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Original Article

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Clinical Outcomes after Isolated Infrapopliteal Revascularization in Hemodialysis Patients with Critical Limb Ischemia:

Endovascular Therapy versus Bypass Surgery

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Aim: To investigate the long-term clinical outcome of endovascular therapy (EVT) or bypass surgery in patients on hemodialysis (HD) with critical limb ischemia due to isolated infrapopliteal disease.

Methods: We enrolled 254 consecutive HD patients successfully undergoing infrapopliteal revascularization by EVT (126 patients) and bypass surgery (128 patients). They were followed up for five years. Amputation-free survival (AFS) and incidence of any re-intervention were evaluated. A propensity score from all baseline variables was incorporated into Cox analysis.

Results: In the EVT group, age was higher ($p=0.039$), diabetes and coronary artery disease were more frequent ($p=0.004$ and $p=0.0052$, respectively), and tissue loss was more rarely observed ($p<0.0001$) than in the bypass group. During the follow-up period, 21 major amputations and 64 deaths occurred. The propensity score-adjusted AFS rate at 5 years was comparable between groups (61.0% in EVT group vs. 55.1% in the bypass group, adjusted hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.52–1.42, $p=0.58$). The adjusted survival rates were also similar between groups for amputation and all-cause mortality. However, freedom from any re-intervention was markedly lower in the EVT than in the bypass group (48.6% vs. 84.6%, adjusted-HR, 3.56, 95% CI 1.95-6.75, $p<0.0001$).

Conclusions: The rate of AFS was broadly comparable between the two strategies, although compared with bypass surgery, EVT had much higher rates for re-intervention.

Key words: Infrapopliteal, Critical limb ischemia, Hemodialysis, Endovascular therapy, Bypass surgery

Introduction

Patients with end-stage renal failure requiring chronic hemodialysis (HD) are at high-risk of atherosclerosis including peripheral artery disease (PAD)[1]. Even after revascularization of lower limbs, poorer prognosis has been a perennial clinical problem in HD patients with critical limb ischemia (CLI) as compared with non-HD patients[2-4]. In particular, isolated infrapopliteal disease, which accounts for 25% of patients with CLI[5], is frequently observed in HD patients and correlates with poor clinical outcomes such as restenosis, major amputation, and death after revascularization[6-8]. Although bypass surgery is considered the first-line strategy for infrapopliteal disease[9], HD patients as well as diabetic patients have been regarded

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as a challenging population with poor prognosis after surgical revascularization[4]. Currently, endovascular therapy (EVT) is being widely performed to treat CLI due to isolated infrapopliteal disease[6, 10-12], but only limited reports on outcomes of EVT for HD patients are available[4-7].

Recent reports have presented that rates of major amputation and death are broadly comparable between the two procedure groups in HD patients with infrainguinal disease[13, 14], although compared with EVT, bypass surgery had lower rates of any re-intervention[13]. However, there have been few reports on the clinical outcomes after revascularization in HD patients with CLI due to isolated infrapopliteal disease. Moreover, whether EVT is an optimal procedure in this high-risk population remains controversial.

Aim

The present study aimed to investigate the long-term clinical outcome after EVT or after bypass surgery in HD patients with CLI due to isolated infrapopliteal disease.

Methods

Patients

This study was conducted as a retrospective record review. From May 2006 to June 2015, a total of 254 consecutive HD patients with CLI due to isolated infrapopliteal disease who successfully underwent revascularization at the Matsunami General Hospital (Kasamatsu, Japan) and the Nagoya Kyoritsu Hospital (Nagoya, Japan) were enrolled. Of them, 126 patients underwent EVT and 128 patients underwent bypass surgery. Patients who underwent emergency revascularization for acute limb ischemia were excluded. CLI was defined as ischemic rest pain or tissue loss, consistent with Rutherford Classes 4–6[15].

All patients underwent preoperative contrast arteriography and had >75% angiographic stenosis before revascularization. Vascular specialists including vascular surgeons and interventionalists decided whether EVT or bypass surgery was indicated for each patient considering angiographical findings, degree of tissue loss, general health conditions, comorbidities, and presence of a suitable great saphenous vein for grafting. Generally, for patients with extensive tissue loss, bypass surgery was recommended. In cases of unsuitable anastomosis site, unavailable vein graft and intolerable conditions for open surgery, EVT was preferred. Patients in Rutherford class 4 status and with short diseased lesions were initially recommended for EVT.

