesh stent for CAS is expected. According to the results of several clinical studies, CAS with the double-layer micromesh stent has the potential to minimize distal embolism during or after the procedure even in patients with unstable plaques. However, it may not be suitable for emergency CAS at this point. Also, since results of only short- to medium-term follow-up have been reported, longer-term follow-up will be required in the near future.

Keywords ▶ carotid artery stenosis, stroke, carotid artery stenting, plaque protrusion, double-layer micromesh stent

Introduction

Carotid artery stenting (CAS) has become a potential alternative to carotid endarterectomy (CEA). Recent randomized controlled trials showed that the risk of the composite primary outcome, including stroke, myocardial infarction, and death, did not differ significantly between CAS and CEA in both patients with symptomatic and asymptomatic carotid artery stenosis.[1–3] Moreover, in Japan, the number of CAS procedures performed has been increasing in the last decade. In 2017, CAS was performed more than twice as much as CEA (9502 CASs and 4115 CEAs).[4] On the other hand, one of the disadvantages of CAS is the higher incidence of distal embolism during or after CAS as compared to CEA. Due to improvements in embolic protection devices, the incidence of procedure-related embolic events decreased.[5–7] Recently, it was reported that plaque protrusion (PP) through the stent struts after stent deployment is probably one of the major causes of post-procedure ischemic complications, especially in patients with unstable plaques.[8–11] To reduce PP after stenting, new generation double-layer micromesh stents (micromesh stent) have been developed. The micromesh stent basically consists of novel thin-strut nitinol stents with a mesh covering. This design allows the device to trap and exclude thrombus and plaque debris, in order to prevent embolic events originating from the stenotic lesion[12] (**Fig. 1**).

Clinical studies have indicated the superiority of micromesh stents over conventional stents for CAS. These stents have already been clinically used in European countries and have demonstrated good short- to medium-term follow-up results.[13–17] A clinical trial using the micromesh stent has been performed in Japan as well (UMIN trial ID: UMIN000023562). Therefore,

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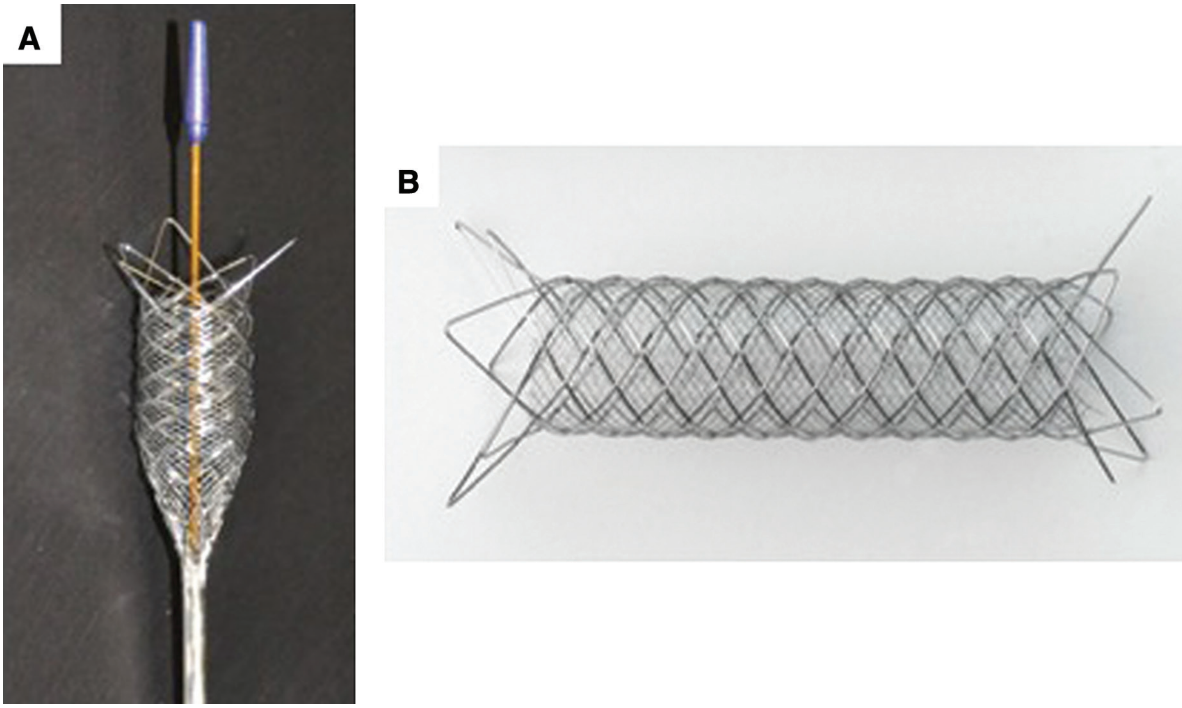

