Comparison of Clinical Outcomes after Surgical and Endovascular Revascularization in Hemodialysis Patients with Critical Limb Ischemia

Tatsuya Shiraki1, Osamu Iida1, Mitsuyoshi Takahara2, Yoshimitsu Soga3, Shinsuke Mii4, Jin Okazaki5, Sosei Kuma6, Terutoshi Yamaoka6, Daisuke Kamoi7, Yoshiaki Shintani8, Toshinobu Ishikawa9, Ikuro Kitano10 and Masaaki Uematsu1

1 Kansai Rosai Hospital Cardiovascular Center, Amagasaki, Japan
2 Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
3 Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan
4 Department of Vascular Surgery, Saiseikai Yahata General Hospital, Kitakyushu, Japan
5 Department of Vascular Surgery, Kokura Memorial Hospital, Kitakyushu, Japan
6 Department of Vascular Surgery, Matsuyama Red Cross Hospital, Matsuyama, Japan
7 Department of Cardiology, Nagoya Kyoritsu Hospital, Nagoya, Japan
8 Department of Cardiology, Shin-Koga Hospital, Kurume, Japan
9 Department of Cardiology, Oita Oka Hospital, Oita, Japan
10 Department of Surgery, Shinsuma General Hospital, Kobe, Japan

Aim: The treatment strategy for hemodialysis (HD) patients with critical limb ischemia (CLI) has been clinically debatable. Here we compared clinical outcomes after bypass surgery (BSX) and after endovascular therapy (EVT) using propensity score matching.

Methods: A retrospective multicenter database of 246 (68 BSX and 178 EVT) consecutive HD patients with CLI (79% with tissue loss) who underwent infrainguinal revascularization from 2007 to 2009 was used to compare clinical outcomes, including overall survival (OS), major amputation (MA), major adverse limb event (MALE: repeat EVT, surgical reconstruction, or MA), and MALE-free survival after BSX vs. EVT using propensity score matching.

Results: The median (interquartile range) follow-up duration after revascularization was 21 (8 – 33) months. The analysis of the 63 propensity score-matched pairs revealed no significant difference in OS (53% vs. 52%, *P*=0.96), MA (25% vs. 14%, *P*=0.71), MALE (42% vs. 58%, *P*=0.63), and MALE-free survival (33% vs. 11%, *P*=0.37) at 3 year after BSX vs. EVT using propensity score matching.

Conclusions: In HD patients with CLI who underwent infrainguinal revascularization, OS, MA, MALE, and MALE-free survival rates were not significantly different after EVT vs. BSX. The less invasive EVT should be considered as the first-choice therapeutic strategy for HD patients with CLI.

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

Copyright©2017 Japan Atherosclerosis Society
This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

Introduction

The number of patients on hemodialysis (HD) therapy with end-stage renal disease has been increasing worldwide1). Patients on HD generally have multiple systemic comorbidities, and their arteries are affected by severe calcification leading to lower extremity peripheral artery disease (LE-PAD)2,3). Because the incidence of critical limb ischemia (CLI) is 16% at 5 years from HD initiation4), it is important to choose the optimal treatment strategy for HD patients with CLI.

Either revascularization [bypass surgery (BSX) or endovascular therapy (EVT)] is recommended as the optimal treatment for patients with CLI5). A recent systematic review of patients with CLI regarding the
vascular surgeons, and radiologists, judged whether EVT or BSX was indicated for each patient based on each clinical setting. All baseline characteristics were entered during first admission, and the registry was periodically updated with patient follow-up data generally obtained at 1, 3, and 6 months, and thereafter, at every 3 months. If a patient did not return to the hospital, the patient’s general condition and limb status were followed-up via a phone interview. Assessment procedures were performed in accordance with the principles of the Declaration of Helsinki and were approved by the ethics committee in Kansai Rosai Hospital (approval number: 150404).

**BSX Procedure**

BSX was performed under general anesthesia using standard techniques with an autogenous vein graft. The vein was harvested, flushed with heparinized saline solution, and reversed. Prosthetic vascular grafts were used in cases lacking appropriate usable autogenous vein grafts. Post procedural medications were selected according to the local angioplasty that was initially performed. A nitinol stent was provisionally implanted if the post balloon result was suboptimal. For infrapopliteal lesions, only balloon angioplasty was performed. Dual antiplatelet therapy (aspirin at 100 mg/day and clopidogrel at 75 mg/day, ticlopidine at 200 mg/day, or cilostazol at 200 mg/day) was generally initiated at least 1 week prior to effectiveness of BSX vs. EVT demonstrated that there was no statistically significant difference in the long-term clinical outcomes. However, a recent prospective observational study (CRITISCH registry), in which in-hospital outcomes after revascularization were analyzed, revealed that patients with CLI who received BSX were at a higher risk of in-hospital death and repeat intervention than those who received EVT. Patients with CLI and HD were notably associated with a higher incidence of death or limb loss after revascularization than those with CLI alone. Treatment for HD patients with CLI is the most challenging, and the optimal revascularization strategy for them is still debatable. The current study aimed to investigate clinical outcomes by comparing HD patients with CLI who underwent BSX vs. EVT using propensity score matching.

