Coil Embolization for Unruptured Intracranial Aneurysms at the Dawn of Stent Era: Results of the Japanese Registry of Neuroendovascular Therapy (JR-NET) 3

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Abstract

Endosaccular coiling is recognized as a feasible method for treating unruptured intracranial aneurysms (UIAs). We retrospectively reviewed cases of UIAs treated by coiling in the Japanese Registry of Neuroendovascular Therapy (JR-NET) 3, a nationwide survey of NET between 2010 and 2014, the beginning period of intracranial stents in Japan. Data were extracted for 6844 UIAs (6619 procedures) from 40,169 registered records of all NETs in the JR-NET 3 databases. The features of the aneurysms and procedures, immediate radiographic findings, procedure-related complications, and clinical outcomes at 30 days after the procedures were assessed. Of 6844 UIAs, 81.8% were located in the anterior circulation. The mean patient age was 61.3 years (72.4% females). Compared with the preceding JR-NET 1 and 2, there were significant increases (P <0.05) in the rates of the following in JR-NET 3: wide-necked and small UIAs measuring <10 mm (from 56.4% to 58.8%), adjunctive techniques (54.8% to 71.8%), and stent usage (1.1% to 22.1%). Both pre- (85.6% to 96.7%) and post-procedural (84.0% to 94.6%) antiplatelet therapy were more frequently administered in JR-NET 3. Although procedure-related complication rates did not differ between the two groups, ischemic complication rates increased from 4.6% to 5.9%, leading to an increase in the 30-day morbidity (modified Rankin Scale >2) from 2.1% to 2.8%. In conclusion, introduction of neck-bridge stent was associated with an increase in cases of wide-necked aneurysms. However, the ischemic complication rate increased despite the greater use of periprocedural antiplatelet therapy.

Key words: unruptured intracranial aneurysms, coil embolization, Japanese Registry of Neuroendovascular Therapy

Introduction

The management of asymptomatic, unruptured intracranial aneurysms (UIAs) has been controversial. Several reports regarding the natural history of UIAs showed that factors such as size, location, can be the predictors of their rupture including those among Japanese people who are believed to be at higher risk.1–3 Nowadays, endosaccular coiling of intracranial aneurysms is prevailing worldwide with its less invasiveness, lower incidence of complications compared with clipping4,5) and long-term durability.6,7) However, the complication rate and the possibility of retreatment due to recanalization have each been reported at 5–10%.6,8–10) Therefore, the assessment of current status of coiling is important for the management of patients with UIAs to compare the benefits and risks of this modality with surgical clipping or conservative management.

The Japanese Registry of Neuroendovascular Therapy (JR-NET) study group endorsed by Japanese
Society for Neuroendovascular Therapy (JSNET) have conducted retrospective studies (JR-NET 1&2) to clarify the general status of neuroendovascular therapy delivered by JSNET-certified physicians, and to standardize endovascular procedures and to assist with education planning for Japanese neuro-interventionists based on outcomes. This report details the results of JR-NET 3, in which clinical and procedural data were collected retrospectively from January 2010 through December 2014 for all endovascular procedures to further assess and guarantee the quality of NET in Japan. The primary end point was the 30-day clinical outcome [modified Rankin Scale (mRS)] and secondary end points comprised technical success, adverse events arising within 30 days.\(^{11}\)

Here, we collected a considerable amount of clinical data on NET for UIAs through the JR-NET 3 investigations and evaluated the outcomes of NET, especially endovascular coiling for patients with asymptomatic UIAs in Japan.

**Materials and Methods**

**JR-NET 3 protocols**
The JR-NET 3 was conducted between 2010 and 2014 as the third nationwide survey of neuroendovascular treatment in Japan, targeting all endovascular procedures during the study period by JSNET board-certified physicians, who were instructed to register their endovascular procedures in the JR-NET 3 database. Patient-identifying information was anonymized, retrospectively registered via website (https://jr-net.tri-kobe.net/jr-net, and collected at the Translational Research Informatics Center (http://www.tri-kobe.org/). The Institutional Review Board (IRB) at the participating centers approved the use of the patient data for research (local IRB approval number: M25-024-2). A total of 40 169 endovascular procedures were registered for the JR-NET 3.\(^{11}\) For the current report, we extracted data for all cases of elective endovascular coiling of UIAs. Cases with incomplete data were excluded.

