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Long-term Durability of Coil Embolization for Unruptured Aneurysm after Introduction of the Neck-bridge Stent: Comparison between the Pre-stent Era and the Stent Era

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Abstract

More complex aneurysms can be treated by coil embolization with neck-bridge stent assistance. However, concerns about postprocedural ischemic or hemorrhagic complications remain. In this study, we assessed the long-term durability after introduction of neck-bridge stent in the context of coil embolization for unruptured aneurysm by comparing re-treatment and neurological events between the pre-stent and stent eras. Unruptured aneurysms treated by coil embolization between April 2005 and May 2018 were analyzed retrospectively. We divided cases into two groups: the pre-stent era and the stent era. The cumulative rate of re-treatment and neurological events were assessed and compared. During the period, 177 aneurysms were treated in the pre-stent era and 354 aneurysms were treated in the stent era. The median follow-up was 55 months. In the stent era, the dome/neck (D/N) ratio was significantly lower (P <0.001) and the number of aneurysms located at the posterior circulation was higher (P <0.001). A stent was used in 31.92% of cases in the stent era. The cumulative rate of re-treatment was significantly higher in the pre-stent era than it was in the stent era in univariate and multivariate analyses (P = 0.008, P = 0.008, respectively). The cumulative rate of neurological events was not significantly different between the two groups. The re-treatment rate has been improved without increasing neurological complications after introduction of the neck-bridge stent.

Keywords: coil embolization, neck-bridge stent, cerebral aneurysm

Introduction

Coil embolization of intracranial aneurysms is a less-invasive and promising treatment alternative to surgical clipping. The International Subarachnoid Aneurysm Trial Collaborative Group (ISAT) reported the safety, effectiveness, and long-term durability of coil embolization for ruptured aneurysms.[1,2] Regarding unruptured aneurysms, a very low rate of postprocedural rupture and long-term durability are also reported.[3,4] In this decade, the development and introduction of neck-bridge stents clearly contributed to the expansion of the indications for coil embolization of cerebral aneurysms. In addition to the enabling of the treatment of more-complex or wider-neck aneurysms, stent-assisted coil embolization (SACE) affords improvement of occlusion rates and a decrease in recurrence rates.[5–8] However, for SACE, in addition to the risk of intraprocedural complications, concerns remain about postprocedural ischemic or hemorrhagic events caused by in-stent stenosis or the continuation of antiplatelet

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treatment.[9,10] For asymptomatic patients harboring small- or medium-sized unruptured aneurysms, the safety and durability of this treatment are very important because the rupture rate of untreated asymptomatic unruptured aneurysms is not very high.[11,12] Therefore, long-term follow-up, especially after SACE, is essential.

The aim of this retrospective study was to assess the long-term durability after the introduction of the neck-bridge stent in the context of coil embolization of unruptured aneurysms by comparing the clinical results and long-term follow-up, including the rate of re-treatment and the occurrence of neurological events, between the pre-stent and stent eras.

Materials and Methods

Patients and aneurysms

The unruptured cerebral aneurysms treated at our hospital by coil embolization between April 2005 and May 2018 were retrospectively analyzed. The following cases were excluded: fusiform or dissecting aneurysms, mycotic aneurysms, aneurysms associated with arteriovenous malformation or moyamoya disease, aneurysms treated by parent artery occlusion or with use of a flow-diverting stent, and aneurysms for which the first treatment was performed at another hospital. We divided cases into two groups, the pre-stent era (cases between April 2005 and June 2010) and the stent era (cases between July 2010 and May 2018). In our country, the first neck-bridge stent was approved for the management of unruptured aneurysms in July 2010. This study was approved by our institutional review board and all patients provided informed consent for the anonymous use of their clinical data.

Pharmacological management and endovascular procedure

All the procedures of coil embolization were performed under general anesthesia. An initial intravenous bolus of heparin (4000–5000 U) was administered, and an activated clotting time of 250–300 s was maintained via additional heparin administration appropriately throughout the procedure.

