CLINICAL STUDY

Independent Predictors of Major Adverse Cardiovascular Events at 3 Years after Aortoiliac Stent Implantation

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ABSTRACT

Purpose: To identify the risk factors for major adverse cardiovascular events (MACEs) in real-world practice for symptomatic peripheral artery disease in Japan.

Materials and Methods: Data on Japanese patients (N = 880) from the Observational Prospective Multicenter Registry Study on Outcomes of Peripheral Arterial Disease Patients Treated by Angioplasty Therapy for Aortoiliac Artery who underwent de novo aortoiliac stent placement. The 3-year risk of incident MACEs was investigated.

Results: The median age of the patients was 72.6 years (range, 34–97 years), and 83.1% of the patients were men. The patients had the following conditions: smoking (35.6%), hypertension (94.1%), dyslipidemia (81.7%), diabetes (48.0%), renal failure on dialysis (12.6%), myocardial infarction (12.7%), stroke (15.8%), and chronic limb-threatening ischemia (7.1%). Femoropopliteal lesions were present in 38.8% of the limbs with aortoiliac lesions. The 3-year rate of freedom from MACEs was 89.1%. Baseline characteristics, such as age, renal failure on dialysis, myocardial infarction, stroke, and femoropopliteal lesions, were independently associated with the risk of incident MACEs. When the study population was stratified according to these risk factors, the rate of MACEs was highest in patients with at least 3 risk factors (32.9% at 3 years).

Conclusions: The 3-year rate of freedom from MACEs was reported. Baseline characteristics, such as age, renal failure on dialysis, myocardial infarction, stroke, and femoropopliteal lesions, are independent risk factors for MACEs after aortoiliac stent placement.

ABBREVIATIONS

CI = confidence interval, CLTI = chronic limb-threatening ischemia, EVT = endovascular therapy, MACE = major adverse cardiovascular event, non-HDL = non–high-density lipoprotein, OMOTENASHI = Observational Prospective Multicenter Registry Study on Outcomes of Peripheral Arterial Disease Patients Treated by Angioplasty Therapy for Aortoiliac Artery, PAD = peripheral artery disease, PTA = percutaneous transluminal angioplasty, TASC II = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II

Because of the ongoing aging of populations and the increase in lifestyle-related diseases, the number of people with peripheral artery disease (PAD) is growing and is estimated to be more than 200 million globally (1,2). PAD causes intermittent claudication or chronic limb-threatening ischemia (CLTI), which reduces the quality of life and has a poor prognosis (3). The disease is closely linked to advanced age and various lifestyle-related illnesses, such as type 2 diabetes, tobacco smoking, obesity, and dyslipidemia (4,5). Moreover, it has a high probability of causing cardiovascular events.

Endovascular techniques have progressed in recent years, and endovascular therapy (EVT) for aortoiliac lesions is now considered to be a standard interventional modality

Tables E1–E4 can be found by accessing the online version of this article on www.jvir.org and selecting the Supplemental Material tab.

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RESEARCH HIGHLIGHTS

- This prospective multicenter registry study examined the use of endovascular treatment (EVT) in Japanese real-world practice in 880 patients with peripheral artery disease and aortoiliac arterial stent placement.
- After EVT, the rate of freedom from major adverse cardiovascular events (MACEs) at 3 years was 89.1%.
- Baseline characteristics, such as age, renal failure on dialysis, myocardial infarction, stroke, and femoropopliteal lesions, were independent risk factors for MACEs at 3 years.

STUDY DETAILS

Study type: prospective, observational, descriptive study
Level of evidence: 3 (SIR-C)

that is as well established as percutaneous coronary intervention for coronary artery disease (6,7). EVT with stent placement is now commonly performed, as recommended by the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (TASC II) and European Society of Cardiology guidelines (3,8). However, no large-scale prospective studies have evaluated the risk of major adverse cardiovascular events (MACEs) after aortoiliac stent placement. Therefore, this study aimed to examine the MACE risk at 3 years after aortoiliac stent placement in patients with symptomatic PAD.

MATERIALS AND METHODS

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of each participating center. Written informed consent was obtained from each participant.

