Outcomes of Endovascular Repair for Abdominal Aortic Aneurysms: A Nationwide Survey in Japan

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Objective: To analyze data on patients treated with a bifurcated stent graft for abdominal aortic aneurysm (AAA).

Background: The Japan Committee for Stentgraft Management (JACSM) was established in 2007 to manage the safety of endovascular aortic aneurysm repair (EVAR) in Japan. The JACSM registry includes detailed anatomical and clinical data of all patients who undergo stent graft insertion in Japan.

Methods: Among 51,380 patients treated with bifurcated stent graft for AAA, we identified 38,008 eligible patients (excluding those with rupture or insufficient data). The analyzed factors included age, sex, comorbidities, AAA pathology and etiology, aneurysm and neck diameters, 7 anti-instructions for use (IFU) factors, and endoleaks at hospital discharge. The endpoints were death, adverse events, sac dilatation (>5 mm), and reintervention.

Results: The rates of intraoperative and in-hospital mortality were 0.08% and 1.07%, respectively. Infectious aneurysm and pseudo-aneurysm were associated with overall survival and reintervention. Older age, large aneurysm diameter, and all types of persistent endoleaks were strong predictors of adverse events, sac dilatation, and reintervention. Comorbid cerebrovascular disease, renal dysfunction, and respiratory disorders were also risk factors. In total, 47.6% of patients violated the IFU; among the anti-IFU factors assessed, poor access and severe neck calcification were strong risk factors for mortality, reintervention, and adverse events. The sac dilatation rate at 5 years was 23.3%.

Conclusions: Although the analysis included EVAR with poor anatomy, the perioperative mortality rate was acceptable compared with that in previous large population studies.

Keywords: EVAR, JACSM, Japan, registry, stent graft

Several large population studies have evaluated the outcomes of endovascular aortic aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA), mainly comparing EVAR to open surgery (OS). Two milestone randomized controlled trials (RCTs) published in 2004 had great impact in revealing the superiority of EVAR to OS with respect to short-term mortality.1,2 However, the mortality of EVAR cases may have been underestimated, because only patients anatomically suitable for EVAR were selected. A later RCT from the United States (enrollment period 2002–2008) also demonstrated the superiority of EVAR, with lower mortality in both groups.3 Although the study used newer-generation stent grafts, a patient selection bias still existed because of the anatomical criteria and inclusion of many veterans, who do not represent the general population. Thus, there is an ongoing need for data on EVAR outcomes that are current and reflective of real-world EVAR procedures.

Several reports employing Medicare data have compared EVAR to OS using a propensity score-matched cohort, with an extremely large population and less selection bias.4,5 However, these studies have critical limitations; they were observational, subject to potential coding error, and lacked anatomical and clinical details. In contrast, the European collaborators on stent graft techniques for abdominal aortic aneurysm repair (EUROSTAR) is a prospective multicenter registry (launched in 1996).6 Unfortunately, the outcomes in the EUROSTAR study, including operative mortality,7 are worse compared with those reported in previous studies, possibly because the devices used were of an older generation. Considering recent advances in stent graft devices and EVAR procedures, the effect of new-generation devices on improved outcomes should be investigated.

In July 2006, a commercial stent graft was first approved in Japan (lagging behind other countries). The Japan Committee for Stentgraft Management (JACSM) was established to ensure the safe and appropriate use of commercial stent grafts after their regulatory approval.8 The JACSM registry is a nationwide EVAR registry in Japan with unique features, including detailed data on preoperative anatomical factors. As data were collected from 2007 to 2015, data from older devices are not included. Another advantage concerns its coverage of almost all EVAR procedures in Japan.

Using JACSM data, we aimed to analyze the factors (including detailed anatomical and clinical characteristics) influencing EVAR outcomes (mortality, adverse events, reintervention, and sac dilatation).

METHODS

Database

Before the approval of stent grafts in Japan, the Japanese Society for Vascular Surgery established a practice standards management committee to serve as the directors’ advisory board and develop a regulatory system for stent graft treatments. The JACSM, established in December 2006, was composed of 10 societies related to endovascular treatment, and determined the practical standards for institutions, and practicing and supervising surgeons. Participating institutions were obligated to report data, including preoperative findings and postoperative outcomes, using a web-based
case-registry form (http://www.stentgraft.jp/). Intraoperative and postoperative data (at discharge, 6 and 12 months postoperative, and every 12 months thereafter) were registered. Participants were obliged to register outcomes for survival, aneurysm diameter, and aneurysm rupture for up to 10 years, and other outcomes for 5 years. For AAA, 494 institutes in Japan were certified, and 51,690 patients were registered as of 2015. Among the 1309 certified operators, there were 1035 surgeons (79%), 171 radiologists (13%), 74 cardiologists (6%), and 19 others (2%).