The EVT procedure was performed generally through the antegrade approach from the ipsilateral common femoral artery. Target vessels were identified by anatomical status of diseased vessels and networking of distal vessels for achieving straight artery flow to the foot. A 4–6 French sheath was inserted and 5,000 IU of heparin was injected in the beginning. A 0.014-inch wire was used for crossing in most cases, and balloon angioplasty was performed. Technical success was defined as achieving <30% residual stenosis and straight flow to the foot without flow-limiting dissection. Even when residual stenosis or dissection was observed after balloon angioplasty, no stent was used because of unavailability for the infrapopliteal artery in Japan. Bypass surgery was performed using general anesthesia and the primary choice of graft was the ipsilateral or contralateral great saphenous vein. No upper extremity veins were used because the veins had to be reserved for the arteriovenous fistula for HD. Proximal inflow of bypass graft was arranged via popliteal artery. For distal outflow, artery was selected in accordance with runoff to the foot.

Demographics, risk factors including patient gender, age, diabetes, hypertension, dyslipidemia, smoking status, body mass index (BMI), history of cardiovascular disease and stroke, indication of revascularization, ankle brachial index, and procedural variables were obtained from the medical records in each hospital. In this study, pre-procedural C-reactive protein (CRP) level was also measured because elevated CRP was reportedly associated with poor prognosis in CKD patients[16]. Geriatric nutritional risk index (GNRI), a marker for nutritional status, was also calculated from serum albumin levels and body weight, as follows: GNRI = 14.89 × albumin (g/dL) + (41.7 × [body weight/ideal body weight]). The ideal body weight was defined as the value calculated from the height and a BMI of 22 kg/m^2[17].

Follow-up Study

Patients were routinely followed up at discharge: at 1, 3, and 6 months after the procedure for 1 year; and then at yearly intervals, using duplex ultrasound. Amputation-free survival (AFS), as a composite endpoint defined as freedom from amputation above the ankle or any-cause death, was primarily evaluated. The incidence of re-intervention was also analyzed. These endpoints were defined as was reported by a previous study[15]. Patients were followed up for five years or until December 2015 if the follow-up period was less than five years. The study protocol and chart reviews used were approved by the institutional ethics committee in each hospital and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Statistical Analyses

Variables with a normal distribution are expressed as mean values ± standard deviation (SD), and asymmetrically distributed data are given as median and interquartile range. Differences between the two groups were evaluated by Mann–Whitney *U*-test or Student's *t*-test for continuous variables and by chi-square test for categorical variables. Differences in the event-free survival between the two groups were examined using the Kaplan-Meier method and compared using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each endpoint by a Cox proportional hazards analysis. To adjust for the differences in baseline characteristics between the two procedures, a propensity score analysis was performed using a multivariate logistic regression model which included all baseline variables. The score was then incorporated into a Cox proportional hazards model as a covariate. Variables with $p < 0.05$ on univariate analysis and diabetes and presence of tissue loss as established risk factors were also entered into the multivariate model with the propensity score to determine independent predictors for each endpoint. Differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed using the SPSS 21 software program (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

Clinical and lesion characteristics are shown in **Table 1**. Patient age was higher (71 ± 10 vs. 68 ± 9 years, $p = 0.039$), and diabetes and coronary artery disease were more frequent in the EVT than in the bypass group (76.8% [96 patients] vs. 60.2% [77 patients], $p = 0.004$; and 67.9% [76 patients] vs. 45.3% [58 patients], $p = 0.0052$, respectively). In contrast, Rutherford Classes 5 and 6 were more rarely observed (62.7% [79 patients] vs. 97.7% [125 patients], $p < 0.0001$), and CRP levels were lower (13.5 vs. 24.2 mg/L, $p = 0.003$) in the EVT than in the bypass group. The GNRI was higher (91.6 vs. 89.2, $p = 0.042$) in the EVT than in the bypass group. HbA1c levels and the rate of insulin use were similar between groups. No major procedural complications occurred in either group. Retrograde approaches were performed in four cases (3.2%) in the EVT group.