**Primary and secondary endpoints**
The primary endpoint was activities of daily living, as indicated by the mRS scores. The secondary endpoints were the technical success of procedures and major adverse events within 30 days of the procedures. Adverse events were classified as minor and major when mRS scores deteriorated by 1 and ≥2 points, respectively.

**Statistical methods**
Variables are presented as mean ± standard deviation (SD), count, or percentage, as appropriate. The $\chi^2$-test was used to compare the categorical variables. The Wilcoxon signed-rank test was used to compare the ordinal variables while Student’s $t$-test was used to compare continuous variables. $P$-values <0.05 were considered statistically significant. Highly significant data with $P$-values <0.001 are indicated in the text. We used the JMP 10 software (SAS Institute Inc., Cary, NC, USA) to perform all the analyses.

**Results**

**Patients characteristics and multiplicity of the procedure**
In total, 6844 cases were selected for analysis, among which 6619 procedures were performed. Of these, 1811 (27.4%) were for men and 4808 (72.6%) were for women. The flowchart for data selection is shown in Fig. 1. The mean patient age was 61.3 ± 11.6 years (range 17–89 years), and 98.9% were independent (mRS 0–2) at the time of the procedure. The numbers of treated UIAs were one (96.8%) of 6404, two of 205, and three of 10 procedures.

**Aneurysm characteristics**
The features of the aneurysms are summarized in Table 1. Most UIAs were located in the anterior circulation (n = 5599; 81.8%), while the remainder were located in the posterior circulation (n = 1245: 18.2%). Specifically, 33.8% were in the paraclinoid region, followed by the internal carotid artery–posterior communicating artery (14.7%), anterior communicating artery (13.9%), bifurcation of the basilar artery (9.0%), and middle cerebral artery (5.2%).

As for the maximal diameters, 2318 (33.9%) were 5–6 mm and 1436 (21.0%) were 7–9 mm. Regarding the minimal diameters, 2125 (31.0%) were 3–4 mm and 124 (1.8%) were <3 mm. Notably, 3548 (58.8%) UIAs with diameters <10 mm had wide necks (neck diameter >4 mm or dome-to-neck ratio <1.5).\(^{10}\)

**Endovascular modalities**
The techniques used for endovascular coiling are shown in Table 2. Simple technique by which a single catheter and coils were used were performed in 1933 cases (28.2%), while adjunctive techniques were used in the remaining 4911 (71.8%) cases. Among them, balloon assist, double catheter, stent-assisted, stent monotherapy techniques were used in 2806 (41.0%), 439 (6.4%), 1253 (18.3%), 23 (0.3%), respectively. A combination of techniques was used.
Data set of aneurysms treated by endovascular treatment without intentional parent artery occlusion
n=14,737

Ruptured aneurysms, dissecting aneurysms, non-saccular aneurysms, symptomatic UIAs, and/or UIAs treated with other diseases
n=7,454

excluded

Data set of asymptomatic UIAs treated by endovascular coiling without any other stand-by lesion
n=7,283

excluded

Data of pre-procedural status not available
n=187

Data of procedural status not available
n=197

excluded

Data of post-procedural status not available
n=55

excluded

Data set of asymptomatic UIAs treated by endovascular coiling (with complete data for all variables)
n=6,844

Fig. 1 Figure shows the flowchart of data extraction from the JR-NET 3. The pre-procedural status included sex, age, date of treatment, pre-procedural modified Rankin Scale (mRS), antithrombotic therapy, and aneurysm characteristics. The intra-procedural status included the techniques and antithrombotic therapy. The post-procedural status included the radiographic outcome, procedure-related adverse events and mRS 30 days after the procedures. JR-NET: Japanese Registry of Neuroendovascular Therapy. UIA: unruptured intracranial aneurysm.

Feasibility and immediate angiographic outcome
Failure of endosaccular coiling was noted in for 78 (1.1%) aneurysms (Table 3) at rates of 5.4%, 1.2%, 0.8%, 0.7%, 1.4%, and 0% for aneurysms with diameters of <3, 3–4, 5–7, 7–9, 10–25, and >25 mm, respectively (Table 4).