Devices
Utilized devices included the Zenith AAA endovascular graft (Cook Medical Inc., Bloomington, IN; Japan edition; n = 3681, 9.7%), Gore Excluder aortic stent graft (W.L. Gore & Associates, Inc., Flagstaff, AZ; approved January, 2007; n = 13,315, 35%), the Powerlink system (Endologix, CA; approved February, 2008; n = 2365, 6.2%), and the Talent Stent Graft System (Medtronic, Santa Rosa, CA; approved December, 2010; n = 77, 0.2%). The next-generation devices included the Zenith (Zenith flex; n = 4689, 12.3%), Excluder (C3 Excluder; n = 3502, 9.2%), Talent (Endurant; n = 9815, 25.8%), and Aorfix AAA stent graft system (Lombard Medical, Oxfordshire, UK; approved August 2014; n = 253, 0.7%). The number of stent grafts implanted in Japan has dramatically increased to date (Fig. 1A), and also the number of surgically treated patients with AAA (Fig. 1B).

Inclusion and Exclusion Criteria for Data
Given our interest in “typical” EVAR cases, we selected cases of AAA or AAA with iliac aneurysm that underwent bifurcated stent graft insertion. We excluded cases of solitary iliac aneurysm and ruptured AAA with emergency surgery. Cases were also excluded if all baseline data were not registered or unreasonable data were registered (ie, AAA diameter < 40 mm, neck diameter < 10 mm, or ≥40 mm, proximal landing zone ≥ 100 mm). Finally, we excluded cases in which stent graft implantation failed.

Collected Data
The database included age, sex, comorbidities, pathology, and etiology of the AAA, and anatomical factors. Comorbidities included hypertension, diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular disease (CVD), renal dysfunction (serum creatinine level ≥ 1.20 mg/dL), respiratory disorder, and hostile
TABLE 1. Patient Characteristics and Logistic Regression Analysis of In-hospital Mortality

| Univariate Analysis for the Risk Factors of In-hospital Death | Cox Proportional-hazard Regression Analysis for the Risk Factors of In-hospital Mortality |
|---------------------------------------------------------------|-------------------------------------------------------------------------------------|
| **Alive At Discharge (n = 36,852)**                           | **In-hospital Death (n = 409)**                                                    | **Hazard Ratio** | **95% CI** | **P** |
| Age, yrs                                                      |                                                                                     |                  |           |      |
| <60                                                          |                                                                                     | 0.57             | 0.25–1.31 | 0.186 |
| 61–70                                                        |                                                                                     | 0.45             | 0.30–0.68 | <0.001 |
| 71–80                                                        |                                                                                     | Reference        |            |      |
| 81–90                                                        |                                                                                     | 1.52             | 1.22–1.90 | <0.001 |
| 91–                                                          |                                                                                     | 2.48             | 1.56–3.95 | <0.001 |
| Sex                                                          |                                                                                     |                  |           |      |
| Female                                                       |                                                                                     | 1.09             | 0.84–1.43 | 0.511 |
| Comorbidities                                                |                                                                                     |                  |           |      |
| Hypertension (n = 26,124, 68.7%)                             |                                                                                     |                  |           |      |
| Diabetes mellitus (n = 4611, 12.1%)                          |                                                                                     |                  |           |      |
| Coronary artery disease (n = 10,713, 28.2%)                  |                                                                                     |                  |           |      |
| Cerebrovascular disease (n = 5861, 15.4%)                    |                                                                                     |                  |           |      |
| Renal dysfunction (n = 7333, 19.3%)                          |                                                                                     |                  |           |      |
| Respiratory disorder (n = 7565, 19.9%)                       |                                                                                     |                  |           |      |
| Hostile abdomen (n = 6674, 17.6%)                            |                                                                                     |                  |           |      |
| Aneurysm diameter, mm                                        |                                                                                     |                  |           |      |
| <50                                                          |                                                                                     | Reference        |            |      |
| 50–<55                                                       |                                                                                     |                  |           |      |
| 55–<60                                                       |                                                                                     |                  |           |      |
| 60–<70                                                       |                                                                                     |                  |           |      |
| 70–<80                                                       |                                                                                     |                  |           |      |
| 80–                                                          |                                                                                     |                  |           |      |
| Neck diameter, mm                                            |                                                                                     |                  |           |      |
| <22                                                          |                                                                                     | Reference        |            |      |
| 22–<25                                                       |                                                                                     |                  |           |      |
| 25–<28                                                       |                                                                                     |                  |           |      |
| 28–<31                                                       |                                                                                     |                  |           |      |
| 31–                                                          |                                                                                     |                  |           |      |
| Pathology                                                    |                                                                                     |                  |           |      |
| Atherosclerotic (n = 37,266, 98.1%)                          |                                                                                     |                  |           |      |
| Infectious (n = 144, 0.4%)                                   |                                                                                     |                  |           |      |
| Inflammatory (n = 281, 0.7%)                                 |                                                                                     |                  |           |      |
| Etiology                                                     |                                                                                     |                  |           |      |
| True (n = 37,266, 98.1%)                                     |                                                                                     |                  |           |      |
| Pseudo (n = 367, 1%)                                         |                                                                                     |                  |           |      |
| Dissection (n = 312, 0.8%)                                   |                                                                                     |                  |           |      |
| Others                                                       |                                                                                     |                  |           |      |
| Anatomical factors                                           |                                                                                     |                  |           |      |
| Short proximal neck (n = 2294, 6.0%)                         |                                                                                     |                  |           |      |
| Severe suprarenal angulation (n = 4673, 12.2%)                |                                                                                     |                  |           |      |
| Severe neck angulation (n = 6623, 17.4%)                     |                                                                                     |                  |           |      |
| Poor access (n = 2201, 5.7%)                                 |                                                                                     |                  |           |      |
| Short distal landing zone (n = 4381, 11.5%)                  |                                                                                     |                  |           |      |
| Severe neck calcification (n = 3330, 8.7%)                   |                                                                                     |                  |           |      |
| Severe neck thrombus (n = 4844, 12.7%)                       |                                                                                     |                  |           |      |