A simple or adjunctive technique (balloon-assisted, double-catheter, or stent-assisted technique) was selected according to the morphology of the targeted aneurysms and the origin of the branching vessels. In the stent era, a variety of stents could be used, including Enterprise VRD (Codman & Shurtleff, Inc., Raynham, MA, USA), Neuroform EZ or Neuroform ATLAS (Stryker Neurovascular, Kalamazoo, MI, USA), and LVIS or LVIS Jr (MicroVention, Inc., Aliso Viejo, CA, USA). A neck-bridge stent might be adopted for a wide neck aneurysm when the dome/neck ratio (D/N ratio) was <2.0 and/or neck length was >4 mm. Furthermore, it was also considered, when sufficient embolization could not be achieved without stent, or when the coil loops protruded into the parent vessel (i.e. rescue stenting).

Patients were prescribed 100 mg of aspirin and 75 mg of clopidogrel (dual antiplatelet therapy [DAPT]) 7–14 days before the procedure. In cases of SACE, patients were medicated with DAPT for 12 months. After the performance of a follow-up angiography at 12 months after the procedure, one of the antiplatelet agents was discontinued and the other was continued. In cases without stent assistance, both of the antiplatelet drugs were terminated 1 month after the procedure.

Data collection and endpoints

We collected clinical data prior to coil embolization, including age, sex, and the following aneurysm characteristics: location, maximum size, and D/N ratio. The locations of aneurysms were divided into the following groups: internal carotid (IC aneurysms, with the exception of for IC-posterior communicating artery (IC-Pcom) aneurysms, such as IC-anterior choroidal artery, IC paraclinoid, and IC siphon aneurysms), anterior communicating artery + anterior cerebral artery (Acom+ACA), IC-Pcom, middle cerebral artery (MCA), and posterior circulation.

We analyzed the rates of re-treatment and neurological events associated with coil embolization and the postprocedural course. Re-treatment was performed for major recanalization after treatment if the recanalized space was enough for insertion of additional coils or applying a surgical clip, or the aneurysm size was enlarged. The date of the initial coil embolization was defined as day 0, for the follow-up. A neurological event was defined as any event that increased the score on the modified Rankin Scale (mRS), such as intraprocedural complications, postprocedural rupture, and postprocedural cerebral ischemic or hemorrhagic events.

Statistical analysis

Continuous variables are expressed as means and standard deviations. Categorical data are summarized as percentages and were compared using Fisher's exact test. Continuous data between groups were compared by Student's *t*-test for parametric variables or the Mann–Whitney *U* test for nonparametric variables.

The cumulative rates of neurological events or re-treatment were calculated using the Kaplan–Meier method, and the curves of the pre-stent era and the stent era were compared by log-lank test. A multivariate analysis was performed using a Cox

proportional-hazard model, and the hazard ratio (HR) was calculated. Significance was set at $P < 0.05$.

Results

Characteristics of the patients and aneurysms

After excluding the cases in which the follow-up data were not sufficient (15 cases), we analyzed 531 cases retrospectively. In all, 177 aneurysms were treated in the pre-stent era and 354 aneurysms were treated in the stent era. Among the patients in pre-stent era, 76.27% were females ($P = 0.463$). The mean age of the pre-stent era group was 60.35 ± 10.56 years, vs. 60.33 ± 10.97 years in the stent era group ($P = 0.989$). The maximum size of aneurysms was not significantly different (pre-stent era vs. stent era; 7.65 ± 3.59 vs. 7.11 ± 3.07 mm; $P = 0.093$) while the D/N ratio was significantly smaller in the stent era (pre-stent era vs. stent era; 1.92 ± 0.57 vs. 1.57 ± 0.53; $P < 0.001$). In the stent era, the number of aneurysms of the posterior circulation was higher ($P < 0.001$). The rate of utilization of neck-bridge stents was 31.92% (113/354) in the stent era. Among them, a single stent was used in most cases (108/113; 86.73%). The type of stent used was as follows: Enterprise VRD in 66 cases, Neuroform EZ in 14 cases, Neuroform ATLAS in 11 cases, LVIS in eight cases, and LVIS Jr in nine cases. Conversely, a multiple stent technique was applied in five cases (Y configuration stent technique in three cases, T stent in one case, and overlapping stent in one case). The details of the baseline characteristics of the aneurysms and the technique used for coil embolization in the two groups are shown in Table 1.