Followed-up Results

During the follow-up period (median, 32 months), 21 major amputations (5 in the EVT group and 16 in the bypass group), 64 deaths (27 in the EVT group and 37 in the bypass group) and 60 re-interventions (44 in the EVT group and 16 in the bypass group) occurred. Cardiovascular disease, from which 29 patients (45.3%) died, was the greatest cause of death, and other causes of death included sepsis, pneumonia, and gastrointestinal bleeding. With regard to re-intervention strategies, 28 (63.6%) bypass surgeries and 16 (36.4%) repeat EVTs were performed in the EVT group, while all patients who underwent re-intervention in the bypass group were treated endovascularly. AFS rate at 5 years was comparable (60.8% in the EVT group vs. 54.3% in the bypass group, HR 0.87, 95% CI 0.55–1.37, $p = 0.55$) between groups (**Table 2** and **Fig. 1A**). The survival rates for amputation and all-cause mortality were also similar (91.1% vs. 75.3%, HR 0.46, 95% CI 0.15–1.18, $p = 0.11$ and 67.0% vs. 61.9%, HR 0.98, 95% CI 0.58–1.62, $p = 0.93$ for the EVT and bypass groups, respectively) (**Table 2** and **Fig. 1B** and **1C**). Freedom from any re-intervention was markedly lower in the EVT than in the bypass group (47.4% vs. 85.2%, HR 3.79, 95% CI 2.17–6.96, $p < 0.0001$; **Table 2** and **Fig. 1D**). Even after adjustment by propensity score, the rates of AFS, limb salvage, and survival rate at 5 years were still comparable between groups (61.0% vs. 55.1%, adjusted HR 0.87, 95% CI 0.52–1.42, $p = 0.58$; 93.9% vs. 86.4%, adjusted HR 0.65, 95% CI 0.21–1.69, $p = 0.39$; and 68.8% vs. 60.5%, adjusted HR 0.84, 95% CI 0.47–1.49, $p = 0.56$ in the EVT and bypass groups, respectively) (**Table 2** and **Fig. 2A**, **2B**, and **2C**). Freedom from any re-intervention was significantly lower in the EVT than in the bypass group, as before (48.6% vs. 84.6%, adjusted HR 3.56, 95% CI 1.95–6.75, $p < 0.0001$; **Table 2** and **Fig. 2D**).

Significant Predictors

For the composite endpoint with amputation or death, the independent risk factors were age (HR 1.03, 95% CI 1.01–1.06, $p = 0.016$), declined GNRI (HR 0.98, 95% CI 0.95–0.99, $p = 0.045$), and elevated CRP levels (HR 1.04, 95% CI 1.01–1.07, $p = 0.041$) on Cox multivariate analysis (**Table 3**). Further, elevated CRP levels and declined GNRI were identified as independent risk factors for amputation (HR 1.05, 95% CI 1.01–1.10, $p = 0.049$) and death (HR 0.97, 95% CI 0.94–0.99, $p = 0.027$), respectively.

Discussion

This study was conducted to comparatively investigate the long-term clinical outcomes after EVT or after bypass surgery in HD patients with CLI due to isolated infrapopliteal disease. Patients in the bypass group had severe CLI, with higher frequency of tissue loss. Further, higher CRP levels and lower GNRI,

Table 1. Clinical Characteristics

	All patients (n = 254)	EVT (n = 126)	Bypass surgery (n = 128)	p value
Male (%)	174 (68.5)	84 (66.7)	90 (70.3)	0.53
Age (years)	69 ± 10	71 ± 10	68 ± 9	0.039
Duration of HD (years)	6.1 (3.5-9.0)	6.6 (4.8-9.2)	4.0 (1.4-8.4)	0.012
Diabetes (%)	174 (68.4)	97 (76.8)	77 (60.2)	0.0042
HbA1c (%)§	6.4 ± 1.3	6.4 ± 1.2	6.4 ± 1.3	0.86
Insulin use (%)§	41 (23.6)	25 (25.7)	16 (20.8)	0.44
Hypertension (%)	161 (63.4)	96 (76.2)	65 (50.8)	< 0.0001
Hyperlipidemia (%)	62 (24.4)	37 (29.4)	25 (19.5)	0.068
Smoking (%)	45 (17.7)	27 (21.4)	18 (14.1)	0.10
Body mass index	21.2 (19.3-23.3)	21.3 (19.3-21.3)	21.1 (19.1-22.8)	0.58
Coronary artery disease (%)	144 (56.7)	86 (67.9)	58 (45.3)	0.0052
Stroke (%)	40 (15.7)	25 (19.8)	15 (11.7)	0.18
GNRI	90.4 ± 9.4	91.6 ± 9.3	89.2 ± 9.4	0.042
Rutherford classification (%)				< 0.0001
4	50 (19.7)	47 (37.3)	3 (2.3)	
5	147 (57.9)	60 (47.6)	87 (68.0)	
6	57 (22.4)	19 (15.1)	38 (29.7)	
Ankle brachial index	0.57 (0.37-0.78)	0.56 (0.35-0.77)	0.66 (0.37-0.88)	0.15
C-reactive protein (mg/l)	17.1 (5.0-42.5)	13.5 (2.8-35.3)	24.2 (7.3-47.8)	0.0029
Number of limb	268	133	135	
Target artery (%)				0.71
Tibioperoneal	14 (5.2)	5 (3.8)	9 (6.7)	
Anterior tibial / Dorsal pedis	154 (57.5)	79 (59.4)	75 (55.6)	
Posterior tibial / Plantar	75 (28.0)	39 (29.3)	36 (26.7)	
Peroneal	25 (9.3)	10 (7.5)	15 (11.0)	
Medication (%)				
Cilostazol	31.0	42.9	19.1	< 0.0001
Other antiplatelets	90.6	90.6	90.6	0.99
ACE-inhibitor/ARB	34.0	35.3	33.3	0.78
Statin	17.0	17.7	16.7	0.86
β blocker	21.3	22.1	20.6	0.82
Calcium channel blocker	29.9	36.8	26.2	0.13