The failure rate decreased significantly with increasing aneurysmal size. There was no significant difference in failure rate between aneurysms in the anterior (1.1%) and posterior (0.7%) circulations. The immediate radiographic outcomes of 6766 successfully treated aneurysms demonstrated that 3147 (46.5%) were completely occluded, 2324 (34.3%) had residual necks, 1288 (19.0%) had residual aneurysmal domes, and 7 (0.1%) resulted in unpredicted parent artery occlusion (Table 3).

Periprocedural antithrombotic management
Table 2 also shows the antithrombotic therapy. Systemic heparinization was used in 6458 (97.6%) procedures. Continuous anticoagulation therapy was applied in 3786 procedures (55.3%). Argatroban, a direct thrombin inhibitor, was preferentially used (41.2%).

Notably, pre- and post-procedural antiplatelet therapy (APT) was executed in 6398 (96.6%) and 6263 (94.6%), respectively.

Mode of the APT in the pre-procedural period were single in 1647 (24.9%), dual in 4405 (66.5%), and triple or more in 346 (5.2%); the corresponding figures in the 30-day post-procedural period were 1739 (26.3%), 3872 (58.5%), and 652 (9.8%), respectively.

in 391 cases (5.7%). Specifically, neck bridge stents were used in 1512 cases (22.1%).
Table 1  Characteristics of unruptured intracranial aneurysms treated by endosaccular coiling, based on data in JR-NET 3

| Location | n (%) |
|----------|-------|
| Anterior circulation | 5599 (81.8) |
| ICA-cav | 295 (4.3) |
| Paraclinoid | 2316 (33.8) |
| ICA-PCom | 1006 (14.7) |
| ICA-AChA | 233 (3.4) |
| ICA-bif | 191 (2.8) |
| MCA | 354 (5.2) |
| A1 | 76 (1.1) |
| ACoA | 952 (13.9) |
| DACA | 130 (1.9) |
| Other (AC) | 46 (0.7) |
| Posterior circulation | 1245 (18.2) |
| VA | 154 (2.3) |
| BA-trunk | 64 (0.9) |
| BA-SCA | 208 (3.0) |
| BA-bif | 617 (9.0) |
| PCA | 56 (0.8) |
| VA-PICA | 131 (1.9) |
| Other (PC) | 15 (0.2) |
| Size | (r, mm) |
| <3 | 124 (1.8) |
| 3 to <5 | 2125 (31.0) |
| 5 to <7 | 2318 (33.9) |
| 7 to <10 | 1436 (21.0) |
| 10 to <25 | 827 (12.1) |
| ≥25 | 14 (0.2) |
| Appearance (% of UIA <10 mm) | (n = 6003) |
| Narrow neck† | 2475 (41.2) |
| Wide neck‡ | 3528 (58.8) |

†: maximal diameter, †: Neck: ≤4 mm and dome-to-neck (D/N) ratio ≥1.5, †: Neck: >4 mm or D/N ratio <1.5. ACoA: anterior communicating artery, A1: anterior cerebral artery proximal to anterior communicating artery, BA: basilar artery, BA-bif: basilar bifurcation, BA-SCA: junction of basilar artery and superior cerebellar artery, BA-trunk: trunk of basilar artery, DACA: anterior cerebral artery distal to anterior communicating artery, ICA-AChA: anterior choroidal artery, ICA-bif: bifurcation of internal carotid artery, ICA-cav: cavernous segment of ICA, ICA-Pcom: posterior communicating artery, JR-NET 3: Japanese Registry of Neuroendovascular Therapy 3, MCA: middle cerebral artery, Other (AC): other locations in anterior circulation, Other (PC): other locations in posterior circulation, PCA: posterior cerebral artery, UIA: unruptured intracranial aneurysm, VA: vertebral artery.