Periprocedural and remote neurological events, re-treatment cases

The median follow-up duration was 55 months (interquartile range [IQR]: 27–82 months). The re-treatment rate was higher in the pre-stent era than it was in the stent era ($P = 0.004$). The frequencies of periprocedural complication (<1 week) ($P = 0.590$) and remote neurological events ($P = 0.390$) were not different between groups. In terms of the details of remote neurological events, we encountered three postprocedural ruptures of the aneurysm in two of pre-stent era cases and in one stent era case over 2503 aneurysm-year. The annual probability of rupture of a targeted coiled aneurysm during the follow-up was 0.12%. *De novo* aneurysm rupture occurred in two cases (one case in the pre-stent era and one case in the stent era). In stent era cases, ischemic complications related with stent thrombosis or in-stent stenosis occurred in two cases, and hemorrhagic complications (intracerebral hemorrhage during antiplatelet therapy, rather than aneurysm rupture) occurred in four cases. Furthermore, an ischemic remote event was encountered in one pre-stent era case in which a neck-bridge stent was used at the time of re-treatment. These results are summarized in Table 1.

Cumulative rate of re-treatment

The unadjusted cumulative probability of re-treatment between pre-stent era and the stent era is shown in Fig. 1A. Univariate analysis revealed that the cumulative rate of re-treatment was significantly higher in cases of the pre-stent era compared with the stent era ($P = 0.008$; log-rank test). Subsequently, multivariate analyses using Cox regression were performed. These analyses confirmed that stent era (HR: 0.411; 95% confidence interval [CI]: 0.214–0.792; $P = 0.008$) and older age (HR: 0.961; 95% CI: 0.934–0.988; $P = 0.005$) were significantly associated with a lower risk of re-treatment, whereas female sex (HR: 3.341; 95% CI: 1.246–8.964; $P = 0.017$), aneurysms with a larger dome size (HR: 1.136; 95% CI: 1.080–1.195; $P < 0.001$), and aneurysm location at the posterior circulation compared with ICA (HR: 4.254, 95% CI: 1.906–9.457; $P < 0.001$) were significantly associated with a higher risk of re-treatment (Table 2). The adjusted cumulative probability of re-treatment is shown in Fig. 1B.

Cumulative rate of neurological events

The unadjusted cumulative probability of neurological events between the pre-stent era and the stent era is shown in Fig. 2A. Univariate analysis revealed that the cumulative rate of neurological events was not significantly different between cases of the pre-stent and stent eras ($P = 0.512$; log-rank test). Subsequently, a multivariate analysis using Cox regression was performed. These analyses confirmed that female sex (HR: 10.128, 95% CI: 1.337–76.581; $P = 0.025$), aneurysms with a larger dome size (HR: 1.160, 95% CI: 1.098–1.226; $P < 0.001$), and aneurysm location at the IC-Pcom compared with other ICA aneurysm (HR: 3.171, 95% CI: 1.190–8.447; $P = 0.021$) were significantly associated with a higher risk of neurological events (Table 3). The adjusted cumulative probability of neurological events in the pre-stent and stent eras is shown in Fig. 2B (not significant).