Data from the clinical database of the Observational Prospective Multicenter Registry Study on Outcomes of Peripheral Arterial Disease Patients Treated by Angioplasty Therapy for AortoIliac Artery (OMOTENASHI) were analyzed. The OMOTENASHI enrolled 893 patients (1,128 limbs) with symptomatic PAD (Rutherford classification categories 2, 3, and 4) who underwent EVT for de novo aortoiliac lesions between April 2014 and April 2016 at 64 centers in Japan and followed the participants for 3 years (9,10). The registry included CLTI in combination with exacerbated rest pain more than 2 weeks later (11). The registry did not exclude patients who had a history of revascularization of iliac segments, other than those that required revascularization at the time of entry into the registry. In the OMOTENASHI registry, all registered patients underwent EVT for de novo iliac lesions; however, the registry did not exclude cases of continuous placement in the aorta. Of the 893 enrolled patients, 13 underwent unilateral percutaneous transluminal angioplasty (PTA) with no stent; 7 underwent unilateral PTA plus contralateral stent implantation; 645 underwent unilateral revascularization with stent implantation, and 228 underwent bilateral stent implantation. No patient underwent bilateral PTA with no stent. Therefore, the current study excluded the 13 patients who underwent PTA with no stent and included the remaining 880 patients. The characteristics of the 880 patients are summarized in **Table 1**, and the limb and lesion characteristics are summarized in **Table 2**. Femoropopliteal lesions were defined as stenosis ≥50%, as assessed by tomography or angiography. The main patient characteristics were as follows: mean age, 72.6 years ± 8.7; male, 83.1%; current tobacco smoking, 35.6%; hypertension, 94.1%; dyslipidemia, 81.7%; diabetes, 48.0%; renal failure on dialysis, 12.6%; history of myocardial infarction, 12.7%; history of stroke, 15.8%; CLTI, 7.1%; TASC II type D lesions, 18.3%; and chronic total occlusion, 39.0%.

Procedure-related adverse events were defined as retroperitoneal bleeding, puncture-site bleeding, transfusion requirement, distal embolism, renal impairment, surgery, vascular perforation or rupture, stent thrombosis, systemic embolism, and prolonged hospitalization. The current study examined the 3-year risk of incident MACEs in the 880 patients who underwent iliac stent placement. The permissible time window at the 3-year follow-up was set as ± 2 months. Health-related quality of life at baseline and 1 year was assessed using the Japanese versions of the EuroQol 5 Dimensions and the Walking Impairment Questionnaire (WIQ) (12,13).

Endpoints

The primary endpoint was MACEs during the 3-year follow-up. MACEs were defined as a composite of myocardial infarction, stroke, and all-cause mortality, and this study did not distinguish between MACEs related to aortoiliac stent placement and MACEs caused by cardiovascular diseases. An independent panel on clinical events, consisting of 5 experts who were not directly involved in this study and who had relevant expert knowledge, determined the cases of MACEs by reviewing the electronic medical data records in the OMOTENASHI database. Consensus for every case was achieved by a group discussion.

Statistical Analysis

Data on baseline characteristics are presented as means and SDs for continuous variables and as percentages for categorical variables, if not otherwise mentioned. A P value of $<.05$ was considered significant, and 95% confidence intervals (CIs) were reported where appropriate. The cumulative incidence rate of MACEs was estimated using the Kaplan-Meier method. The association of baseline characteristics with the risk of incident MACEs was

Table 1. Patient Characteristics (N = 880)

Characteristics	Statistics*	Missing data
Age, y	72.6 ± 8.7; 73 (67–79); 34–97	
Male sex	731 (83.1%)	
Body mass index, kg/m^2	22.57 ± 3.27; 22.6 (20.3–24.7); 12.7–35.1	
Current tobacco smoker	313 (35.6%)	
Hypertension	828 (94.1%)	
Dyslipidemia	719 (81.7%)	
Diabetes	422 (48.0%)	
Renal failure on dialysis	111 (12.6%)	
History of myocardial infarction	112 (12.7%)	
History of stroke	139 (15.8%)	
Aspirin use	652 (74.1%)	
Thienopyridine use	651 (74.0%)	
Dual antiplatelet therapy	514 (58.4%)	
Cilostazol use	218 (24.8%)	
Anticoagulant use	70 (8.0%)	
Statin use	451 (51.3%)	
Oral hypoglycemic agent use	206 (23.4%)	
Insulin use	78 (8.9%)	
Beta-blocker use	120 (25.4%)	n = 408
Renin-angiotensin-system inhibitor use	225 (47.7%)	n = 408
Non-HDL cholesterol (mg/dL)	129.7 ± 37.0; 126 (104–152); 42–287	n = 184
HDL cholesterol (mg/dL)	50.1 ± 15.3; 47 (40–58); 18–123	n = 98
Triglycerides (mg/dL)	149.0 ± 103.7; 120 (86–185); 8–1,034	n = 84
Hemoglobin A1c (%)	6.30 ± 0.98; 6.1 (5.6–6.7); 3.5–11.1	n = 107
EQ-5D utility	0.715 ± 0.180; 0.69 (0.59–0.77); 0.08–1.00	n = 564
EQ-5D VAS	60.9 ± 18.2; 61 (50–70); 0–100	n = 583
WIQ, pain	43.9 ± 26.1; 50 (25–50); 0–100	n = 566
WIQ, distance	30.8 ± 29.7; 25 (6–49); 0–100	n = 608
WIQ, speed	32.4 ± 26.0; 25 (11–50); 0–100	n = 622
WIQ, climbing	35.8 ± 30.1; 33 (8–54); 0–100	n = 614