Table 2  The techniques and periprocedural antithrombotic therapy used according to data in JR-NET 3

| Technique (pa, 6844 cases) | n (%) |
|----------------------------|-------|
| Simple | 1933 (28.2) |
| Adjunctive | 4911 (71.8) |
| DCT | 439 (6.4) |
| BAT | 2806 (41.0) |
| SAC | 1253 (18.3) |
| DCT + BAT | 129 (1.9) |
| DCT + SAC | 84 (1.2) |
| BAT + SAC | 146 (2.1) |
| DCT + BAT + SAC | 15 (0.2) |
| Stenting only | 23 (0.3) |
| Other | 17 (0.3) |

Antithrombotic therapy (pp, 6619 cases)

| Anticoagulation | n (%) |
|-------------------|-------|
| Intraprocedural systemic heparinization | 6457 (97.6) |
| Continuous anticoagulation | 3995 (60.4) |
| heparin | 949 (14.3) |
| argatroban | 2730 (41.2) |
| heparin + argatroban | 107 (1.6) |

Antiplatelet therapy

| Preprocedural | n (%) |
|----------------|-------|
| SAPT | 1647 (24.9) |
| DAPT | 4405 (66.6) |
| TAPT or more | 346 (5.2) |

Postprocedural

| SAPT | 1738 (26.3) |
| DAPT | 3872 (58.5) |
| TAPT or more | 652 (9.9) |

Adverse events related to endosaccular coiling

Procedure-related adverse events occurred in 664 patients (10.0%), of whom 23.2% (n = 154; 2.3% of total) had increases in their 30-day mRS scores (Table 3). Intracranial hemorrhage and ischemia were noted in 143 (2.2%) and 389 (5.9%), respectively; there were 89 intra-procedural aneurysmal ruptures, or 1.3% per procedure. The anterior communicating artery was the most frequent site of these ruptures.
Table 3  Outcomes of coiling for unruptured intracranial aneurysms

| Feasibility (pa, 6844 cases) | n  | (%) |
|-----------------------------|----|-----|
| Success                     | 6766 | 98.9 |
| Failure                     | 78  | 1.1 |

Anatomic outcome (per successfully treated UIA, 6766 cases)

| Complete occlusion | 3147 | 46.5 |
| Residual neck      | 2324  | 34.3 |
| Residual aneurysm  | 1288  | 19.0 |
| Unpredicted parent artery occlusion | 7 | 0.1 |

Adverse events (pp, 6619 cases)

| Procedure-related complications | 664 (154) | 10.0 (2.3) |
| Hemorrhagic                     | 143 (46)  | 2.2 (0.7)  |
| Intraprocedural aneurysmal rupture | 86 (20) | 1.3 (0.3) |
| Aneurysmal rupture in post-treatment period | 5 (3) | 0.1 (0.05) |
| Ischemic                        | 389 (103) | 5.9 (1.6) |
| Puncture site                   | 89       | 1.3 |
| Other                           | 67       | 1.0 |

mRS 30 days after EVT (pp, 6619 cases)

| mRS 30 days after EVT | n  | (%) |
|-----------------------|----|-----|
| 0                     | 5988 | 90.5 |
| 1                     | 337  | 5.1 |
| 2                     | 153  | 2.3 |
| 3                     | 58   | 0.9 |
| 4                     | 45   | 0.7 |
| 5                     | 23   | 0.3 |
| 6                     | 15   | 0.2 |

Clinical outcome (pp = 6619)

| 30-day morbidity | 186 | 2.8 |
| 30-day mortality | 15  | 0.2 |

Table 4  Failure rate, anatomic outcome, and complication rate by the aneurysm location and maximal radius (6404 cases)

| Location of the aneurysms (n, %) | Number | 5 to <7 | 7 to <10 | 10 to <25 | 25 to <50 | ≥50 |
|----------------------------------|--------|---------|----------|-----------|-----------|-----|
| Anterior Circ.                   | 5216   | 51 (1.0)| 3 (0.1)  | 0.0       | <0.001    |     |
| Posterior Circ.                  | 1188   | 54 (4.6)| 2 (0.1)  | 0.0       | 0.002     |     |
| CO                               | 2452   | 458 (19.0)| 21 (0.9) | 0.001     | 0.015     |     |
| RA                               | 2174   | 492 (22.8)| 22 (1.0) | 0.001     | 0.014     |     |
| Ischemic                         | 2950   | 628 (21.5)| 32 (1.1) | 0.001     | 0.016     |     |
| Procedure-related complications  |        |         |          | <0.001    | <0.001    | <0.001|
| Hemorrhagic                      |        |         |          | <0.001    | <0.001    | <0.001|
| Ischemic                         |        |         |          | <0.001    | <0.001    | <0.001|

(30 cases or 3.0% of aneurysms in this region). Delayed aneurysmal rupture occurred in five cases within 30 days (Table 3).