abdomen. Anatomical factors included aneurysm diameter, neck diameter, and factors provided by the manufacturer’s instructions for use (IFU), subsequently referred to as “anti-IFU” factors: short proximal neck (<15 mm), severe suprarenal angulation (>45°), severe neck angulation (>60°), poor access (iliac artery diameter ≤7.5 mm), short distal landing zone (<20 mm), severe neck calcification, and severe neck thrombus. Age, AAA diameter, and neck diameter were each categorized into several groups (see Table 1).

Endoleaks
Endoleaks were evaluated using postoperative enhanced computed tomography (CT) during hospitalization, and were classified into 6 categories: no endoleak; type 1, 2, 3, or 4 endoleak; and 2 or more types of endoleaks (multiple). If the type of endoleak could not be determined, the case was excluded from analyses of long-term outcomes.

Outcomes
The evaluated outcomes included in-hospital mortality, overall survival, event-free survival, dilatation rate, and reintervention-free survival. Event-free survival was defined as survival without stent graft migration, stenosis or occlusion of the stent graft, stent graft infection, acute arterial thrombus or embolus of the lower legs, or rupture of the aortic aneurysm. Reintervention-free survival was...
survival without reintervention for any reason. Dilatation was an increase ≥5 mm in the aneurysmal diameter from any diameter previously measured and registered. We censored data at the date when the outcome of interest was first recorded, the patient was deregistered, or the end of follow-up was reached. For event-free survival and reintervention-free survival, follow-up ended at 5 years.

Statistical Analyses
Categorical variables are presented as numbers and percentages, and continuous variables are presented as median and interquartile range (IQR). Categorical variables were compared using chi-square tests. Multivariable logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality. Multivariable Cox regression analyses were used to estimate hazard ratios (HRs) and 95% CIs for long-term outcomes (overall survival, event-free survival, dilatation, and reintervention-free survival). To analyze specific factors (age, diameters, pathology, etiology, and endoleaks), we set the subcategory with the highest frequency of patients as the reference. The Kaplan–Meier method with the log-rank test was used to analyze the overall survival and sac dilatation-free rates. All statistical analyses were performed using SPSS software version 23 (IBM Corp, Armonk, NY). The threshold for statistical significance was \( P < 0.05 \).

RESULTS
Between 2006 and 2015, 51,380 cases were registered. After applying the exclusion criteria, a remaining 38,003 cases were analyzed. The mean follow-up period was 2403 ± 15 days.

Preoperative Characteristics
The median age was 77 years (IQR 71–82 years). The mean aneurysm diameter was 51 mm (47–57 mm), and mean proximal neck diameter was 21 mm (19.7–23.8 mm). Females accounted for 17.3% of the cohort (6566 cases). The majority of cases in this population presented with true and atherosclerotic aneurysms (Table 1).

Anatomical Anti-IFU Factors
Information regarding anti-IFU factors is provided in Table 1. A total of 19,907 cases (52.4%) did not violate the IFU. However, 10,512 cases (27.7%) had 1 anti-IFU factor, 5486 cases (14.4%) had 2 anti-IFU factor, 1609 cases (4.2%) had 3 anti-IFU factor, 418 cases (1.1%) had 4 anti-IFU factor, 64 cases (0.2%) had 5 anti-IFU factor, 6 cases (0.02%) had 6 anti-IFU factor, and 1 case had 7 anti-IFU factor.

Short-term (Intraoperative and At Discharge) Outcomes
The rates of intraoperative and in-hospital mortality were 0.08% and 1.07%, respectively. The blood transfusion rate during surgery was 3.84%. Observed complications (with rates intraoperatively and at discharge, respectively) included stent graft migration (0.3% and 0.1%), vascular injury (2.3% and 0.7%), thromboembolism (0.8% and 0.9%), paralysis (0.2% and 0.3%), and rupture (0.2% and 0.1%). Stenosis or occlusion (1.4%), wound complications (1.4%), cerebrovascular events (0.4%), and renal dysfunction (2.6%) were observed during the hospital stay.