Fig. 1 Dual-layer micromesh stent (Courtesy of Terumo). (**A**) and (**B**) In Japan, clinical trials studying the use of the CASPER stent (Terumo, Tokyo, Japan) have been completed.

performance of CAS using micromesh stents, which is expected to reduce post-procedure ischemic complications, is likely to increase in frequency in Japan. In this article, we report the effectiveness and limitations of CAS using the micromesh stent.

PP and Ischemic Complication during and after CAS

Several reports showed the association between PP and ischemic complications after CAS.

Kotsugi et al. reported a strong association between the presence of PP detected by intravascular ultrasound (IVUS) and perioperative ischemic stroke. According to their study, of a total of 354 CASs were analyzed using IVUS, PP was observed in 2.6% of cases, with ischemic stroke occurring in 66.7% of them.[11]

Funatsu et al. reported a significant relationship between PP with attenuation detected by optical frequency domain imaging (OFDI) and new ipsilateral ischemic brain lesions detected by diffusion-weighted imaging (DWI) on MRI after CAS. OFDI is an intravascular imaging technique that uses near-infrared light rather than ultrasound to generate high-resolution images. A total of 65 CASs were analyzed using OFDI. PP was observed in 46% of cases. Patients in the DWI-positive group had a significantly higher incidence of PP with attenuation ($p = 0.04$). They also reported that multivariate analysis demonstrated that the presence of PP with attenuation on OFDI (OR, 2.94; 95% CI, 1.05–8.68, $p = 0.04$) was an independent predictor of new periprocedural brain lesions after CAS.[18]

Although the detectability of PP might differ between imaging modalities, the results of the above studies indicated that it is important to prevent and treat PP to reduce ischemic complications after CAS.

Clinical Results of CAS Using a Micromesh Stent

Micromesh stents have already been used clinically in European countries and have demonstrated good short- to medium-term follow-up results.[14–18]

Stabile et al. reported the results of a patient-based meta-analysis of four clinical studies using micromesh stents. They analyzed 556 CASs with micromesh stents. Among them, the incidence of ischemic stroke at 30 days was only 1.25% (7/556) and any stroke and death rate at 30 days was 1.44% (8/556). Even though their study was not a meta-analysis, based on the number of patients, randomized controlled trials, and consisted from relatively more number of asymptomatic patients, they concluded that micromesh stents can be safely used for CAS[17] (**Table 1**).

Table 1 Overview of clinical trials using double-layer micromesh stent

	CLEAR-ROAD (13) (n = 100)	IRON-Guard (14) (n = 200)	PARADIGM (15) (n = 106)	Italian Roadsaver Registry (16) (n = 150)
Age, years	73.4 ± 9.5	72.6 ± 7.1	68.9 ± 7.5	74 ± 7.8
Male, % (n)	70 (70)	66 (132)	69.8 (74)	75.3 (113)
Symptomatic, % (n)	31 (31)	1.5 (3)	46.2 (49)	8.7 (13)
High-risk characteristics, % (n)	100 (100)	46.5 (93)	52.8 (56)	25.3 (38)
Stenosis, %	85.3 ± 8.0	78.6 ± 6.7	83 ± 9.7	81 ± 7.6
Use of EPD, % (n)	58 (58)	100 (200)	100 (106)	100 (150)
MAE, % (n)	2 (2)	2.5 (5)	0.9 (1)	0 (0)
Minor stroke	1	5	1	0
Major stroke	0	0	0	0
MI	1	0	0	0

EPD: Emboric protection device; MAE: Major adverse event; MI: Myocardial infarction