EVT, endovascular therapy; HD, hemodialysis; GNRI, geriatric nutritional risk index; ACE, angiotensin-converting-enzyme; ARB, Angiotensin II receptor blocker
§; diabetic patients only

despite the younger age of patients in the bypass group, could reflect a more comorbid condition such as malnutrition or inflammation, compared with those observed in the EVT group. The inferior status in the bypass group may possibly lead to worse outcomes of AFS, limb salvage and mortality rate. However, no significant differences between the two groups were observed; further, similar results were derived even after adjustment for the differences of clinical characteristics using propensity score.

Both chronic HD status and isolated infrapopliteal disease are risk factors for poor prognosis[6-8, 18], and clinical outcomes of HD patients after EVT for isolated infrapopliteal disease were reported to be poorer than those of non-HD patients[19]. In terms of the revascularization method for HD patients with infrapopliteal disease, there have been limited studies describing EVT outcomes, as compared with those of bypass surgery. In the general population, a retrospective study using propensity score analysis by Söderström *et al.*[6] showed that EVT and bypass surgery achieved similar 5-year AFS, limb salvage, and survival in patients with infrapopliteal disease. Similarly, even in HD patients, our propensity-adjusted comparison showed no significant difference between the two procedures EVT and bypass surgery.

The survival rate of CLI patients on HD reported by Ramdev P *et al.*[20] was much lower than

Table 2. Hazard ratio of EVT vs. Bypass surgery for clinical outcomes

	Crude		Propensity score-adjusted	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Amputation or death	0.87 (0.55-1.37)	0.55	0.87 (0.52-1.42)	0.58
Amputation	0.46 (0.15-1.18)	0.11	0.65 (0.21-1.69)	0.39
All-cause death	0.98 (0.58-1.62)	0.93	0.84 (0.47-1.49)	0.56
Revascularization	3.79 (2.17-6.96)	<0.0001	3.56 (1.95-6.75)	<0.0001