Endoleaks
Endoleaks were observed intraoperatively in 12,735 cases (33.5%); no endoleak, \( n = 25,260 \), 66.5%; type 1, \( n = 2032 \), 5.3%; type 2, \( n = 6143 \), 16.2%; type 3, \( n = 348 \), 0.9%; type 4, \( n = 3427 \), 9.0%; multiple endoleaks, \( n = 785 \), 2.1%). In addition, endoleaks were observed in 9471 cases at discharge (24.9%); no endoleak, \( n = 25,184 \), 66.3%; type 1, \( n = 2559 \), 6.7%; type 2, \( n = 6301 \), 16.6%; type 3, \( n = 235 \), 0.6%; type 4, \( n = 229 \), 0.6%; multiple endoleaks, \( n = 147 \), 0.4%).

Factors Affecting In-hospital Mortality
Older age, infectious aneurysms, and pseudo-aneurysms were associated with in-hospital mortality (Table 1). Among comorbidities, CVD, renal dysfunction, and respiratory disorders were significantly associated with mortality. Among the anatomical factors, an aneurysm diameter ≥50 mm, neck >31 mm, poor access, severe neck calcification, and thrombus were risk factors for in-hospital mortality (Table 1).

Background Characteristics and Endoleaks
According to Overall Survival
A Cox hazard regression analysis, with endoleak as a background factor, revealed a strong association of mortality with older age, CVD, renal dysfunction, respiratory disorders, hostile abdomen, an aneurysm diameter ≥50 mm, neck diameter 25 to 28 mm, infectious aneurysm, pseudo-aneurysm, short proximal neck, poor access, severe neck calcification, and type 1, type 3, and multiple endoleaks (Table 2). Female sex and hypertension negatively correlated with mortality (Table 2). The overall survival rates were 96.2% at 6 months, 93.5% at 1 year, 88.3% at 2 years, 82.8% at 3 years, 76.2% at 4 years, 69.4% at 5 years, 63.7% at 6 years, 54.4% at 7 years, and 38.8% at 8 years.

Adverse Event-free Survival
Cases with adverse events were compared with cases without adverse events (Table 3). In a Cox hazard regression analysis, older age, female sex, CVD, renal dysfunction, respiratory disorders, and hostile abdomen were significantly associated with adverse events. In addition, an aneurysm diameter ≥55 mm, neck ≥25 mm, short proximal neck, severe neck angulation, poor access, severe neck calcification, and all types of endoleaks were risk factors for adverse events. DM was the only factor that negatively correlated with adverse events (Table 4).

Rupture (a fatal and miserable outcome) was analyzed separately. A subanalysis revealed that female sex, an aneurysm diameter ≥60 mm, infectious and inflammatory aneurysms, and type 1, type 2, and multiple endoleaks were independently associated with rupture (Table 5). No case with a type 3 endoleak resulted in rupture.

Sacc Dilatation Rate
Patients with sac dilation >5 mm within 5 years of follow-up were compared with those without dilation (Table 3). Age >60 years, female sex, renal dysfunction, an aneurysm diameter ≥0 mm, neck 22 to 25 mm and ≥28 mm, neck severe angulation, and all types of endoleaks were independently associated with sac dilation. Factors negatively correlating with sac dilation included DM, respiratory disorders, and severe neck thrombus (Table 4). The dilatation rates were 2.6% at 6 months, 4.4% at 1 year, 8.8% at 2 years, 13.7% at 3 years, 18.5% at 4 years, and 23.3% at 5 years.

Reintervention-free Survival
Patients with reintervention were compared with those without reintervention (Table 3). In a Cox hazard regression analysis, older age, infectious aneurysm, pseudo-aneurysm, CVD, renal dysfunction, respiratory disorder, and hostile abdomen were significantly associated with reintervention. In addition, an aneurysm diameter ≥55 mm, neck 25 to 28 or ≥31 mm, short proximal neck, poor access, severe
TABLE 2. Baseline Characteristics and Endoleaks According to Overall Survival and the Cox Hazard Regression Analysis