**Methods**

**Participants**

This study used a retrospective registry, involving eight institutions in Japan, to identify all consecutive HD patients with CLI due to infrainguinal arterial lesions who first underwent BSX or EVT from January 2007 to December 2009. In this study, one limb was included per enrolled patient. In patients with bilateral CLI, the first treated limbs were registered. A group of vascular specialists, including cardiologists,
including surgical or endovascular revascularization, was conducted in the cases with recurrent rest pain or ischemic wounds.

Non-ambulatory status was regarded as requiring a wheelchair or being bedridden. Diabetes mellitus was based on the World Health Organization criteria or on the need for treatment with insulin and/or oral hypoglycemic agents. Coronary artery disease (CAD) was defined as stable angina with documented coronary arterial lesions, a history of percutaneous coronary intervention or coronary artery bypass graft surgery, or a previous myocardial infarction. Chronic heart failure (CHF) was defined as a past history of admission for treating heart failure or a left ventricular ejection fraction of ≤50%. The ejection fraction was evaluated by transthoracic echocardiography. Cerebrovascular disease was defined as the presence of symptoms or a past history of infarction. CLI severity was determined according to the Rutherford classification. Isolated tibial disease was defined as a lesion located only in below-the-knee arteries. Lesion severity was classified according to the TASC II guideline after evaluation by aortography or computed tomog-

EVT and continued lifelong. Medical treatment was left to the physician’s discretion.

Outcome Measures and Variables
The outcome measures of this study were overall survival (OS), major amputation (MA), major adverse limb event (MALE: repeat EVT, surgical reconstruction, or major amputation), and MALE-free survival after revascularization.

Definitions
CLI was defined in accordance with the TransAtlantic Inter-Society Consensus (TASC) guideline as tissue loss or rest pain due to chronic ischemia associated with ankle pressure of <70 mmHg or toe pressure of <50 mmHg. When these measurements could not be obtained, skin perfusion pressure (SPP) was measured at the dorsum and plantar side of the foot for evaluating ischemia. An ischemic limb was indicated by an SPP of <40 mmHg. These non-invasive blood flow measurements were essentially conducted on non-dialysis day. MA was regarded as an amputation above the ankle. Repeat intervention, including surgical or endovascular revascularization, was conducted in the cases with recurrent rest pain or ischemic wounds.

Non-ambulatory status was regarded as requiring a wheelchair or being bedridden. Diabetes mellitus was based on the World Health Organization criteria or on the need for treatment with insulin and/or oral hypoglycemic agents. Coronary artery disease (CAD) was defined as stable angina with documented coronary arterial lesions, a history of percutaneous coronary intervention or coronary artery bypass graft surgery, or a previous myocardial infarction. Chronic heart failure (CHF) was defined as a past history of admission for treating heart failure or a left ventricular ejection fraction of ≤50%. The ejection fraction was evaluated by transthoracic echocardiography. Cerebrovascular disease was defined as the presence of symptoms or a past history of infarction. CLI severity was determined according to the Rutherford classification. Isolated tibial disease was defined as a lesion located only in below-the-knee arteries. Lesion severity was classified according to the TASC II guideline after evaluation by aortography or computed tomog-
4IJSBLJFUBM

Matching and the paired t test or the Wilcoxon signed-rank test after propensity score matching. Categorical variables were compared using the chi-square test before propensity score matching and the McNemar and Wilcoxon signed-rank tests after propensity score matching. The outcome measures in the matched population were assessed using the Kaplan–Meier method, and curves were compared using the stratified log-rank test. A P value of \( <0.05 \) was considered statistically significant. Propensity score matching was performed using R version 3.1.0 software (R Development Core Team, Vienna), whereas other statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, Ill., USA).