EQ-5D = EuroQol 5 Dimensions; HDL = high-density lipoprotein; VAS = visual analog scale; WIQ = Walking Impairment Questionnaire.

*Data are shown as mean ± SD, median (interquartile range), range for continuous variables, and as frequencies (percentages) for discrete variables.

Table 2. Limb and Lesion Characteristics (N = 880)

Characteristics	Statistics*	Missing data
History of aortoiliac revascularization	104 (11.8%)	
Chronic limb-threatening ischemia	62 (7.1%)	
Ankle-brachial index	0.69 ± 0.21; 0.7 (0.6–0.8); 0.0–1.3	n = 16
Aortic lesion	81 (9.2%)	
Bilateral iliac lesions	235 (26.7%)	
TASC II class D†	161 (18.3%)	
Chronic total occlusion†	343 (39.0%)	
Calcification	719 (81.7%)	
Treated location		n = 1
Unilateral EIA	284 (32.3%)	
Bilateral EIA	92 (10.5%)	
Unilateral CIA	203 (23.1%)	
Bilateral CIA	68 (7.7%)	
Unilateral CIA and EIA	114 (13.0%)	
Bilateral CIA and EIA	56 (6.4%)	
Unilateral CIA and contralateral EIA	9 (1.0%)	
Unilateral CIA and bilateral EIA	24 (2.7%)	
Bilateral CIA and unilateral EIA	29 (3.3%)	
Number of treated locations	1.6 ± 0.9; 1 (1–2); 1–4	n = 1
Ipsilateral femoropopliteal lesion	319 (38.8%)	n = 57

CIA = common iliac artery; EIA = external iliac artery; TASC II = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II.

*Data are shown as mean ± SD, median (interquartile range), range for continuous variables, and as frequencies (percentages) for discrete variables.

†The number of cases with chronic total occlusion was larger than that with TASC II class D because not all occlusions are classified as TASC II class D (unilateral CIA occlusion and unilateral EIA occlusion not involving the origin of the internal iliac artery or common femoral artery are classified as TASC II class B; bilateral CIA occlusions and unilateral EIA occlusion that involve the origin of the internal iliac artery and/or common femoral artery are classified as TASC II class C).

investigated using the Cox proportional hazards regression model. Variables that were significantly associated with the outcome in the univariate model were entered into the multivariate model to explore their independent association with the outcome. All 30 patient-related characteristics listed in **Table 1** and 10 of the limb- and lesion-related characteristics listed in **Table 2** (ie, all characteristics apart from the nominal variable of treated lesions) were included in the analysis as variables with a potential impact on the incidence of MACEs. Hazard ratios for continuous variables were expressed per 1-SD increase. Although the primary purpose of the current study was to explore preoperative risk factors for MACEs, the association of endovascular procedures and perioperative and postoperative parameters with the risk of MACEs was also examined using the Cox proportional hazards regression model. Updated information on health-related quality of life (baseline values until 1 year and 1-year values thereafter) was treated as the time-dependent covariate in the model. The multiple imputation by chained equations method was used for missing data. Five imputed datasets were generated, and the analytic results were combined in accordance with the Rubin rule. All statistical analyses were performed using R version 3.6.0 (R Core Team, Vienna, Austria).

RESULTS

The EVT procedures performed in the study population are summarized in **Table E1** (available online on the article's Supplemental Material page at *www.jvir.org*). One or more self-expandable stents were implanted in 94.0% of the patients; the total stent length was 103.4 mm ± 79.2, and the mean stent diameter was 8.9 mm ± 1.3. Procedure-related adverse events occurred in 2.6% of the study