| Univariate Analysis for the Risk Factors of Overall Survival | Cox Proportional-hazard Regression Analysis for the Risk Factors of Overall Survival |
|-------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Alive (n = 34,094) | Dead (n = 3500) | P | Hazard Ratio | 95% CI | P |
| Age, yrs | | | | | |
| <60 | 1198 (3.5) | 56 (1.6) | <0.001 | 0.47 | 0.36–0.62 | <0.001 |
| 61–70 | 6585 (19.3) | 530 (14.8) | 0.62 | 0.55–0.70 | <0.001 |
| 71–80 | 15,310 (44.9) | 1429 (40.8) | | | |
| 81–90 | 10,448 (30.6) | 1534 (43.8) | 1.74 | 1.61–1.88 | <0.001 |
| >90 | 553 (1.6) | 101 (2.9) | 2.46 | 1.98–3.05 | <0.001 |
| Sex | | | | | |
| Female | 5930 (17.4) | 557 (15.9) | 0.027 | 0.88 | 0.80–0.98 | 0.015 |
| Comorbidities | | | | | |
| Hypertension | 23,451 (68.8) | 2382 (68.1) | 0.378 | 0.88 | 0.81–0.94 | 0.001 |
| Diabetes mellitus | 4147 (12.2) | 412 (11.8) | 0.499 | 1.01 | 0.91–1.13 | 0.805 |
| Coronary artery disease | 9565 (28.1) | 1033 (29.5) | 0.068 | 1.04 | 0.96–1.12 | 0.360 |
| Cerebrovascular disease | 5090 (14.9) | 679 (19.4) | <0.001 | 1.27 | 1.16–1.38 | <0.001 |
| Renal dysfunction | 6233 (18.3) | 943 (26.9) | <0.001 | 1.51 | 1.40–1.64 | <0.001 |
| Respiratory disorder | 6452 (18.9) | 994 (28.4) | <0.001 | 1.52 | 1.41–1.64 | <0.001 |
| Hostile abdomen | 5816 (17.1) | 793 (22.7) | <0.001 | 1.29 | 1.19–1.40 | <0.001 |
| Aneurysm diameter, mm | | | | | |
| <50 | 12,797 (37.5) | 1071 (30.6) | <0.001 | Reference | |
| 50–<55 | 9818 (28.8) | 875 (25.0) | 1.13 | 1.03–1.24 | 0.012 |
| 55–<60 | 4742 (13.9) | 546 (15.6) | 1.35 | 1.21–1.50 | <0.001 |
| 60–<70 | 4482 (13.1) | 636 (18.2) | 1.66 | 1.50–1.85 | <0.001 |
| 70–<80 | 1508 (4.4) | 234 (6.7) | 1.91 | 1.64–2.22 | <0.001 |
| 80–<90 | 747 (2.2) | 138 (3.9) | 2.37 | 1.95–2.86 | <0.001 |
| Neck diameter, mm | | | | | |
| <22 | 17,934 (52.6) | 1663 (47.5) | <0.001 | Reference | |
| 22–<25 | 10,441 (30.6) | 1099 (31.4) | 1.07 | 0.98–1.16 | 0.119 |
| 25–<28 | 3986 (11.6) | 519 (14.8) | 1.26 | 1.13–1.39 | <0.001 |
| 28–<31 | 1351 (4.0) | 169 (4.8) | 1.13 | 0.96–1.34 | 0.140 |
| 31– | 400 (1.2) | 50 (1.4) | 1.30 | 0.96–1.77 | 0.094 |
| Pathology | | | | | |
| Atherosclerotic | 33,473 (98.2) | 3410 (97.4) | <0.001 | Reference | |
| Infectious | 105 (0.3) | 27 (0.8) | 2.37 | 1.55–3.61 | <0.001 |
| Inflammatory | 248 (0.7) | 31 (0.9) | 1.23 | 0.85–1.77 | 0.266 |
| Others | 268 (0.8) | 32 (0.9) | 0.74 | 0.50–1.10 | 0.138 |
| Etiology | | | | | |
| True | 33,498 (98.3) | 3386 (96.7) | <0.001 | Reference | |
| Pseudo | 272 (0.8) | 79 (2.3) | 2.65 | 2.05–3.43 | <0.001 |
| Dissection | 282 (0.8) | 26 (0.7) | 1.33 | 0.89–1.99 | 0.159 |
| Others | 42 (0.1) | 9 (0.3) | 2.80 | 1.42–5.51 | 0.003 |
| Anatomical factors | | | | | |
| Short proximal neck | 2007 (5.9) | 255 (7.3) | <0.001 | 1.31 | 1.15–1.50 | <0.001 |
| Severe suprarenal angulation | 4095 (12.0) | 502 (14.3) | <0.001 | 1.05 | 0.94–1.18 | 0.381 |
| Severe neck angulation | 5787 (17.0) | 731 (20.9) | <0.001 | 1.04 | 0.94–1.15 | 0.420 |
| Poor access | 1876 (5.5) | 271 (7.7) | <0.001 | 1.47 | 1.29–1.69 | <0.001 |
| Short distal landing zone | 3857 (11.3) | 451 (12.9) | 0.005 | 0.94 | 0.85–1.05 | 0.277 |
| Severe neck calcification | 2862 (8.4) | 390 (11.1) | <0.001 | 1.37 | 1.22–1.53 | <0.001 |
| Severe neck thrombus | 4281 (12.6) | 477 (13.6) | 0.069 | 1.06 | 0.96–1.18 | 0.259 |
| Perioperative endoleak during hospital stay | | | | | |
| No endoleak | 22,750 (73.1) | 2287 (69.2) | <0.001 | Reference | |
| Type 1 endoleak | 2152 (6.9) | 353 (10.7) | 1.53 | 1.36–1.71 | <0.001 |
| Type 2 endoleak | 5696 (18.3) | 591 (17.9) | 1.00 | 0.91–1.10 | 0.988 |
| Type 3 endoleak | 189 (0.6) | 40 (1.2) | 1.59 | 1.16–2.18 | 0.004 |
| Type 4 endoleak | 215 (0.7) | 13 (0.4) | 1.01 | 0.59–1.75 | 0.958 |
| Multiple endoleaks | 125 (0.4) | 22 (0.7) | 1.59 | 1.04–2.44 | 0.033 |

Discussion

In the current healthcare system in Japan, all shipping information regarding EVAR devices is reported to the JACSM. There were some cases (very few) not reported during the EVAR introduction period (2006–2008), mainly involving an emergency EVAR. Thus, this registry includes nearly all stent grafts implanted in Japan. Using this registry, we provided real-world data on the perioperative and long-term outcomes of bifurcated stent graft placement for the treatment of AAA.