**Results**

The initial revascularization strategy is shown in

| Table 2. Baseline characteristics of the study population before and after propensity score matching |
|---------------------------------------------------------------|
| | EVT \((n=178)\) | BSX \((n=68)\) | P \(\) | EVT \((n=63)\) | BSX \((n=63)\) | P \(\) |
|---------------------------------------------------------------|
| Patients status |
| Age | 69 ± 10 | 70 ± 9 | 0.348 | 69 ± 10 | 69 ± 9 | 0.844 |
| Male | 70% (124) | 71% (48) | 0.887 | 76% (48) | 70% (44) | 0.503 |
| Body mass index | 21 ± 3 | 21 ± 3 | 0.349 | 21 ± 3 | 20 ± 4 | 0.858 |
| Non-ambulatory status | 45% (111) | 37% (25) | 0.103 | 46% (29) | 40% (25) | 0.571 |
| Hypertension | 83% (148) | 79% (54) | 0.467 | 81% (51) | 79% (50) | 1.000 |
| Dyslipidemia | 28% (49) | 25% (17) | 0.689 | 24% (15) | 25% (16) | 1.000 |
| Diabetes mellitus | 67% (120) | 74% (50) | 0.353 | 70% (44) | 71% (45) | 1.000 |
| Current smoking | 31% (65) | 16% (11) | 0.019 | 21% (13) | 17% (11) | 0.815 |
| Coronary artery disease | 59% (176) | 60% (41) | 0.852 | 60% (38) | 60% (38) | 1.000 |
| Chronic heart failure | 28% (69) | 24% (16) | 0.524 | 33% (21) | 25% (16) | 0.499 |
| Ejection fraction | 59 ± 14 | 60 ± 13 | 0.461 | 59 ± 14 | 60 ± 13 | 0.537 |
| Cerebrovascular disease | 22% (53) | 34% (23) | 0.180 | 32% (20) | 32% (20) | 1.000 |
| Hemoglobin (g/dL) | 10.6 ± 1.7 | 10.5 ± 1.7 | 0.625 | 10.3 ± 1.5 | 10.6 ± 1.7 | 0.413 |
| Albumin (g/dL) | 3.3 ± 0.5 | 3.4 ± 0.5 | 0.790 | 3.4 ± 0.5 | 3.4 ± 0.5 | 0.826 |
| CRP (mg/dL) | 0.7 (0.2-2.6) | 1.1 (0.4-3.4) | 0.730 | 1.0 (0.3-3.6) | 1.0 (0.4-3.0) | 0.459 |
| Limb status |
| Rutherford category | | | | | | |
| IV | 26% (46) | 9% (6) | 0.011 | 10% (6) | 10% (6) | 0.782 |
| V | 63% (113) | 75% (51) | 0.103 | 79% (50) | 75% (47) | 0.571 |
| VI | 11% (19) | 16% (11) | 0.467 | 11% (7) | 16% (10) | 1.000 |
| Lesion status |
| Isolated tibial disease | 37% (66) | 41% (28) | 0.554 | 48% (30) | 44% (28) | 0.850 |
| TASC II classification |
| Femoropopliteal lesions | | | | | | |
| A/B/C/D | 24/28/37/23 | 5/15/8/12 | 0.680 | 4/10/10/9 | 5/12/7/11 | 0.841 |
| Infrapopliteal lesions | | | | | | |
| A/B/C/D | 1/7/9/121 | 0/1/2/50 | 0.571 | 0/2/2/47 | 0/1/2/48 | 0.883 |

**Statistical Analysis**

Data are expressed as mean and standard deviation (SD), median (25th—75th, quartiles) for continuous variables, or percentage for dichotomous variables, unless otherwise mentioned. The propensity score was developed using a logistic regression model in which the following variables were entered: sex, age, ambulatory status, body mass index, hypertension, diabetes mellitus, dyslipidemia, current smoking, CAD, CHF, ejection fraction, cerebrovascular disease, hemoglobin, albumin, C-reactive protein, Rutherford category, TASC classification, and isolated tibial disease. Using Austin’s recommendation \(^{11} \), we matched the logit of the propensity score within the caliper of 0.2 SD of the value. Continuous variables were examined using the unpaired t test before propensity score matching and the paired t test or the Wilcoxon signed-rank test after propensity score matching. Categorical variables were compared using the chi-square test before propensity score matching and the McNemar and Wilcoxon signed-rank tests after propensity score matching. The outcome measures in the matched population were assessed using the Kaplan–Meier method, and curves were compared using the stratified log-rank test. A P value of \( <0.05 \) was considered statistically significant. Propensity score matching was performed using R version 3.1.0 software (R Development Core Team, Vienna), whereas other statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, Ill., USA).
After propensity score matching, there was no significant difference in the baseline characteristics (Table 2). In the matched population, the median follow-up period was 21 (8–33) months.