Ischemic complication rates occurred at a lower rate in smaller aneurysms (3–7 mm) and at a higher rate in larger aneurysms (7–25 mm); however, there was no statically significant correlation between hemorrhagic complications and aneurysmal size (Table 4).
Concerning the location, aneurysms in the posterior circulation (8.8%) were more prone to ischemic complications than those in the anterior circulation (5.1%), which resulted in a higher incidence of procedure-related complications (13.7% versus 8.9%, respectively; Table 4).

### 30-Day clinical outcomes

The 30-day morbidity and mortality rates were 2.8% and 0.2% among 6404 procedures, respectively (Table 3). Of the 15 deaths within 30 days of treatment, 12 were associated with hemorrhagic complications (11 aneurysmal ruptures and one vessel rupture). A total of 6478 patients (97.9%) remained independent (mRS score 0–2).

#### Impact of stent-assisted coiling in JR-NET 3

Table 5 shows the comparison between stented and non-stented cases in this study.

Neck bridge stents were used in 1462 cases, but were used more frequently in the posterior circulation (404 of 1188 cases; 34.0%) than in the anterior circulation (1058 of 5116 cases; 20.3%) \( (P < 0.001) \). Also, the proportion of aneurysms >7 mm and aneurysms with unfavorable anatomy (i.e., either wide-necked or >10 mm) in terms of initial occlusion status and recanalization for non-stented coiling \(^{31} \) were larger in the stented cases than those in non-stented cases (62% versus 26.1%; \( P < 0.001 \), 93.9% versus 56.0%; \( P < 0.001 \), respectively).

The rate of complete obliteration was lower in the stented cases (39.7%) than in the non-stented cases (47.9%) \( (P < 0.001) \). Compared with patients who treated without stents, those who treated with stents had higher rates of procedure-related (14.0% versus 8.6%, \( P < 0.001 \)) and ischemic (8.9% versus 4.8%, \( P < 0.001 \)) complications. Although the overall rates of hemorrhagic complications were similar between the two groups (2.1% versus 2.0%, \( P = 0.834 \)), there was a significant difference in 30-day morbidity between the stented (6.0%) and non-stented (1.9%) cases \( (P < 0.001) \).

#### Comparison between JR-NET 3 and JR-NET 1&2

Table 6 shows the comparison of data from JR-NET 3 with that from JR-NET 1&2, \(^{12} \) which covered the data of UIAs treated by endosaccular coiling between 2005 and 2009.

The number of patients with UIAs in JR-NET 3 \( (n = 6844) \) was higher than in JR-NET 1&2 \( (n = 4767) \). The mean age was also older \( (P < 0.001) \), and the ratio of anterior circulation aneurysms was higher \( (P = 0.006) \), in JR-NET 3. The rate of involvement of anterior communicating arteries increased from 12.3% in JR-NET 1&2 to 13.9% in JR-NET 3. As to the size and appearance of the treated aneurysms, there was a decrease in aneurysms smaller than 5 mm from JR-NET 1&2 to JR-NET 3 (35.4–32.8%, \( P = 0.004 \)) while the rate of wide-necked, small aneurysms (<10 mm) were higher in JR-NET 3 than that in JR-NET 1&2 (58.8% versus 56.4%, \( P = 0.017 \)). Angiographically, the rate of complete obliteration was lower in JR-NET 3 (46.5%) compared with JR-NET 1&2 (57.7%) \( (P < 0.001) \).

The use of adjunctive technique was more frequent in JR-NET 3 than in the previous two cohorts (71.8% versus 54.8%, \( P < 0.001 \)), and the use of stent markedly increased from JR-NET 1&2 to JR-NET 3 (1.1–22.1%, \( P < 0.001 \)).