The mortality rate in the present study (1.15%) is similar to that in previous large population studies.\(^1\)\(^2\)\(^3\) However, the initial study from

neck calcification, and all types of endoleaks were risk factors. Only hypertension was negatively correlated with reintervention (Table 4).
The initial data were primarily collected from high-volume centers, which generally achieve better outcomes, as reported for EVAR. The number of participating institutes sharply increased after 2009, which might have worsened overall outcomes. In addition, operators may tend to violate the IFU as indications for EVAR were extended. As EVAR should be a treatment of last resort for high-risk aneurysm patients, violating the IFU for unfavorable anatomy may be inevitable, and indeed approximately half of all patients had at least 1 anti-IFU factor in the present study. Although several reports have discussed the effect of violating the IFU, focusing on the anatomical factors related to EVAR outcome, the factors analyzed and parameter definitions were

![Image of a table containing data on patient demographics, disease characteristics, and treatment outcomes.](annalsofsurgery.com)
| Age, yrs | Event-free Survival | Dilatation | Reintervention-free Survival |
|---------|---------------------|-----------|-----------------------------|
|         | Hazard Ratio | 95% CI | P    | Hazard Ratio | 95% CI | P    | Hazard Ratio | 95% CI | P    |
| <50     | Reference       |         |      | Reference       |         |      | Reference       |         |      |
| 50–<55  | 1.02            | 0.96–1.09 | 0.447 | 1.09            | 1.01–1.18 | 0.023 | 1.09            | 1.00–1.18 | 0.060 |
| 55–<60  | 1.09            | 1.01–1.17 | 0.032 | 1.14            | 1.04–1.26 | 0.007 | 1.16            | 1.05–1.29 | 0.005 |
| 60–<65  | 1.28            | 1.19–1.38 | <0.001 | 1.19            | 1.08–1.32 | 0.001 | 1.53            | 1.39–1.70 | <0.001 |
| 65–<70  | 1.25            | 1.11–1.41 | <0.001 | 1.22            | 1.04–1.43 | 0.014 | 1.64            | 1.41–1.91 | <0.001 |
| 70–<75  | 1.56            | 1.34–1.83 | <0.001 | 1.45            | 1.17–1.80 | 0.001 | 1.83            | 1.49–2.25 | <0.001 |
| <75     | Reference       |         |      | Reference       |         |      | Reference       |         |      |
| 75–<80  | 1.04            | 0.99–1.10 | 0.128 | 1.08            | 1.00–1.16 | 0.046 | 1.07            | 0.99–1.15 | 0.095 |
| 80–<85  | 1.09            | 1.01–1.18 | 0.026 | 1.07            | 0.96–1.18 | 0.214 | 1.24            | 1.12–1.37 | <0.001 |
| 85–<90  | 1.14            | 1.10–1.29 | 0.040 | 1.18            | 1.00–1.40 | 0.045 | 1.17            | 0.99–1.38 | 0.063 |
| >90     | 1.37            | 1.10–1.71 | 0.006 | 1.68            | 1.27–2.24 | <0.001 | 1.45            | 1.09–1.93 | 0.012 |

Pathology

| Type                  | Event-free Survival | Dilatation | Reintervention-free Survival |
|-----------------------|---------------------|-----------|-----------------------------|
| Atherosclerotic        | Reference           |          |                            |
| Infectious             | 0.94                | 0.57–1.56 | 0.813                       |
| Inflammatory           | 0.80                | 0.58–1.11 | 0.184                       |
| Else                  | 0.90                | 0.68–1.19 | 0.458                       |
| True                  | Reference           |          |                            |
| Pseudo                | 1.29                | 0.99–1.69 | 0.057                       |
| Dissection            | 1.05                | 0.78–1.40 | 0.750                       |
| Eise                 | 1.65                | 0.85–3.21 | 0.142                       |

Anatomical factors

| Type                   | Event-free Survival | Dilatation | Reintervention-free Survival |
|------------------------|---------------------|-----------|-----------------------------|
| Short proximal neck    | 1.21                | 1.09–1.34 | <0.001                      |
| Severe suprarenal angulation | 1.02 | 0.94–1.11 | 0.637                       |
| Severe neck angulation | 1.13                | 1.05–1.21 | 0.001                       |
| Poor access            | 1.20                | 1.08–1.34 | 0.001                       |
| Short distal landing zone | 1.04            | 0.97–1.12 | 0.257                       |
| Severe neck calcification | 1.10            | 1.00–1.20 | 0.041                       |
| Severe neck thrombus   | 0.95                | 0.88–1.03 | 0.235                       |