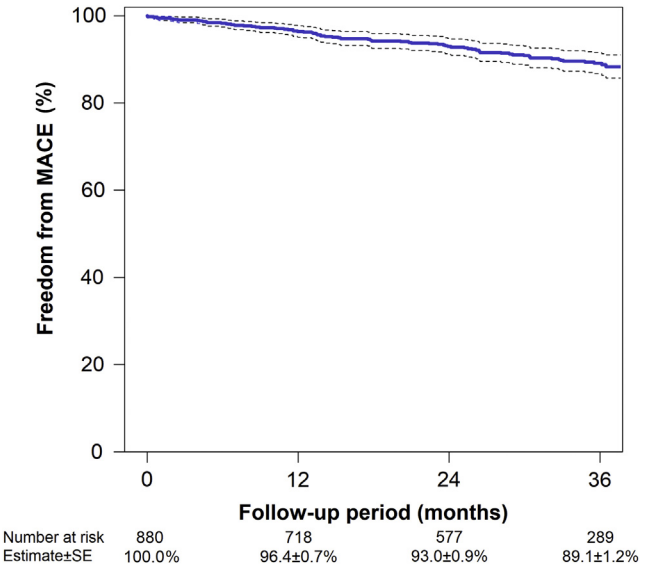


Figure 1. Kaplan-Meier estimates of the 3-year risk of major adverse cardiovascular events (MACEs). Dotted lines represent 95% confidence intervals. Estimate represents the Kaplan-Meier estimate. SE = standard error.

population (**Table E2**, available online at *www.jvir.org*). The median follow-up period was 2.9 years (interquartile range, 1.1–3.0 years), and 83 incident MACEs (70 deaths, 3 myocardial infarctions, and 10 strokes) were observed during this time. The 36-month rate of freedom from MACEs was 89.1% (95% CI, 86.8%–91.6%), as shown in **Figure 1**. The OMOTENASHI registry followed the patients for 3 years, and the permissible time window at the 3-year follow-up was set as ± 2 months. Therefore, some patients attended the 3-year follow-up at 34 months, and their follow-up period ended at that time; consequently, data on prognosis at 36 months were available only for 289 patients.

As shown in **Tables 3** and **4**, advanced age (≥75 years), renal failure on dialysis, history of myocardial infarction, history of stroke, insulin use, decreased non–high-density lipoprotein (non-HDL) cholesterol levels, CLTI, and ipsilateral femoropopliteal lesions were significantly associated with the risk of MACEs in the univariate model but the other analyzed patient-, limb-, or lesion-related characteristics were not. The multivariate model showed that advanced age, renal failure on dialysis, history of myocardial infarction, history of stroke, and ipsilateral femoropopliteal lesions were independently associated with the risk of incident MACEs ($P < .05$ for all) (**Table 5**). The adjusted hazard ratios (95% CIs) and per 1-SD increase were as follows: advanced age, 1.47 (1.15–1.89) ($P = .002$); renal failure on dialysis, 3.10 (1.88–5.11) ($P < .001$); history of myocardial infarction, 1.91 (1.14–3.19) ($P = .013$); history of stroke, 2.00 (1.22–3.26) ($P = .006$); and ipsilateral femoropopliteal lesions, 1.81 (1.11–2.96) ($P = .018$). Baseline medications, ankle-brachial index, and TASC II class D were not significantly associated with the risk of

Table 3. Univariate Analysis of the Association of Patient Characteristics with the Risk of Major Adverse Cardiovascular Events

Characterisitics	Unadjusted hazard ratio*
Age	1.38 (1.10–1.74), $P = .01$
Male sex	0.89 (0.50–1.59), $P = .70$
Body mass index	0.84 (0.68–1.04), $P = .12$
Current tobacco smoker	0.78 (0.49–1.27), $P = .32$
Hypertension	1.55 (0.49–4.90), $P = .46$
Dyslipidemia	0.91 (0.52–1.60), $P = .75$
Diabetes	1.40 (0.90–2.16), $P = .13$
Renal failure on dialysis	3.54 (2.21–5.65), $P < .001$
History of myocardial infarction	2.18 (1.32–3.59), $P = .002$
History of stroke	2.31 (1.42–3.76), $P = .001$
Aspirin use	0.81 (0.50–1.31), $P = .38$
Thienopyridine use	0.79 (0.49–1.27), $P = .33$
Dual antiplatelet therapy	0.73 (0.47–1.14), $P = .17$
Cilostazol use	1.06 (0.64–1.76), $P = .81$
Anticoagulant use	1.24 (0.60–2.57), $P = .57$
Statin use	0.87 (0.56–1.34), $P = .52$
Oral hypoglycemic agent use	1.15 (0.69–1.91), $P = .58$
Insulin use	1.92 (1.06–3.48), $P = .03$
Beta-blocker use	1.21 (0.50–2.91), $P = .64$
Renin-angiotensin-system inhibitor use	0.62 (0.39–1.00), $P = .05$
Non-HDL cholesterol	0.72 (0.56–0.94), $P = .01$
HDL cholesterol	0.82 (0.63–1.07), $P = .15$
Triglycerides	0.73 (0.47–1.14), $P = .16$
Hemoglobin A1c	0.89 (0.66–1.20), $P = .43$
EQ-5D utility	0.74 (0.35–1.58), $P = .36$
EQ-5D VAS	1.02 (0.74–1.41), $P = .90$
WIQ, pain	1.01 (0.73–1.41), $P = .95$
WIQ, distance	0.80 (0.64–1.01), $P = .06$
WIQ, speed	1.04 (0.29–3.69), $P = .94$
WIQ, climbing	0.85 (0.54–1.32), $P = .42$