Comparison between the non-stent and stent groups in the stent era (sub-analysis)

A similar analysis was performed using only the patients of the stent era. In all, 113 aneurysms were treated via neck-bridge stent assistance (stent group) and 241 aneurysms were treated by other techniques

Table 1 Baseline characteristics, clinical outcomes, and retreatment cases

	Pre-stent era	Stent era	*P* value
N	177	354	
Gender (female)	135 (76.27)	259 (73.16)	0.463
Age (y)	60.35 ± 10.56	60.33 ± 10.97	0.989
Maximum size(mm)	7.65 ± 3.59	7.11 ± 3.07	0.093
D/N ratio	1.92 ± 0.57	1.57 ± 0.53	<0.001
Location of aneurysm			<0.001
IC	67 (37.85)	147 (41.52)	
Acom+ACA	28 (15.82)	59 (16.67)	
IC-Pcom	48 (27.12)	49 (13.84)	
MCA	6 (3.39)	19 (5.37)	
Posterior	28 (15.82)	80 (22.60)	
Technique of coiling			<0.001
Simple	35 (19.77)	40 (11.30)	
Balloon	129 (72.88)	193 (54.51)	
Double catheter	12 (6.78)	8 (2.26)	
Stent	1 (0.56)	113 (31.92)	
Periprocedural complication	6 (3.39)	12 (3.33)	0.590
Ischemic	3	2	
Hemorrhagic	3	6	
Others	0	4	
Remote complication	7 (3.95)	11 (3.11)	0.390
Ischemic	1	2	
Hemorrhagic	4	6	
Others	2	3	
Retreatment	23 (12.99)	20 (5.65)	0.004

ACA: anterior cerebral artery, Acom: anterior communicating artery, D/N: dome/neck, IC: internal carotid, MCA: middle cerebral artery, Pcom: posterior communicating artery.

(non-stent group). The maximum size of aneurysms was significantly larger in the stent group, further the D/N ratio was significantly lower in the stent group. In the multivariate analysis of the cumulative probability of re-treatment rate, maximum size and the aneurysms located at the posterior circulation were significant risk factors for re-treatment. In the multivariate analysis of the cumulative probability of neurological events, the maximum size and aneurysms located at the ICPC were significant risk factors for neurological events. The details of these results of sub-analysis were described in the supplementary materials (available online).

Discussion

We confirmed that the reduction of the re-treatment rate without increasing neurological complications after introduction of the neck-bridge stent. Although a higher number of wide-neck aneurysms were treated in the stent era vs. the pre-stent era, the re-treatment rate was substantially decreased in the

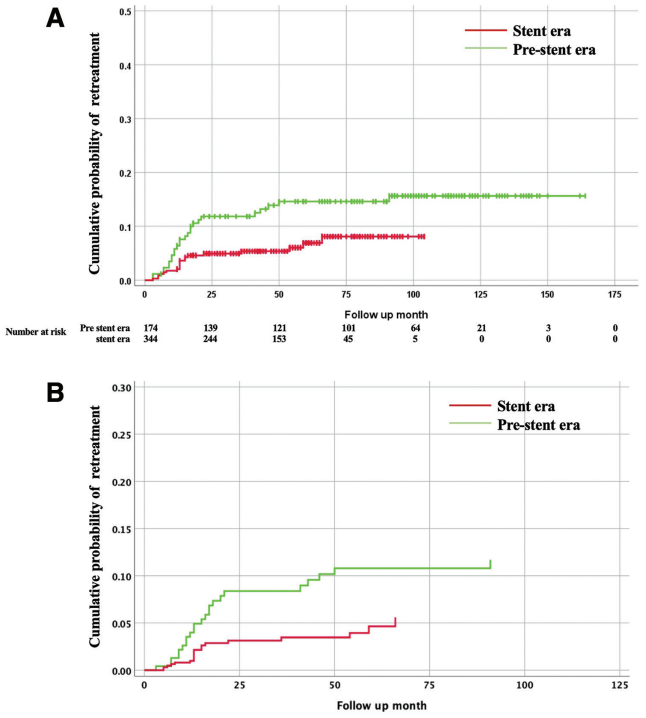

Fig. 1 Cumulative probability of re-treatment. Unadjusted Kaplan–Meier curve (A) and adjusted Kaplan–Meier curve (B) for comparing the pre-stent era with the stent era. The green curve represents the pre-stent era and the red curve represents the stent era.