HR, hazard ratio; CI, confidence interval

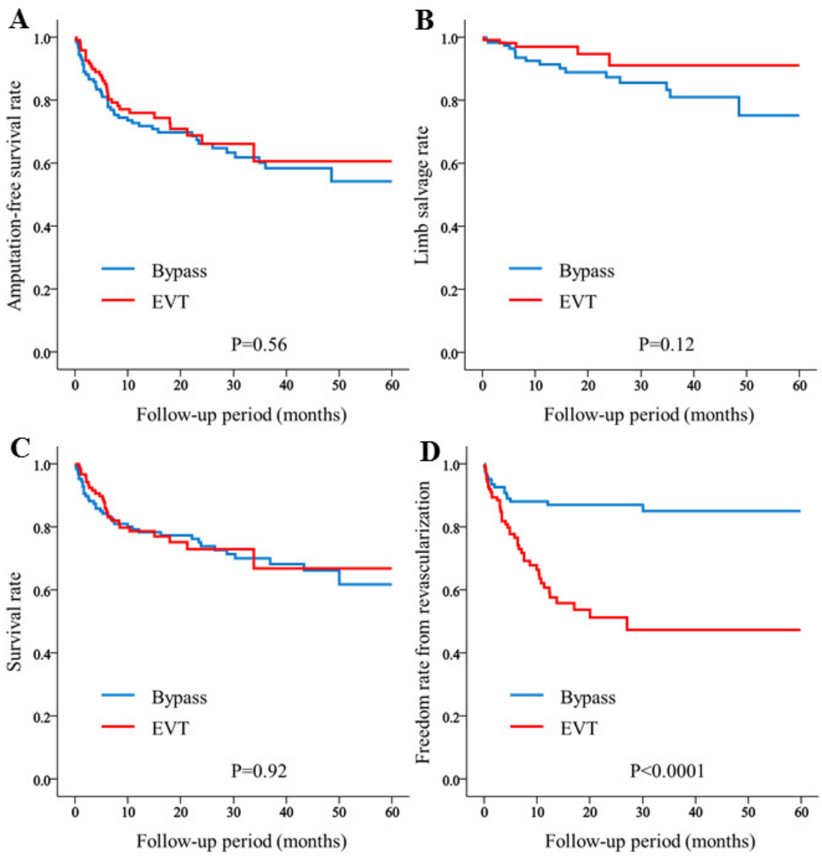

Fig. 1.
Kaplan-Meier estimated (A) amputation-free survival (AFS) rate, (B) limb salvage rate, (C) survival rate, and (D) rate of freedom from any revascularization in the endovascular therapy (EVT) and bypass groups

that of our study. A possible reason for this discrepancy is that all enrolled subjects in the present study were Japanese, who are at a lower risk for atherosclerosis and cardiovascular mortality than patients in Europe or in the US[21-23]. In a previous report[24], the 5-year survival rate was about 83% in non-HD Japanese patients who underwent infrapopliteal revascularization, which was higher than the survival rate in our study. However, the 5-year survival rate in our population was slightly better than the average survival rate of Japanese patients on HD (59%), as reported by the Japanese Society of Dialysis Therapy[25], or the rates in Europe (48%) or the US (40%), reported by Held *et al.*[21] In this regard, our results seemed to be fully acceptable.

For aortoiliac occlusive disease, EVT was associated with acceptable clinical outcomes even in HD patients[26, 27]. As for HD patients with CLI due to

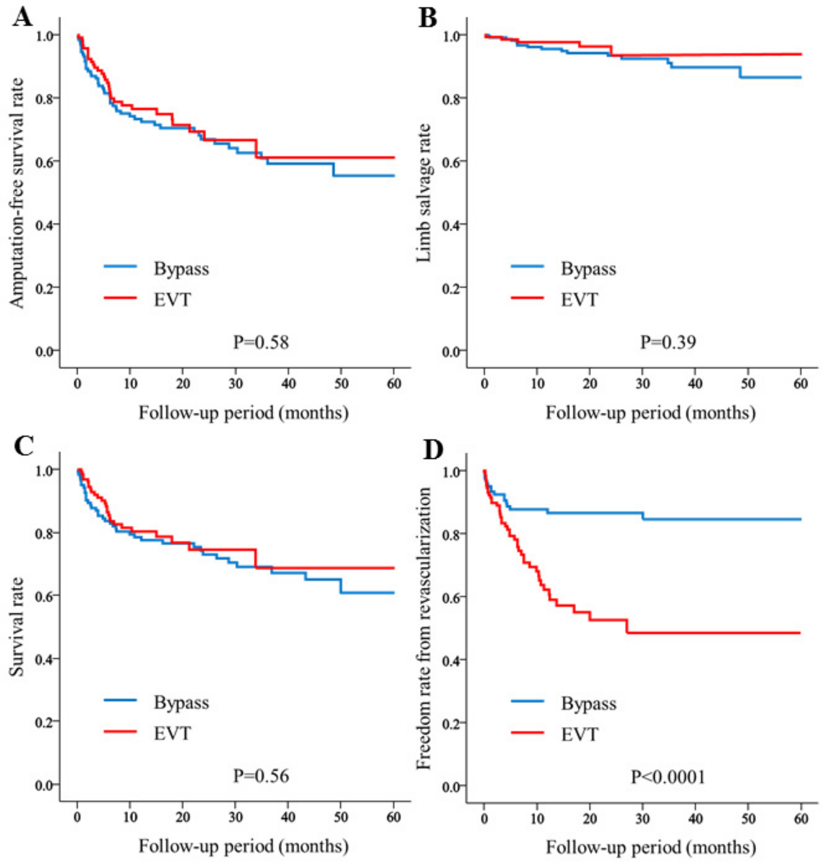

Fig. 2.
Propensity score-adjusted (A) amputation-free survival (AFS) rate, (B) limb salvage rate, (C) survival rate, and (D) rate of freedom from any revascularization in the endovascular therapy (EVT) and bypass groups