EQ-5D = EuroQol 5 Dimensions; HDL = high-density lipoprotein; VAS = visual analog scale; WIQ = Walking Impairment Questionnaire.
*Data are unadjusted hazard ratios (95% confidence intervals), *P* values. The values represent the unadjusted hazard ratios per 1-SD for continuous variables.

Table 4. Univariate Analysis of the Association of Limb and Lesion Characteristics with the Risk of Major Adverse Cardiovascular Events

Characterisitics	Unadjusted hazard ratio*
History of aortoiliac revascularization	1.45 (0.81–2.58), $P = .21$
Chronic limb-threatening ischemia	2.41 (1.24–4.68), $P = .01$
Ankle-brachial index	0.92 (0.74–1.15), $P = .48$
Aortic lesion	1.03 (0.50–2.14), $P = .94$
Bilateral iliac lesions	0.91 (0.55–1.51), $P = .71$
TASC II class D	0.85 (0.47–1.54), $P = .59$
Chronic total occlusion	0.70 (0.44–1.12), $P = .14$
Calcification	1.00 (0.57–1.76), $P = .99$
Number of treated locations	1.06 (0.86–1.31), $P = .61$
Ipsilateral femoropopliteal lesion	2.59 (1.63–4.11), $P < .001$

TASC = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II.
*Data are unadjusted hazard ratios (95% confidence intervals), *P* values. The values represent the unadjusted hazard ratios per 1-standard deviation for continuous variables.

Table 5. Adjusted Association of Baseline Characteristics with the Risk of Major Adverse Cardiovascular Events

Characterisitics	Adjusted hazard ratio*
Age	1.47 (1.15–1.89), *P* = .002
Renal failure on dialysis	3.10 (1.88–5.11), *P* < .001
History of myocardial infarction	1.91 (1.14–3.19), *P* = .01
History of stroke	2.00 (1.22–3.26), *P* = .01
Insulin use	1.64 (0.89–3.00), *P* = .11
Non-HDL cholesterol	0.78 (0.60–1.01), *P* = .06
Chronic limb-threatening ischemia	1.67 (0.85–3.30), *P* = .14
Ipsilateral femoropopliteal lesion	1.81 (1.11–2.96), *P* = .02

HDL = high-density lipoprotein.

*Data are adjusted hazard ratios (95% confidence intervals) (*P* values) derived from the multivariate model. The variables in the table were all entered into the multivariate model because they showed a statistically significant association in the univariate model (**Tables 3** and **4** and **Tables E3** and **E4**). The values represent the adjusted hazard ratios per 1-standard deviation for continuous variables.

MACEs. **Figure 2** illustrates the risk of incident MACEs in subgroups according to the accumulation of these 5 risk factors. The 3-year rates of freedom from MACEs were 97.0% (95% CI, 94.4%–99.7%) in patients with none of the 5 risk factors, 92.0% (95% CI, 88.5%–95.9%) in those with 1 risk factor, 85.4% (95% CI, 79.8%–91.3%) in those with 2 risk factors, and 67.1% (95% CI, 56.8%–79.1%) in those with 3–5 risk factors. Supplementary analysis showed that EVT procedures and perioperative and postoperative characteristics were not significantly associated with the risk of MACEs (**Tables E3** and **E4**, available online at *www.jvir.org*).

DISCUSSION

The current study prospectively evaluated the cumulative incidence rate of MACEs after 1, 2, and 3 years. The results showed that the respective cumulative incidence rates were 3.6%, 7.0%, and 10.9% and that age, renal failure on dialysis, myocardial infarction, stroke, and femoropopliteal lesions were independent risk factors for MACEs.