At 3 years after revascularization, the OS rates, as revealed by Kaplan–Meier analysis, were 53% ± 7% in the BSX group and 52% ± 9% in the EVT group (Fig. 2. P = 0.715). The freedom from MA rates at 3 years was 75% ± 7% in the BSX group and 86% ± 5% in the EVT group (Fig. 3. P = 0.564). The freedom from MALE at 3 years was 58% ± 7% in the BSX group and 42% ± 11% in the EVT group (Fig. 4. P = 0.577). The MALE-free survival at 3 years was 33% ± 6% in the BSX group and 11% ± 9% in the EVT group (Fig. 5. P = 0.405). Death within 30 days was observed in four patients (6%) in the BSX group and two patients (3%) in the EVT group (P = 0.687).

The causes of death within 30 days after BSX were infection (n = 2), stroke (n = 1), and bowel ischemia (n = 1), whereas those death within 30 days after EVT was cardiac death (n = 1) and gastrointestinal bleeding.

**Table 1.** Surgical bypass and EVT were performed in 68 (28%) and 178 (72%) patients, respectively. Among those undergoing EVT, stents were implanted in 64% of the limbs (72/112) with femoropopliteal lesions. BSX with an autogenous vein graft was conducted in 88% of the limbs (60/68). Patients with a history of current smoking and with ischemic tissue loss were more frequently observed in the BSX group than in the EVT group (all P < 0.05).

Information on HD duration (the time from dialysis initiation to vascular intervention) was available in 44% (109/246) of the study patients. The median duration of HD was 5 (2–10) months.

The distribution of the propensity score in the study population is shown in **Fig. 1.** The propensity score matching extracted a total of 63 pairs. Technical failure after BSX, defined as the demand of revision surgery within 1 week, was 6% (4/68). Technical failure after EVT, defined as unsuccessful recanalization or over 75% residual stenosis of target lesion, was 2% (4/178). In the propensity analysis, three cases with technical failure after BSX and two cases with technical failure after EVT were included. After propensity score matching, there was no significant difference in the baseline characteristics (Table 2). In the matched population, the median follow-up period was 21 (8–33) months.

At 3 years after revascularization, the OS rates, as revealed by Kaplan–Meier analysis, were 53% ± 7% in the BSX group and 52% ± 9% in the EVT group (Fig. 2. P = 0.715). The freedom from MA rates at 3 years was 75% ± 7% in the BSX group and 86% ± 5% in the EVT group (Fig. 3. P = 0.564). The freedom from MALE at 3 years was 58% ± 7% in the BSX group and 42% ± 11% in the EVT group (Fig. 4. P = 0.577). The MALE-free survival at 3 years was 33% ± 6% in the BSX group and 11% ± 9% in the EVT group (Fig. 5. P = 0.405). Death within 30 days was observed in four patients (6%) in the BSX group and two patients (3%) in the EVT group (P = 0.687).

The causes of death within 30 days after BSX were infection (n = 2), stroke (n = 1), and bowel ischemia (n = 1), whereas those death within 30 days after EVT was cardiac death (n = 1) and gastrointestinal bleeding.
However, their study has several limitations: 1) patients with BSX had higher risk characteristics (high prevalence of smoking, coronary artery disease, and diabetes mellitus) than patients with EVT, and 2) lesion morphology and severity were not recorded. Clinical outcomes for HD patients with CLI after surgical and endovascular revascularization have been reported. In these patients, the mortality rates after BSX were 28% at 1 year and 59% at 3 years, whereas those after EVT were 24% at 1 year and 47% at 3 years. These previous results were similar to those of the current study.

We previously reported the comparison of clinical outcomes after BSX vs. EVT for Japanese patients with CLI. From this registry, amputation-free survival was similar for BSX and EVT as the first revascularization in real-world practice. However, the frequency of repeat revascularization was significantly higher in the EVT group than in the BSX group. Although BSX was generally expected to be a more permanent treatment, the incidence of clinically driven revascularization was not significantly different after BSX.
Conclusion

The current study using propensity score matching suggested that clinical outcomes after EVT and BSX were not significantly different in HD patients with CLI. The less invasive EVT should be considered as the first-line therapeutic strategy for HD patients with CLI.

COI

There is no financial arrangement or other relationship that could be construed as a conflict of interest.