Regarding antithrombotic therapy, the rates of both pre- and post-procedural antiplatelet therapy increased from JR-NET 1&2 (85.6% and 84.0%, respectively) to JR-NET 3 (96.7% and 94.6%, respectively), whereas the rate of continuous heparinization decreased (68.0% in JR-NET 1&2 to 60.4% in JR-NET 3).

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**Table 5** Comparison of stented and non-stented coiling procedure based on data in JR-NET 3 (pa, 6404 cases)

|                      | Stents used \((n = 1462)\) | Stents not used \((n = 4942)\) | \(P\)-value |
|----------------------|----------------------------|-------------------------------|------------|
| **Age**              | 61.5 ± 11.6                | 61.3 ± 11.6                   | 0.500      |
| **Anterior circulation** | 1058 (72.4)              | 4158 (84.1)                  | <0.001     |
| **Posterior circulation** | 404 (27.6)               | 784 (15.9)                   | <0.001     |
| **Maximum radius > 7 mm** | 906 (62.0)                | 1289 (26.1)                  | <0.001     |
| **Unfavorable anatomy** | 1373 (93.9)              | 2772 (56.1)                  | <0.001     |
| **DAPT or more**     | 1368 (93.6)               | 3211 (65.0)                  | <0.001     |
| **Complete obliteration** | 581 (39.7)                | 2369 (47.9)                  | <0.001     |
| **Residual aneurysm** | 391 (26.7)                | 818 (16.6)                   | <0.001     |
| **Procedure-related complications** | 204 (14.0)            | 424 (8.6)                    | <0.001     |
| **Hemorrhagic complications** | 31 (2.1)                | 101 (2.0)                    | 0.834      |
| **Ischemic complications** | 130 (8.9)                | 239 (4.8)                    | <0.001     |
| **30-day morbidity** | 88 (6.0)                  | 94 (1.9)                     | <0.001     |
| **30-day mortality** | 4 (0.3)                   | 9 (0.2)                      | 0.510      |

*Significantly different between anterior circulation and posterior circulation \( (P < 0.001) \). *Aneurysms with wide neck and/or maximal diameter >10 mm. DAPT: dual antiplatelet therapy, pa: per aneurysm.
Table 6 Comparison of the data from JR-NET 1&2 and JR-NET 3

|                                | JR-NET 1, 2 (2005–2009) | JR-NET 3 (2010–2014) | P-value |
|--------------------------------|--------------------------|----------------------|---------|
| UIAs (n)                       | 4767                     | 6844                 |         |
| Procedures (n)                 | 4573                     | 6619                 |         |
| Age (y, mean ± SD, range)      | 60.6 ± 11.1 (6–93)       | 61.3 ± 11.6 (17–89)  | 0.001   |
| Female (n, %)                  | 3311 (72.4)              | 4808 (72.6)          | 0.796   |
| Anterior circulation           | 3814 (80.0)              | 5614 (82.0)          | 0.006   |
| Size                           | (n = 4767)               | (n = 6844)           |         |
| <3                             | 119 (2.5)                | 124 (1.8)            | 0.012   |
| 3 to <5                        | 1569 (32.9)              | 2125 (31.0)          | 0.035   |
| 5 to <10                       | 2476 (51.9)              | 3754 (54.9)          | 0.002   |
| ≥10                            | 603 (12.6)               | 841 (12.3)           | 0.568   |
| Appearance (% of UIA <10 mm)   | n = 4164                 | n = 6003             |         |
| Narrow neck                    | 1816 (43.6)              | 2475 (41.2)          | 0.017   |
| Wide neck                      | 2348 (56.4)              | 3528 (58.8)          |         |
| Technique (pa)                 | n = 4767                 | n = 6844             |         |
| Adjunctive                     | 2612 (54.8)              | 4911 (71.8)          | <0.001  |
| Use of stent                   | 51 (1.1)                 | 1512 (22.1)          | <0.001  |
| Antithrombotic regimen (pp)    | n = 4573                 | n = 6619             |         |
| PRE antiplatelet therapy       | 3914 (85.6)              | 6398 (96.7)          | <0.001  |
| INTRA systemic heparinization  | 4488 (98.1)              | 6457 (97.6)          | 0.043   |
| CONT anticoagulation           | 3108 (68.0)              | 3995 (60.4)          | <0.001  |
| POST antiplatelet therapy      | 3841 (84.0)              | 6262 (94.6)          | <0.001  |
| Feasibility (pa)               | n = 4767                 | n = 6844             |         |
| Technical success              | 4665 (97.9)              | 6766 (98.9)          | <0.001  |
| Anatomic outcome (st)          | n = 4665                 | n = 6766             |         |
| CO                             | 2690 (57.7)              | 3147 (46.5)          | <0.001  |
| RN                             | 1490 (31.9)              | 2324 (34.3)          | 0.007   |
| RA                             | 468 (10.0)               | 1288 (19.0)          | <0.001  |
| uPAO                           | 17 (0.4)                 | 7 (0.1)              | 0.003   |
| Adverse events (pp)            | n = 4573                 | n = 6619             |         |
| Procedure-related complications | 417 (9.1)                | 664 (10.0)           | 0.111   |
| Hemorrhagic complications      | 90 (2.0)                 | 143 (2.2)            | 0.500   |
| Ischemic complications         | 210 (4.6)                | 389 (5.9)            | 0.003   |
| mRS 30 days after EVT (pp)     | n = 4573                 | n = 6619             |         |
| 0 to 2                         | 4481 (98.0)              | 6478 (97.9)          | 0.686   |
| 3 to 6                         | 92 (2.0)                 | 141 (2.1)            |         |
| 30-day morbidity (pp)          | 97 (2.1)                 | 186 (2.8)            | 0.024   |
| 30-day mortality (pp)          | 14 (0.3)                 | 13 (0.2)             | 0.247   |