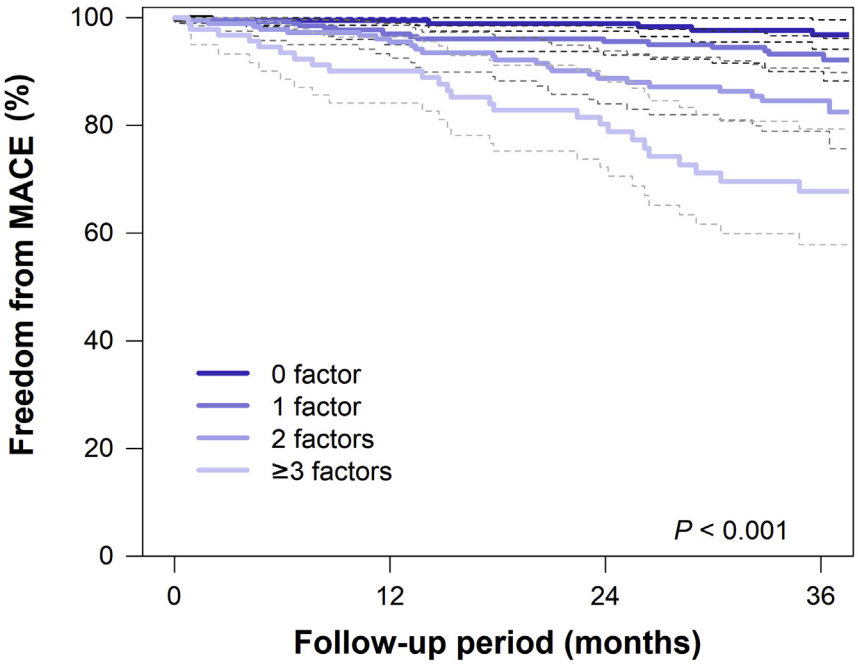
The baseline status of the study patients was poor: 48.0% had type 2 diabetes, and 12.6% had renal failure on dialysis. Regarding lesion characteristics, 39.0% had chronic total occlusion, and 81.7% of the lesions showed calcification. These proportions were higher than those reported in a retrospective study in which Kumakura et al (14) analyzed data from 1993 to 2013 and found that 28.1% patients had diabetes, 5.7% patients were on dialysis, 23.5% patients had chronic total occlusion, and 19.1% lesions were calcified. The differences in the respective proportions suggest that, in the past 2 decades, aortoiliac stent placement has become the standard treatment in patients with more severe comorbidities and arterial lesions.

Kumakura et al (14) found a rate of freedom from MACEs of approximately 80% at 3 years. In 2005–2009, Soga et al (6) and Miura et al (15) found corresponding rates of 84.4% and 88.6%, respectively. Thus, the MACE rate was higher in these previous studies (6,14,15) than in the current study. The recent advances in EVT techniques may have contributed at least partially to the reduction in risk; that is, safer and more effective revascularization may reduce the risk of incident MACEs. Another possible explanation is that systematic management before revascularization, including optimal medical therapy, has improved. Although the proportion of patients using statins in the current study (51.3%) was suboptimal, it was higher than those in the aforementioned studies: 34.5% in the study by Soga et al (6), 37.9% in the study by Kumakura et al (14), and 40.9% in the study by Miura et al (15). Careful and early therapeutic intervention based on optimal medical therapy may help to reduce the risk of incident MACEs.

On the other hand, previously identified risk factors, such as obesity, dyslipidemia, smoking, and type 2 diabetes, were not found to be risk factors for MACEs in the current study. In the Reduction of Atherothrombosis for Continued Health Registry, Japanese people had a better prognosis than people of other ethnicities (16). The current study may not have detected the traditional risk factors because of the small number of MACEs. Some large-scale studies (17) found that tobacco smoking and obesity were not always risk factors for MACEs. Another possible explanation why this study did not identify these traditional risk factors is that many of the patients were on dialysis. Patients on dialysis with type 2 diabetes often show an apparent improvement in glycemic control because of insulin metabolism deficiency, and many patients on dialysis quit smoking because of poor activities of daily living and the lack of physical strength to smoke (18,19). Furthermore, 1 study (20) found that low cholesterol levels appeared to affect noncardiovascular mortality in patients on dialysis. The reverse association between cholesterol level and mortality in patients on dialysis is of short duration and may be related to malnutrition (20). This study may not have identified type 2 diabetes, dyslipidemia, and smoking as risk factors for MACEs because of the high number of patients on dialysis in the sample. In addition, previous studies analyzed only baseline data and did not consider changes in these factors after EVT. This study did not directly compare Japanese people with people in Western countries; therefore, further investigation limited to aortoiliac lesions is needed.

The independent predictors of MACEs were age, renal failure on dialysis, myocardial infarction, stroke, and femoropopliteal lesions, and the rate of freedom from MACEs was 20%–30% lower in patients with ≥3 risk factors (67.1%; 95% CI, 56.8%–79.1%) than in those with no risk factors (97.0%; 95% CI, 94.4%–99.7%) or 1 risk factor (92.1%; 95% CI, 88.5%–95.9%). Four of the risk factors were systematic factors, and the presence of femoropopliteal lesions was the only lesion-related risk factor.