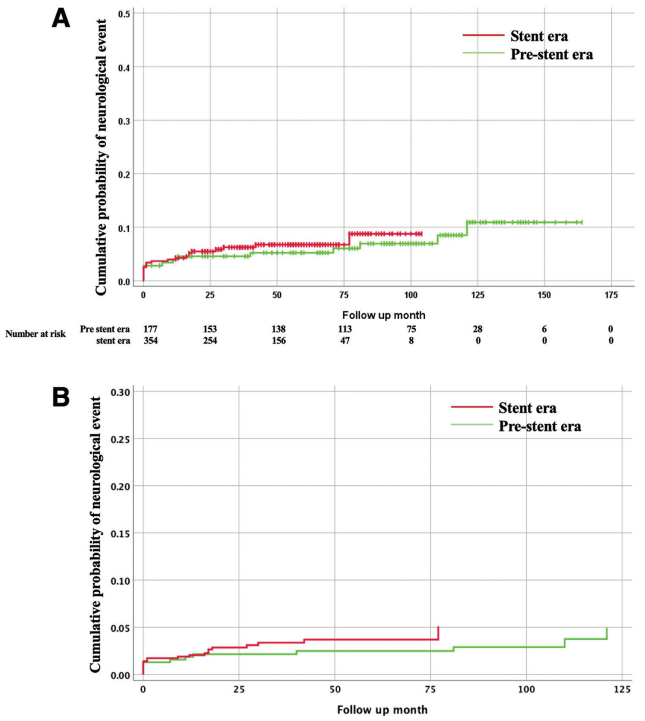

Fig. 2 Cumulative probability of neurological events. Unadjusted Kaplan–Meier curve (A) and adjusted Kaplan–Meier curve (B) for comparing the pre-stent era with the stent era. The green curve represents the pre-stent era and the red curve represents the stent era.

Table 2 Risk factor associated with retreatment

	Hazard ratio (95% CI)	*P* value
Sex (F)	3.341 (1.246–8.964)	0.017
Age	0.961 (0.934–0.988)	0.005
MAX	1.136 (1.080–1.195)	<0.001
D/N	0.874 (0.507–1.508)	0.629
Pre-stent era	Reference	
Stent era	0.411 (0.214–0.792)	0.008
Location of aneurysm		
IC	Reference	
Acom + ACA	2.916 (0.927–9.174)	0.067
IC-Pcom	1.955 (0.771–4.960)	0.158
MCA	4.061 (0.855–19.279)	0.078
Posterior	4.254 (1.906–9.457)	<0.001

ACA: anterior cerebral artery, Acom: anterior communicating artery, D/N: dome/neck, IC: internal carotid, MCA: middle cerebral artery, Pcom: posterior communicating artery.

former. As postprocedural aneurysmal rupture was extremely rare (0.12%/aneurysm year), follow-up and re-treatment were adequately performed.

A neck-bridge stent was used for the larger aneurysms and those with a wider neck in the stent era (sub-analysis). A univariate analysis showed that the re-treatment rate of the stent group was higher than that of the non-stent group. However, after multivariate analysis, the significance of the difference between the groups was lost. This analysis also revealed that stent use was not significantly associated with neurological event worsening on the mRS.

The neck-bridge stent might be one of the significant factors which contributed the reduction of the re-treatment rate. However, we could not assess the other factors which might be associated with treatment results, including volume embolization ratio (VER) and the development of the devices other than neck-bridge stent such as microcatheter, micro-balloon, and novel coils. With the recent development of various softer, smaller-diameter coils, the VER may have increased and may have contributed to the decrease in re-treatment. Further assessment is needed to evaluate the impact of a neck-bridge stent on the curability of coil embolization for a saccular aneurysm.