CO: complete occlusion, CONT: continuous, EVT: endovascular therapy, INTRA: intraprocedural, JR-NET: Japanese Registry of Neuroendovascular Therapy, mRS: modified Rankin scale, pa: per aneurysm, POST: postprocedural, pp: per procedure, PRE: preprocedural, RA: residual aneurysm, RN: residual neck, UIA: unruptured intracranial aneurysms, uPAO: unpredicted parent artery occlusion.
As to the adverse events and 30-day clinical outcomes, ischemic complication rates were higher in JR-NET 3 (5.9%) than in JR-NET 1&2 (4.6%) \((P < 0.001)\), but there was no significant difference in the procedure-related complication rate (10.0% and 9.1%, respectively). The 30-day morbidity rate was also higher in JR-NET 3 (2.8%) than in JR-NET 1&2 (2.1%) \((P = 0.024)\), but there was no significant difference in the independence rates (mRS 0–2) and 30-day mortality rates between JR-NET 3 and JR-NET 1&2.

**Discussion**

We have reported the current status of endovascular coiling for UIAs in Japan between 2010 and 2014. The most noteworthy event in this study period was that reimbursement was introduced for two neck bridge stents—the Enterprise VRD (Cerenovus, Johnson and Johnson, New Brunswick, NJ, USA) in 2010 and the Neuroform EZ (Stryker Neurovascular, Fremont, CA, USA) in 2012—for treating intracranial aneurysms. Flow diverters were used in some cases, but these were not reimbursed during the study period. Thus, we can consider the main theme of this study as being to verify the feasibility and safety of endovascular treatment for UIAs after the two neck bridge stents were introduced.

The increase in the rate of treated aneurysms in the anterior circulation was considered to be multifactorial, with stents potentially of benefit for aneurysms of both the anterior and posterior circulations.\(^{44}\) Other factors, such as the increased number of neuroendovascular physicians and the increased awareness of coil embolization in Japan, probably contributed to this result. The increases in the number of wide-necked aneurysms and in the use of adjunctive techniques likely resulted from the introduction of stents, which were used in 22.1% of all procedures in the JR-NET 3 period.