Nerla et al. reported the results of a 12-month follow-up of CAS with micromesh stents. They analyzed 150 CASs performed using a Roadsaver stent (Terumo, Tokyo, Japan); data completeness at follow-up in their study was 100%. They reported three deaths (2%) in the entire patient cohort, which were not related to the index procedure. No major or minor cerebrovascular events were reported at the 12-month follow-up. Three patients (2%) developed restenosis, as shown using Doppler ultrasound examination. They concluded that use of the Roadsaver stent is associated with good short- to mid-term results and that the stent does not seem to be associated with a higher rate of in-stent restenosis at the 12-month follow-up.[19]

Montorsi et al. reported a randomized trial comparing micromesh stents with the conventional single-layer closed-cell stent in patients with unstable plaques. They used transcranial Doppler ultrasound (TCD) to count the number of micro-embolic signals (MES). In patients with high risk, lipid-rich plaques undergoing CAS, they showed that the micromesh stent was associated with fewer MES detected by TCD compared with the single-mesh stent.[20]

According to the results of the above studies, CAS with the micromesh stent is safe and might be especially effective in patients with unstable plaques.

Potential of Micromesh Stent in Preventing PP

Several researchers, including our team, evaluated the incidence of PP after CAS using the micromesh stent versus that after conventional stent deployments. Both studies used optical coherence tomography (OCT) or OFDI to qualitatively or quantitatively evaluate PP.

Umemoto et al.[7] reported that the incidence of PP after CAS with micromesh stents was 10.5%–20.7%. Previously, Liu et al.[21] reported an incidence of PP after CAS with conventional stents ranging from 49.1% to 65.5%. They also reported that patients with lipid-rich plaque demonstrated a higher rate of PP compared to patients with non-lipid-rich plaque (65.5% vs 49.1%, $p < 0.001$).[21]

We also recently performed a quantitative analysis to compare the incidence of PP after CAS with micromesh stents versus conventional single-layer stents using OFDI in patients with unstable plaques detected by MRI, under the approval of our institutional ethics committee. We used the Casper stent (Terumo), which is identical to the Roadsaver stent used in Europe. In our study, the presence of PP was definitely lower in the Casper stent group (n = 9) compared with the conventional stent group (n = 37) (44% vs 86%; $p = 0.022$). In addition, the mean PP area was significantly smaller in the Casper stent group (0.013 ± 0.034 mm^2 vs. 0.057 ± 0.09 mm^2, $p = 0.006$)[22] (**Figs. 2–4**). No patient experienced post-procedural neurologic complications.

The results of the above studies suggest that micromesh stents are potentially superior to conventional stents in terms of preventing PP after CAS even in patients with unstable plaques.

Limitations of CAS Using the Micromesh Stent

Although short- to medium-term follow-up studies have demonstrated acceptable results of elective CAS using the micromesh stent, the results of emergency CAS with micromesh stents are not acceptable.

De Vries et al. reported on short-term micromesh stent patency following emergency CAS procedures. Their study included 54 patients, 27 of whom were treated for acute