Postoperative endoleak during hospital stay

| Type                   | Event-free Survival | Dilatation | Reintervention-free Survival |
|------------------------|---------------------|-----------|-----------------------------|
| No endoleak            | Reference           |          |                            |
| Type 1                | 1.38                | 1.26–1.51 | <0.001                      |
| Type 2                | 1.27                | 1.20–1.35 | <0.001                      |
| Type 3                | 1.69                | 1.33–2.13 | <0.001                      |
| Type 4                | 1.37                | 1.00–1.88 | 0.050                       |
| Multiple              | 1.67                | 1.23–2.26 | 0.001                       |

 Arbitrarily determined. In the present study, we selected seven anti-IFU factors, all of which were previously associated with EVAR outcomes. Considering that these factors strongly affected outcomes in the present study, an increase in cases violating the IFU may contribute to worsening outcomes. A large population study reported that the overall survival rate worsened as age increased, even in the EVAR group. Similarly, we confirmed that older age was a strong risk factor for survival, and also for sac dilatation. Furthermore, aneurysm diameter was a strong predictor of all adverse outcomes. Interestingly, diameters <50 mm were clearly differentiated from other sizes in the hazardous risk analysis. Considering that the average diameter in the present study was relatively smaller compared with that in the previous literatures, and that >30% of patients had an aneurysm diameter.
<50 mm, a lower threshold might be necessary for a detailed analysis. In addition, this result might affect future indications for EVAR.

There are several possible reasons for the smaller aneurysm diameter in the present study. The aneurysm diameter threshold, 50 mm, is recommended by the Japanese guidelines, reflecting the smaller stature of Japanese patients. Although the indication of EVAR for small AAAs (>40 mm, <50 mm) in the Japanese guidelines has not changed from class IIb, the level of evidence was upgraded from C (in 2006) to B (in 2011), given RCT results for small AAAs. We assume that some institutions might have lowered the threshold. In addition, operators in Japan have aggressively extended the operative indication of AAA to regions where...

### TABLE 5. Univariate and Cox Regression Analyses for the Risk Factors of Rupture After EVAR

| Rupture (–) | Rupture (+) | P    | Hazard ratio | 95% CI       | P    |
|-------------|-------------|------|--------------|--------------|------|
| Age, yrs    |             |      |              |              |      |
| <60         | 1255 (3.32) | 3 (3.03) | 0.045 | 0.87 | 0.26–2.94 | 0.824 |
| 61–70       | 6906 (18.42) | 13 (13.13) |  | | |
| 71–80       | 16,818 (44.46) | 36 (36.36) | Reference | | |
| 81–90       | 12109 (32.01) | 46 (46.46) | 1.48 | 0.92–2.40 | 0.108 |
| 91–         | 673 (1.78) | 1 (1.01) | | | |
| Sex         |             |      |              |              |      |
| Female      | 6520 (17.24) | 30 (30.30) | 0.001 | 1.98 | 1.20–3.25 | 0.007 |
| Comorbidities |             |      |              |              |      |
| Hypertension | 25,996 (68.73) | 69 (69.70) | 0.836 | | |
| Diabetes mellitus | 4587 (12.13) | 14 (14.14) | 0.540 | | |
| Severe suprarenal angulation | 4521 (11.95) | 15 (15.15) | 0.446 | | |
| Severe neck angulation | 1540 (4.07) | 5 (5.05) | 0.042  | 0.62–1.76 | 0.872 |
| Poor access | 463 (1.22) | 4 (4.04) | | | |
| Pathology   |             |      |              |              |      |
| Atherosclerotic | 37,102 (98.09) | 91 (91.92) | <0.001 Reference | | |
| Infectious  | 139 (0.37) | 4 (4.04) | 13.14 | 3.29–52.47 | <0.001 |
| Inflammatory | 278 (0.73) | 3 (3.03) | 3.50 | 1.05–11.65 | 0.041 |
| Others      | 305 (0.81) | 1 (1.01) | | | |
| Anatomical factors |             |      |              |              |      |
| Short proximal neck | 2273 (6.01) | 12 (12.12) | 0.011 | 1.72 | 0.88–3.37 | 0.115 |
| Severe suprarenal angulation | 4636 (12.26) | 20 (20.20) | 0.016 | 1.04 | 0.55–1.98 | 0.902 |
| Severe neck angulation | 6571 (17.37) | 25 (25.25) | 0.039 | 0.80 | 0.44–1.43 | 0.447 |
| Poor access | 2188 (5.78) | 7 (7.07) | 0.584 | | |
| Short distal landing zone | 4362 (11.53) | 14 (14.14) | 0.417 | | |
| Severe neck calcification | 3302 (8.73) | 10 (10.10) | 0.629 | | |
| Severe neck thrombus | 4820 (12.74) | 14 (14.14) | 0.677 | | |
| Perioperative endoleak during hospital stay | | | | | |
| No endoleak | 25,120 (72.76) | 39 (44.83) | <0.001 Reference | | |
| Type 1 endoleak | 2529 (7.33) | 21 (24.14) | 5.00 | 2.87–8.72 | <0.001 |
| Type 2 endoleak | 6272 (18.17) | 25 (26.44) | 2.37 | 1.41–3.99 | 0.001 |
| Type 3 endoleak | 233 (0.67) | 0 (0.00) | | | |
| Type 4 endoleak | 227 (0.66) | 1 (1.15) | 3.17 | 0.43–23.34 | 0.257 |
| Multiple endoleaks | 144 (0.42) | 3 (3.45) | 7.81 | 1.99–30.57 | 0.003 |

NA denotes not available, because there were not enough number of events.
EVAR was belatedly introduced (given its excellent short-term outcomes), and decide to operate immediately after the AAA reaches 50 mm in diameter, as most of the diameters analyzed in the present study were 50 mm. 