Table 3. Independent risk factors for each clinical outcome

	HR (95% CI)	*P* value
Amputation or death		
Age	1.03 (1.01-1.06)	0.016
GNRI	0.98 (0.95-0.99)	0.045
C-reactive protein	1.04 (1.01-1.07)	0.041
Amputation		
C-reactive protein	1.05 (1.01-1.10)	0.049
Death		
Age	1.06 (1.03-1.10)	0.0001
History of CAD	1.94 (1.15-3.36)	0.013
GNRI	0.97 (0.94-0.99)	0.027

Multivariate model includes age, GNRI, previous CAD, and C-reactive protein level as covariates with $p<0.05$ by univariate analysis, with diabetes and tissue loss.
HR, hazard ratio; CI, confidence interval; GNRI, geriatric nutritional risk index; CAD, coronary artery disease

infrainguinal disease, we reported that the five-year rates of AFS and survival were comparable between the two procedure groups (47.1% and 50.9% in the EVT group, and 51.4% and 60.6% in the bypass group, respectively), and freedom from any re-intervention at five years was significantly lower in the EVT group than in the bypass group (52.3% vs. 81.9%)[13]. In the present study, we focused on HD patients with CLI due to isolated infrapopliteal disease because isolated infrapopliteal disease was common in such patients[6], and seemed to be a persistent problem. With regard to the EVT strategy, drug-eluting stents, drug-coated balloons, and atherectomy devices may provide better clinical outcomes compared with those provided by conventional balloon angioplasty[28-30]. Unfortunately they were not available in Japan at that time, and their role in infrapopliteal disease of patients on HD is unclear.

In the present study, elevated CRP levels and low

GNRI were associated with amputation or death, or both. Currently, protein-energy wasting (PEW), a state of decreased body stores of protein and energy fuels, has been reported to be commonly observed, and is associated with cardiovascular risk in patients with chronic kidney disease (CKD)[31]. PEW or malnutrition was also considered to be due to inflammation rather than poor nutritional intake[32]; therefore, a comorbid condition such as low GNRI or elevated CRP levels is considered to be a part of the manifestation of PEW. Besides, we have previously reported that low BMI and elevated CRP levels could predict amputation or mortality after bypass surgery for infrapopliteal disease[24], and that elevated CRP levels or hypoalbuminemia were associated with poor limb salvage and survival after EVT in this population[33, 34]. In this regard, more attention should be paid in further studies to the pre-procedural PEW state, a CKD-specific comorbidity, in this high-risk population.

Limitations

The present study had some limitations. First, this study was a non-randomized, retrospective record review of patients in regular clinical practice, and the number of enrolled patients was relatively small because they were recruited from only two centers. Randomized control trials with a larger sample size are eagerly awaited. Second, there remains a concern about unobserved risk factors which may affect outcomes such as hemodynamic status, duration of comorbid diseases, and etiology of renal failure. Although propensity score adjustment can reduce the difference of characteristics between the two groups, biases from unrecorded characteristics remain. In addition, about two thirds of enrolled patients were diabetic. Diabetes may present various clinical features of neuropathy, ischemia and sepsis, and these could each lead to limb threats by themselves[35]. Precise risk stratification based on wound, ischemia and foot infection should be considered[36], and, moreover, information about the patients' conditions was incomplete. As well as AFS, status of ambulatory and wound healing at the end of the study was important for assessing clinical outcomes.

Conclusion

The rate of AFS is broadly comparable between the two strategies and the survival rate after both procedures might be fully acceptable in HD patients with CLI due to isolated infrapopliteal disease. However, compared with bypass surgery, EVT had much higher rates for re-intervention; thus, patients with tolerance to invasive surgery may be treated with bypass surgery.

Acknowledgment

None.

Conflict of Interest

H.I. received lecture fees from Astellas Pharma Inc. Daiichi-Sankyo Pharma Inc. and MSD K.K. T. M. received lecture fees from Bayer Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Sanofi-aventis K.K., and Takeda Pharmaceutical Co., Ltd. T.M.received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc, Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K.K., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd.

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