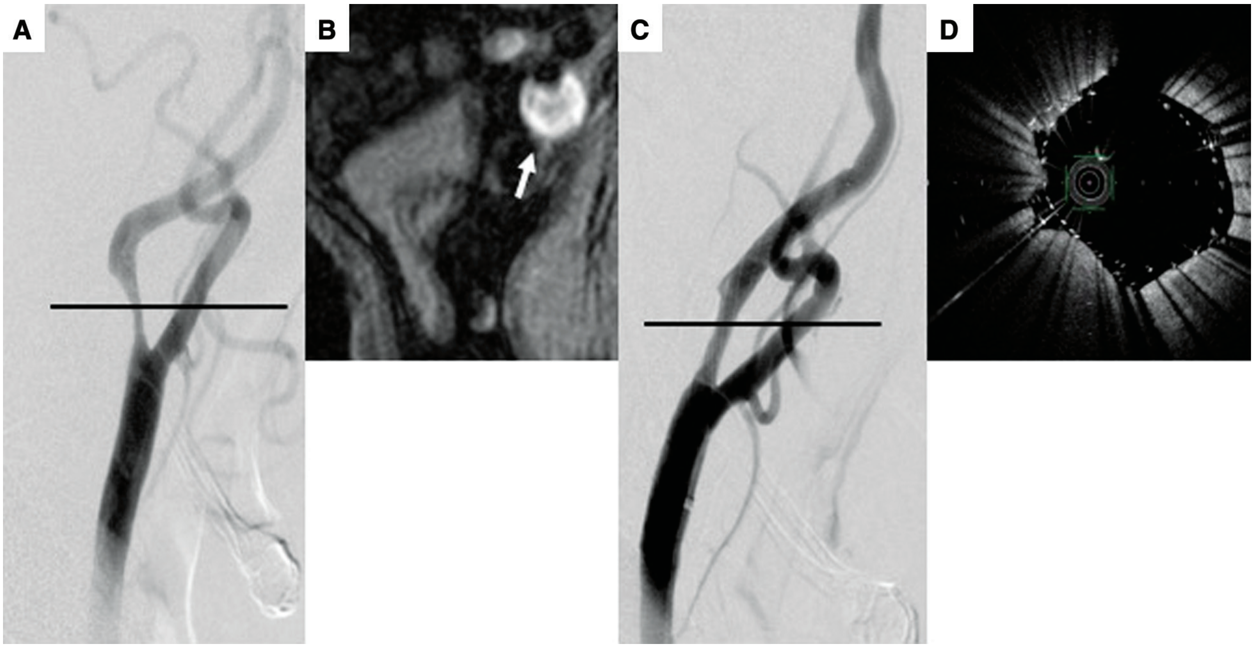

Fig. 2 Representative images that were negative for PP. A case of symptomatic left carotid artery stenosis and unstable plaques treated with a CASPER stent. (Moderated and cited from Yamada et al.[22] with permission from Elsevier). (**A**) DSA before CAS. (**B**) T1-weighted MRI of the carotid plaque demonstrating unstable plaques (signal intensity ratio with adjacent muscle was 2.62: white arrow). (**C**) DSA after CAS. The stenotic lesion was successfully dilated. (**D**) OFDI after CAS showing absence of PP. CAS: carotid artery stenting; DSA: digital-subtraction angiography; OFDI: optical frequency domain imaging; PP: plaque protrusion