Procedure-related factors were not associated with the risk of MACEs (**Table E3**, available online at *www.jvir.org*), supporting the idea that the procedure of aortoiliac EVT itself does not negatively affect outcome. The fact



Number at risk				
0 factor	222	192	167	92
1 factor	300	244	189	98
2 factors	204	159	121	61
≥3 factors	97	80	62	29
Estimate ± SE				
0 factor	100%	99.5±0.5%	99.0±0.7%	96.9±1.4%
1 factor	100%	97.0±1.0%	95.6±1.3%	93.3±1.7%
2 factors	100%	95.5±1.5%	88.8±2.5%	84.6±3.0%
≥3 factors	100%	90.2±3.1%	80.3±4.3%	67.8±5.5%

Figure 2. Kaplan-Meier estimates of the 3-year risk of major adverse cardiovascular events (MACEs) by accumulation of risk factors. The study population was divided according to the presence at baseline of the following 5 risk factors for MACEs: (*a*) an age of ≥75 years, (*b*) renal failure on dialysis, (*c*) history of myocardial infarction, (*d*) history of stroke, and (*e*) femoropopliteal lesions. Dotted lines represent 95% confidence intervals. A *P* value was obtained from the log-rank test. Estimate represents the Kaplan-Meier estimate. SE = standard error.

that femoropopliteal lesions were associated with an increased risk of MACEs suggests that PAD affecting the femoropopliteal arteries is a marker of more severe systematic atherosclerosis, which is associated with a higher risk of MACEs. A previous study (21) showed that a decline in the ankle-brachial index is associated with the risk of MACEs. The study also revealed a consistent and significant association between the progression of PAD to subsequent cardiovascular disease and morbidity and mortality, independent of the severity of PAD and traditional cardiovascular disease risk factors. Multisegment PAD may be a key factor for an increased risk of MACEs: patients with multivessel lesions may have a higher prevalence of undetected disease in other vessels, including in the microcirculation.

In this study, dual antiplatelet therapy was not significantly associated with a reduced risk of MACEs. A previous study (10) found that dual antiplatelet therapy was also not associated with a reduced risk of patency loss. When the OMOTENASHI registry was first established, direct oral anticoagulant use was not approved in Japan. Therefore, the current study could not consider the role of this type of treatment. On the basis of the most recent insights, it can be theorized that MACEs may be further improved if patients receive antiplatelet agents in combination with factor Xa antagonists after aortoiliac stent placement (22). Appropriate use criteria of dual antiplatelet therapy for EVT should be validated in the future. Clinical guidelines strongly recommend dual antiplatelet therapy after stent placement even though insufficient evidence is available for its efficacy. Future studies are needed to evaluate the efficacy of this type of medical therapy.

The non-HDL cholesterol levels were not significant ($P = .060$) in the multivariate model (**Table 2**); furthermore, the hazard ratio was <1, suggesting that non-HDL cholesterol might be inversely associated with an increased risk of MACEs. Although this finding appears to be unusual, it is consistent with the findings of a study (17) that analyzed a large health insurance database in Germany and showed that dyslipidemia was inversely associated with an

increased risk of death ($P < .001$), myocardial infarction ($P = .091$), and stroke ($P = .083$). Although the associated mechanisms remain unclear, malnutrition and frailty may explain this association.

This study has several limitations. First, it included only Japanese patients. Second, no detailed data were available on cardiovascular risk management during the follow-up period, including tobacco smoking reduction and cessation; weight loss; and changes in exercise therapy, medication, and glycemic control. Third, the OMOTENASHI registry did not include patients undergoing covered stent placement because covered stents were not approved at the time of the study. Fourth, none of patients underwent atherectomy or lysis. Fifth, the study did not have sufficient statistical power to assess the risk of MACEs in patients with CLTI. Lastly, the rate of continuous follow-up up to 3 years was low.

In conclusion, the 3-year rate of freedom from MACEs was high. Baseline characteristics, such as age, renal failure on dialysis, history of myocardial infarction, history of stroke, and femoropopliteal lesions, were independent risk factors for MACEs. When placing an aortoiliac stent, the high risk of MACEs in these populations should be considered.