Our results showed that several factors were associated with re-treatment, including pre-stent era,

Table 3 Risk factor associated with neurological event

	HR (95% CI)	*P* value
Sex (F)	10.128 (1.337–76.581)	0.025
Age	1.014 (0.979–1.049)	0.439
MAX	1.160 (1.098–1.226)	<0.001
D/N	1.075 (0.611–1.892)	0.802
Pre-stent era	Reference	
Stent era	1.546 (0.677–3.529)	0.301
Location of aneurysm		
IC	Reference	
Acom+ACA	2.074 (0.516–8.331)	0.304
IC-Pcom	3.171 (1.190–8.447)	0.021
MCA	3.121 (0.634–15.360)	0.161
Posterior	2.276 (0.875–5.919)	0.092

ACA: anterior cerebral artery, Acom: anterior communicating artery, D/N: dome/neck, HR: hazard ratio, IC: internal carotid, MCA: middle cerebral artery, Pcom: posterior communicating artery.

younger age, female sex, larger aneurysm maximum size, and aneurysms located at the posterior circulation compared with ICA aneurysms. Previous reports also revealed the efficacy of neck-bridge stents for the prevention of recurrence.[5–8,13] Lawson MF and colleagues reported that stent use was a significant predictor of the progression of occlusion.[13] Those authors suggested that stents had the effects of neck bridging and flow remodeling, as well as a scaffolding effect. A larger aneurysm size is a well-known risk factor for recanalization of aneurysms and re-treatment.[3,14] Moreover, aneurysms located at the posterior circulation may be a more terminal type of aneurysm represented by a basilar tip, for which complete occlusion is difficult to obtain.[15] Our results seem to support these previous findings.

No significant increase in the incidences of neurological events, including intraprocedural and remote complications, was observed in the stent era. Our study confirmed that female sex, a larger size, and aneurysms located at the IC-Pcom significantly affected the rate of overall neurological events. However, in the stent era, several remote complications were associated with the neck-bridge stent. After the placement of a neck-bridge stent, strict follow-up should be performed in consideration not only of ischemic complications associated with stent thrombosis or in-stent stenosis but also of intracerebral hemorrhagic complications (other than post-procedural aneurysmal rupture) accompanied by DAPT use. In our cohort of the stent era, the remote ischemic complication rate in the stent group was 1.7% (2/113), and the remote hemorrhagic complication rate was 3.5% (4/113), which were not negligible. Regarding hemorrhagic complications during antiplatelet therapy, Toyoda et al. reported the incidence of bleeding events during antithrombotic therapy. The annual incidence of life-threatening or major bleeding events was 1.21% in the single antiplatelet agent group and 2.00% in the dual antiplatelet agent group.[16] While there is a risk of hemorrhagic complications during anti-platelet therapy, evidence of the optimal duration of DAPT after SACE is limited. Hwang et al.[9] recommended more than 9 months of DAPT and a late switch to monotherapy for the prevention of delayed ischemic stroke after SACE. In their report, hemorrhagic events were not mentioned. Hemorrhagic complications were rarely explicitly mentioned in previous reports and, thus, might not be recognized as complications associated with coil embolization. Because most patients with unruptured aneurysms do not require antiplatelet therapy unless a neck-bridge stent is used, cerebral hemorrhagic events may have to be recognized as stent-related complications. Furthermore, to prevent hemorrhagic complications during antiplatelet therapy, it is essential to control blood pressure appropriately.[17] A randomized trial and long-term follow-up are needed to address this issue.

The present study had several limitations. First, this study was limited by its retrospective, single-institute nature. Therefore, the duration or termination of the antiplatelet agent varied in each patient. Second, laser-cut stents, such as Enterprise VRD or Neuroform, were used in 85% of the cases in the stent era. The number of cases of braided stents,

such as LVIS or LVIS jr., was low. Braided stents could be expected to cause a high occlusion rate of aneurysms and might have a somewhat high risk of late thrombotic complications because of their high metal coverage.[18,19] In recent years, braided stent cases have been increasing, which may have a significant impact on the future outcomes of this approach.

Conclusions

The re-treatment rate has been improved without increasing neurological complications after introduction of the neck-bridge stent.

Conflicts of Interest Disclosure

This research did not receive any specific grant from funding agencies from the public, commercial, or not-for-profit sectors. There are no competing interests to declare.

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