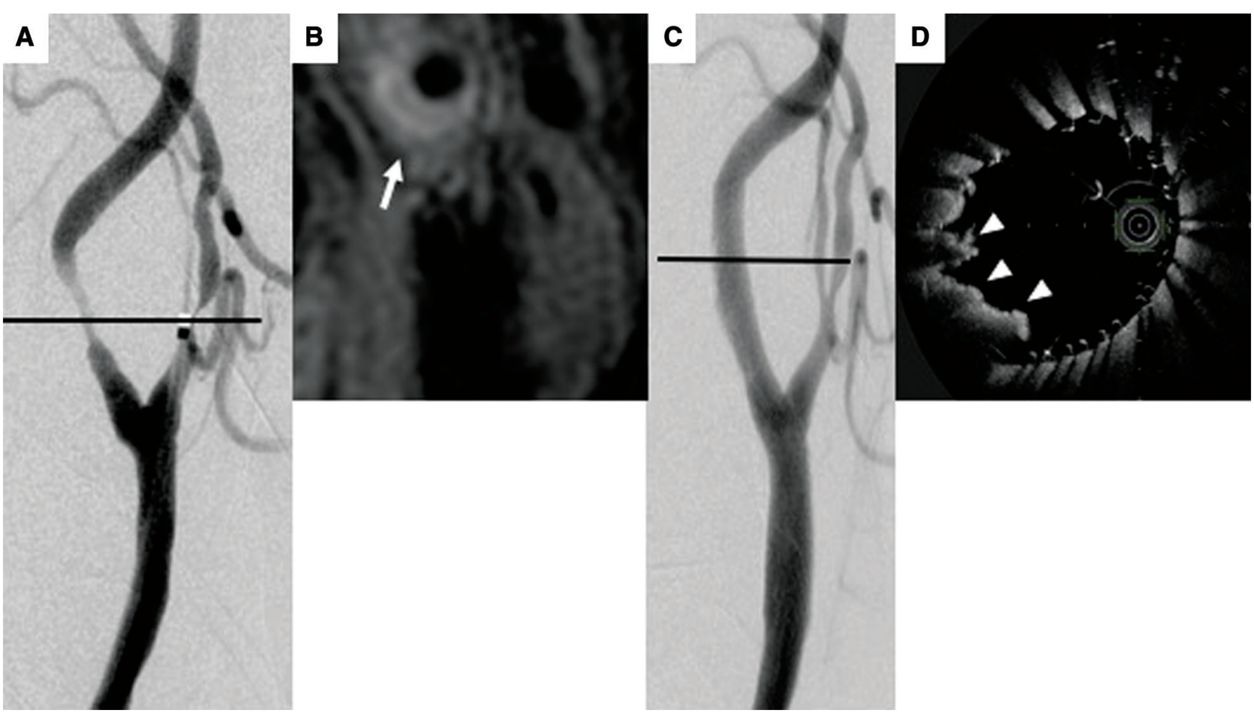

Fig. 3 Representative images positive for PP. A case of symptomatic left carotid artery stenosis and unstable plaques treated with a conventional stent. (Moderated and cited from Yamada et al.[22] with permission from Elsevier) (**A**) Digital-subtraction angiography before CAS. (**B**) T1-weighted MRI of carotid plaque indicated an unstable plaque (signal intensity ratio compared with adjacent muscle was 1.66: white arrow). (**C**) DSA after CAS. The stenotic lesion was successfully dilated. (**D**) OFDI after CAS showed large PP. CAS: carotid artery stenting; DSA: digital-subtraction angiography; OFDI: optical frequency domain imaging; PP: plaque protrusion

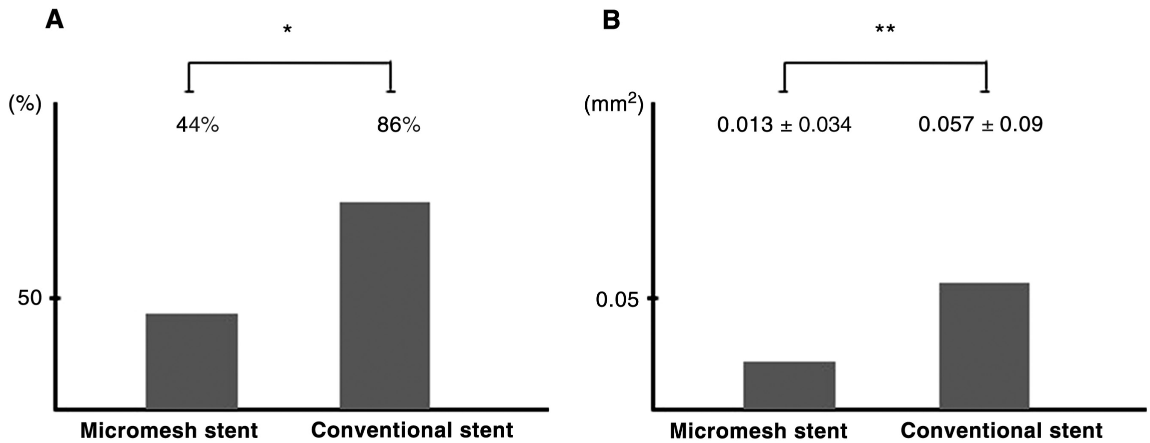

Fig. 4 Degree and mean area of PP after CAS in each stent group. (**A**) Degree of PP. $^{*}p = 0.022$. (**B**) Mean PP area. $^{**}p = 0.006$. CAS: carotid artery stenting; PP: plaque protrusion

stroke with tandem lesions and 27 for elective stenting. Follow-up images were available for nine patients with acute stroke and 19 patients with elective CAS. Stent occlusion was observed in 56% (5/9) of patients with acute stroke and 0% (0/19) of elective CAS cases.[23] Additionally, Yilmaz et al. investigated the use of a micromesh stent in patients treated by emergency CAS for acute stroke. They found an early stent occlusion rate of 45%.[24] This rate seems high compared with published clinical papers on the short-term patency of single layer mesh stents in acute stroke patients, with occlusion rates of conventional stents varying between 1% and 16%.[24–26]

Micromesh stents contain greater amounts of potentially thrombogenic material. This might be of relevance in acute stroke patients with insufficient preparation with antiplatelet drugs. Therefore, at this point, micromesh stents may not be suitable for the treatment of patients with acute stroke with tandem lesions. To establish evidence of the effectiveness of CAS with micromesh stents, a larger number of patients and longer-term follow-up are needed.

Conclusions

According to the results of several clinical studies, CAS with micromesh stents have the potential to minimize distal embolism during or after CAS even in patients with unstable plaques. However, these stents may not be suitable for use in emergency CAS procedures at this point. Additionally, since the results of only short- to medium-term follow-up have been evaluated, longer-term follow-up will be required in the near future.

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