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Supplementary Table E1. Endovascular Procedures (N = 880 Patients)

Procedures	Statistics*	Missing data
Staged revascularization	22 (2.5%)	
Femoral access		n = 4
None	60 (6.9%)	
Unilateral	628 (71.7%)	
Bilateral	188 (21.5%)	
Brachial access		n = 4
None	704 (80.4%)	
Unilateral	169 (19.3%)	
Bilateral	3 (0.3%)	
Radial access		n = 4
None	823 (93.9%)	
Unilateral	52 (5.9%)	
Bilateral	1 (0.1%)	
Other access	21 (2.4%)	n = 4
Number of access sites	1.4 ± 0.6; 1 (1–2); 1–4	n = 4
French size of access site	6.0 ± 0.4; 6 (6–6); 3–9	n = 50
Stent		
Balloon-expandable stent	53 (6.0%)	
Self-expandable stent	798 (90.7%)	
Both types of stent	29 (3.3%)	
Self-expandable stent use	827 (94.0%)	
Balloon-expandable stent use	82 (9.3%)	
Total stent length, mm	103.4 ± 79.2; 80 (40–140); 17–700	
Stent diameter, mm	8.9 ± 1.3; 9 (8–10); 6–12	
Predilatation	656 (74.5%)	
Postdilatation	820 (93.2%)	
Intravascular ultrasound use	611 (69.4%)	
Embolic protection device use	23 (2.6%)	
Vascular closure device use	544 (61.8%)	

*Data are shown as mean ± SD, median (interquartile range), range for continuous variables, and frequencies (percentages) for discrete variables.

Supplementary Table E2. Perioperative and Postoperative Parameters (N = 880 Patients)

Parameters	Statistics*	Missing data
Perioperative parameters		
Procedure-related adverse event	23 (2.6%)	
Postoperative parameters after 1 year		
EQ-5D utility	0.805 ± 0.290; 1.00 (0.68–1.00); 0.00–1.00	n = 559
EQ-5D VAS	74.3 ± 16.6; 80 (70–85); 0–100	n = 610
WIQ, pain	85.4 ± 24.1; 100 (75–100); 0–100	n = 584
WIQ, distance	77.0 ± 34.2; 100 (59–100); 0–100	n = 612
WIQ, speed	65.7 ± 33.2; 72 (37–100); 0–100	n = 649
WIQ, climbing	72.8 ± 34.5; 88 (50–100); 0–100	n = 618

EQ-5D = EuroQol 5 Dimensions; VAS = visual analog scale; WIQ = Walking Impairment Questionnaire.
*Data are shown as mean ± SD; median (interquartile range), range for continuous variables, and frequencies (percentages) for discrete variables.

SupplementaryTable E3. Crude Association of Endovascular Procedures with the Risk of Major Adverse Cardiovascular Events

Procedures	Unadjusted hazard ratio*
Staged revascularization	1.49 (0.47–4.72), *P* = .50
Number of access sites	0.87 (0.69–1.10), *P* = .24
French size of access site	0.98 (0.74–1.29), *P* = .86
Self-expandable stent use	1.48 (0.47–4.69), *P* = .51
Balloon-expandable stent use	1.03 (0.48–2.25), *P* = .93
Total stent length	0.90 (0.70–1.14), *P* = .37
Stent diameter	1.03 (0.82–1.28), *P* = .82
Predilatation	1.24 (0.73–2.11), *P* = .43
Postdilatation	0.83 (0.36–1.91), *P* = .66
Intravascular ultrasound use	1.04 (0.65–1.67), *P* = .87
Embolic protection device use	1.25 (0.31–5.08), *P* = .76
Vascular closure device use	0.76 (0.49–1.19), *P* = .23

*Data are unadjusted hazard ratios (95% confidence intervals), *P* values. The values represent unadjusted hazard ratios per 1-SD for continuous variables.

SupplementaryTable E4. Crude Association of Perioperative and Postoperative Parameters with the Risk of Major Adverse Cardiovascular Events

Parameters	Unadjusted hazard ratio*
Perioperative information	
Procedure-related adverse event	2.21 (0.81–6.05)), *P* = .12
Updated information (time-dependent covariate)	
EQ-5D utility	0.70 (0.42–1.16), *P* = .14
EQ-5D VAS	0.91 (0.48–1.69), *P* = .71
WIQ, pain	1.08 (0.79–1.48), *P* = .61
WIQ, distance	0.83 (0.64–1.07), *P* = .15
WIQ, speed	0.92 (0.38–2.28), *P* = .83
WIQ, climbing	0.86 (0.61–1.23), *P* = .38

EQ-5D = EuroQol 5 Dimensions; VAS = visual analog scale; WIQ = Walking Impairment Questionnaire.
*Data are unadjusted hazard ratios (95% confidence intervals), *P* values. The values are unadjusted hazard ratios per 1-SD for continuous variables.