Abbreviations

ABI: ankle–brachial index
BSX: bypass surgery
CI: confidence interval
CLI: critical limb ischemia
EVT: endovascular therapy
Fig. 5. MALE (major amputation, repeat endovascular, or surgical reconstruction)-free survival for the propensity-matched pairs

| Months | 0 | 12 | 24 | 36 | 48 |
|--------|---|----|----|----|----|
| BSX No. at risk | 63 | 32 | 20 | 12 | 3 |
| Rate±SE (%) | 100±0 | 49±6 | 37±6 | 33±6 | 17±8 |
| EVT No. at risk | 63 | 25 | 14 | 2 | - |
| Rate±SE (%) | 100±0 | 44±6 | 30±6 | 11±9 | - |

HD: hemodialysis
HR: hazard ratio
MA: major amputation
MALE: major adverse limb event
PAD: peripheral artery disease
POD: perioperative death
SPP: skin perfusion pressure
TASC: TransAtlantic Inter-Society Consensus

References
1) Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002; 13: S37-S40
2) Rooke TW, Hirsch AT, Mira T, Sidawy AN, Beckman JA, Findeiss LK, Golzarian J, Gornik HL, Halperin J, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE. 2011 ACCF/AHA focused update of the guideline for management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association task force on practice guide-
lines. J Vasc Surg. 2011; 54: 32-58
3) Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Cucul-ton B, Hamm LL, McCullough PA, Kasiske BL, Kell-epouris E, Klag MJ, Parfrey P, Pfeffer M, Raji L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003; 108: 2154-2169
4) Koch M, Trapp R, Kula W, Grabensee B. Critical limb ischemia as a main cause of death in patients with end-stage renal disease: a single-centre study. Nephrol Dial Transplant. 2004; 19: 2547-2552
5) Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007; 43: S1-67
6) Jones WS, Dolor RJ, Hasselblad V, Vemulapalli S, Subhe-erval S, Schmit K, Heidenfelder B, Patel MR. Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: systematic review of revascularization in critical limb ischemia. Am Heart J. 2014; 167: 489-
7) Bisdas T, Borowski M, Torsello G. Current practice of first-line treatment strategies in patients with critical limb ischemia. J Vasc Surg. 2015; 62: 965-973
8) Iida O, Nakamura M, Yamauchi Y, Fukunaga M, Yokoi YM, Yokoi H, Soga Y, Zen K, Suematsu N, Inoue N, Suzuki K, Hirano K, Shintani Y, Miyashita Y, Urasawa K, Kitano I, Tsuchiya T, Kawamoto K, Yamaoka T, Uesugi M, Shinke T, Oba Y, Ohura N, Uematsu M, Takahara M, Hamasaki T, Nanto S. 3-year outcomes of the OLIVE registry, a prospective multicenter study of patients with critical limb ischemia. J Am Coll Cardiol Intv. 2015; 8: 1493-1502
9) Yamada T, Ohta T, Ishibashi H, Sugimoto I, Iwata H, Takahashi M, Kawanishi J. Clinical reliability and utility of skin perfusion pressure measurement in ischemic limbs—comparison with other noninvasive diagnostic methods. J Vasc Surg. 2008; 47: 318-323
10) Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997; 26: 517-538
11) Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011; 10: 150-161
12) Jaar BG, Astor BC, Berns JS, Powe NR. Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. Kidney Int. 2004; 65: 613-620
13) Yamamoto S, Hosaka A, Okamoto H, Shigematsu K, Miyata T, Watanabe T. Efficacy of revascularization for critical limb ischemia in patients with end-stage real disease. Eur J Endovasc Surg. 2014; 48: 316-324
14) Kodama A, Sugimoto M, Kuma S, Okazaki J, Mii S, Komori K. Clinical outcomes after infrainguinal bypass grafting for critical limb ischemia in patients with dialysis-dependent end-stage renal failure. Eur J Vasc Endovasc Surg. 2014; 48: 685-702
15) Albers M, Romiti M, Bragança Pereira CA, Fonseca RL, da Silva Júnior M. A meta-analysis of infrainguinal arterial reconstruction in patients with end-stage renal disease. Eur J Vasc Endovasc Surg. 2001; 22: 294-300
16) Suematsu N, Iida O, Takahara M, Yamauchi Y, Soga Y, Nakano M, Hirano K, Kawasaki D, Yamaoka T, Suzuki K, Shintani Y, Miyashita Y, Tazaki J, Meno H, Inou T. Prognostic factors in hemodialysis patients undergoing endovascular treatment for critical limb ischemia due to isolated below-the-knee disease. J Atheroscler Thromb. 2015; 22: 404-414
17) Soga Y, Mii S, Aihara H, Okazaki J, Kuma S, Yamaoka T, Kamoi D, Shintani Y, Ishikawa T. Comparison of clinical outcome after bypass surgery vs. endovascular therapy for infrainguinal artery disease in patients with critical limb ischemia. Circ J. 2013; 77: 2102-2109