Several IFU items were analyzed. As severe neck angulation and calcification, and poor access are reflective of systemic atherosclerosis, their significant association with adverse outcomes is plausible. Severe neck angulation is also an important factor for the long-term interaction between the stent graft and native aorta, which might result in adverse events. However, the selection of these seven anti-IFU parameters should be considered a limitation of the present study. For example, we included the neck diameter as a factor in the Cox regression analysis, but not “large neck diameter,” because the IFU for diameter differs widely across devices. In addition, stent grafts in patients with a large neck diameter (≥34 mm) have rarely been performed in Japan due to the device lag. Therefore, the present results cannot be extrapolated to studies performed in other countries. Furthermore, reliable methods for the quantification and qualification of neck thrombus and calcification have not yet been established. Hoshina et al defined a “shaggy aorta” and concluded that EVAR patients with a large neck atheroma tend to develop late-phase complications (ischemic colitis, renal dysfunction, and blue toe syndrome), perhaps related to cholesterol crystal embolization. Therefore, we assumed that a massive atheroma would have a greater negative impact on outcomes than severe calcification; however, neck atheroma (thrombus) was not related to survival. Other studies have reported similar conclusions, with neck thrombus showing a protective effect; however, the endpoints differed from those in the present study. Furthermore, we did not define severe thrombus in detail, which might be related to the unexpected results.

An inverse association between DM and AAA prevalence has been reported, and AAA progresses slowly in patients with DM. This association can be explained by increased arterial wall stiffness, and increased synthesis and formation of advanced glycation end products, leading to smooth muscle proliferation in patients with DM. In addition, increased aortic wall stiffness via increased collagen content has been proposed in patients with chronic obstructive pulmonary disease (COPD). Although COPD is known to associate with AAs, a previous study found no association between COPD and AAA growth. These explanations may account for the observation that DM and respiratory disorders were negative predictors of sac enlargement. Type 2 endoleaks are believed to be a sign of initial success, reflecting intraoperative aneurysm exclusion and sac pressure decompression, and reintervention for type 2 endoleaks remains controversial. However, the present results might indicate the importance of observing all types of persistent endoleaks closely.

Each surgeon determined the timing of reintervention and the causes for reintervention were not evaluated, as the reintervention details were described in a free-comment item. Although we cannot provide data regarding when to intervene, a sac dilatation ≥5 mm is a strong indicator for intervention. As endoleaks, especially type 2, have been reported to cause sac dilatation, we are interested in the relationship between type 2 endoleaks and the sac dilatation rate. Thus, we performed an exploratory analysis, comparing patients who were positive for type 2 endoleak with those who were negative; the Kaplan–Meier curves of the “sac dilatation ratio” are shown in Fig. 2. Given the observed group differences, surgeons should recognize the potential risk of a type 2 endoleak at discharge, and inform the patients of the possibility of an increased dilatation rate. However, other endoleak types must be analyzed in more detail in future studies to exclude confounding biases.

There are several limitations to this study. First, follow-ups were mainly performed at 6 months or 1 year, consequently, the survival curves had a stepwise shape, which does not reflect reality. Second, the differing methods of device selection and institutional characteristics likely introduced some bias. Third, as the indications for reintervention due to sac dilatation have not been established in any guidelines, and the timing and methods of such reinterventions differ across institutes, the outcome of dilatation is difficult to evaluate. Fourth, as the sac dilatation rate was far greater than that in previous studies, the diagnosis of endoleaks might be inaccurate in this large registry. The methodology for discriminating the type of

FIGURE 2. Sac enlargement free ratio.

Endovascular Repair trial was that 16% of isolated type 2 endoleaks appeared >1 year after EVAR. The delayed type 2 endoleak was more associated with sac enlargement than the early endoleak. The present study did not include endoleak time series data. In the future, we plan to perform a subanalysis of endoleak development and reduction, after specific data cleaning has been performed.
endoleaks was not detailed; thus, type 1 or 3 endoleaks might be misdiagnosed as type 2. Furthermore, we did not analyze the free-comment items; thus, we cannot easily derive certain hypotheses from this big dataset, especially regarding the association between sac dilatation and endoleaks. Future subanalyses of outcomes associated with different devices and institutional practices are also necessary to resolve these limitations.

CONCLUSIONS

We analyzed data from 38,008 cases of EVAR for AAA in the JACSM registry, covering nearly all aortic stent grafts implanted in Japan. Although the analysis included EVAR with poor anatomy, the perioperative mortality rate was acceptable compared to that in previous large population studies.

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