The size of the treated aneurysms significantly changed, with the proportion of aneurysms measuring <3 and 3–5 mm decreasing from JR-NET 1&2 to JR-NET 3 (2.5–1.8% and 32.9–31.0%, respectively). This followed the publication of the UCAS Japan in 2012,\(^{21}\) which reported on the natural history of UIAs in Japan. That study reported that the annual rupture rate of UIAs was 0.95%, with aneurysms measuring >7 mm having the greatest risk of rupture. At the same time, the Japanese Guidelines for the Management of Stroke recommended continuing to treat UIAs measuring 5–7 mm.\(^{15}\) Thus, fewer UIAs measuring <5 mm and more UIAs measuring 5–7 mm were treated.

Concerning the antithrombotic therapy, periprocedural APT became more frequent in JR-NET 3 period. Several reports about the efficacy of antiplatelet therapy\(^{16–18}\) including its use with stents,\(^{19,20}\) likely accelerated this increased usage. However, it should be noted that the use of heparinization decreased both intra- and post-procedurally. Although the reduction in post-procedural anticoagulation can be explained by the lack of verification in the literature, no clear explanation can be found to account for the reduction in intra-procedural anticoagulation.

The technical success rate increased marginally from 97.9% in JR-NET 1&2 to 98.9% in JR-NET 3. This may be explained by greater technical skill among Japanese physicians, even though the use of stents will have been associated with a learning curve.\(^{21}\)

That said, the percentage of complete occlusion decreased from 57.7% to 46.5%, with several plausible causes. First, physicians likely avoided the risk of thromboembolic complications by meticulous coiling because progressive thrombosis could be expected, even if complete occlusion was not achieved immediately,\(^{21}\) and because retreatment is not associated with excessive risk.\(^{23}\) Second, stent-assisted coiling tends to show progressive thrombosis of the aneurysms at follow-up.\(^{24,25}\) The fact that stented cases had a significantly lower incidence of complete occlusion compared with non-stented cases probably reflected such reports.

Procedure-related complications were noted in 10.0% in JR-NET 3, representing a non-significant increase from 9.1% in JR-NET 1&2. These rates are consistent with previously reported data, although comparisons between studies are difficult because of the different criteria use for complications.\(^{9,10,26}\)

Unfortunately, the prevalence of ischemic complications increased to 5.9% in JR-NET 3 from a level of 4.6% in JR-NET 1&2. When stents were used, this rate was as high as 8.9% and the 30-day morbidity rate was 6.0% despite dual or triple antiplatelet therapy being given in 93.6% of the cases that received stent-assisted coiling. Coupled with this, the rates of ischemic events associated with non-stented cases were comparable between JR-NET 3 (4.8%) and JR-NET 1&2 (4.6%). We concluded that stent introduction led to an expanded indication of endosaccular coiling, especially for wide-necked aneurysms, but that this was at the expense of an increased incidence of ischemia. By contrast, the rate of hemorrhagic complications, including intra-procedural, was comparable to that in previous studies.\(^{12,27}\)

Although there were no statistically significant differences in patient independence between JR-NET 3 and the preceding JR-NET 1&2 studies, the 30-day
morbidity rate was significantly higher in the former (2.8% versus 2.1%, respectively). Given that the ischemic complication rate contributed heavily to this, we propose using a tailored antiplatelet therapy regimen based on pre-procedural platelet function data of which we could not obtain in this study.

**Limitations**

There are several limitations in this study. First, we relied on retrospectively collected registry data that covered only about 35% of all cases receiving endovascular therapy in Japan. Second, our results could be biased because the radiographic findings, clinical outcomes, and procedure-related complications were only assessed by the treating physicians. Decisions on therapeutic indications might also have introduced inclusion bias. Third, clinical outcomes were recorded at the 30-day follow-up, and there was a lack of information on long-term outcomes after endosaccular coiling, after which recurrence rates are more important than after surgical clipping. In the future, a more complete and prospective registry would help to assess the therapeutic standards in the endovascular treatment of UIAs. The impact of using new devices, such as flow diverters and intrasaccular flow disruptors, should also be assessed.

**Conclusion**

The recent status of endosaccular coiling for UIAs in Japan is reported. The introduction of neck bridge stents has led to an increase in the number of cases of wide-necked aneurysms being treated and has been associated with a higher technical success rate compared with previous cohorts. However, the rate of ischemic complications has increased despite the increased use of periprocedural APT.

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**Conflicts of Interest Disclosure**

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