Midterm Results of a Japanese Prospective Multicenter Registry of Heparin-Bonded Expanded Polytetrafluoroethylene Grafts for Above-the-Knee Femoropopliteal Bypass

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Background: This study prospectively analyzed the midterm results of above-the-knee femoropopliteal bypass (AKb) using bioactive heparin-bonded expanded polytetrafluoroethylene (HB-ePTFE) graft in patients with femoropopliteal occlusive disease.

Methods and Results: This prospective, multicenter, non-randomized study reviewed limbs undergoing AKb with HB-ePTFE graft for femoropopliteal lesion in 20 Japanese institutions between July 2014 and October 2017. Primary efficacy endpoints were primary, primary assisted, and secondary graft patency. Safety endpoints included any major adverse limb event and perioperative mortality. During the study period, 120 limbs of 113 patients (mean age, 72.7 years) underwent AKb with HB-ePTFE grafts. A total of 45 patients (37.5%) had critical limb ischemia and 17 (15.0%) were on hemodialysis (HD). Median duration of follow-up was 16 months (range, 1–36 months). Estimated 1- and 2-year primary, primary assisted, and secondary graft patency rates were 89.4% and 82.7%, 89.4% and 87.2%, and 94.7% and 92.5%, respectively. On univariate analysis of 2-year primary graft patency, having 3 run-off vessels, cuffed distal anastomoses, no coronary artery disease, and no chronic kidney disease requiring HD were significantly associated with favorable patency.

Conclusions: AKb using HB-ePTFE grafts achieved favorable 2-year graft patency. AKb using HB-ePTFE grafts may therefore be an acceptable, highly effective treatment option for femoropopliteal artery lesions.

Key Words: Above-the-knee femoropopliteal bypass; Heparin-bonded expanded polytetrafluoroethylene graft; Japanese registry
In Japanese retrospective single-center studies, the 5-year patency rate of femoropopliteal bypass using prosthetic grafts is 74% or 82%/6,16 which is better than in previous reports.7,8 These Japanese reports, however, relied on clinical investigation only, and objective investigation was lacking. Recently, there has been an increased interest in the use of heparin-coated prosthetic grafts as an option for femoropopliteal bypass surgery;9,16 given that the patency rates are similar to those of autogenous saphenous vein grafts (78–84%/2 years).12,14–19 A bioactive heparin-bonded expanded polytetrafluoroethylene (HB-ePTFE) graft has been shown to offer better long-term patency than the standard polytetrafluoroethylene (PTFE) graft.12,20 and it is now almost the first choice prosthetic graft for femoropopliteal bypass. There are few prospective multicenter registry studies, however, on above-the-knee femoropopliteal bypass (AKb) using HB-ePTFE grafts (Table 1).11–16

In Japan, an HB-ePTFE graft (Gore Propaten; W. L. Gore & Associates, Flagstaff, AZ, USA) was approved for use in 2014. In this study, we examined the midterm results of AKb with HB-ePTFE grafts in patients with femoropopliteal lesion in a prospective multicenter registry involving 20 Japanese vascular centers.

Methods

Study Design and Patients
This observational, prospective, multicenter registry study involved 120 limbs of 113 consecutive patients undergoing AKb using HB-ePTFE graft for femoropopliteal lesions at 20 Japanese institutions between July 2014 and October 2017. The registry was approved by the local ethics committee of each institution; all patients provided informed consent for the review of their personal data and inclusion in this study. Data were collected in a multicenter registry with a dedicated database. Data collection was prospective until October 2017.

Inclusion and Exclusion Criteria
Clinical inclusion criteria for the AKb registry with HB-ePTFE graft were as follows: Rutherford category 2–6,21 target limb ankle-brachial index (ABI) <0.9, and possibility to register cases of a history of EVT for the ipsilateral femoropopliteal lesion. Major exclusion criteria were as follows: expected survival <2 years (i.e., advanced cancer, severe aortic valve stenosis, and congestive heart failure), coagulopathy or contraindication to anticoagulants and antiplatelet drugs, history of deep vein thrombosis of the ipsilateral limb, and history of heparin-induced thrombocytopenia (type II).

Treatment
All surgery was performed by a board-certified vascular surgeon or a vascular resident under the guidance of a board-certified vascular surgeon. The decision to perform EVT or bypass surgery was at the discretion of each surgeon. Usage of vein or prosthetic grafts, the choice of the prosthetic graft size, and use of intraoperative angiography was also dependent on each surgeon’s decision. The surgical bypass procedure was performed according to each institution’s standard of care. In some cases, the graft was anastomosed to the above-knee segment of the femoropopliteal artery with a protruding area created around the anastomotic toe (cuffed anastomosis).9 No vein patches or vein cuffs were used at the anastomosis in this study. The choice of suture, heparin and protamine regimens, and topical hemostatic agents was not protocol-specified and was left to the individual surgeon’s standard of care. Postoperative antiplatelet or anticoagulant therapy also depended on individual surgeon judgment.

Endpoints
The primary efficacy endpoints were primary, primary assisted, and secondary graft patency. The early (intraoperative and <30-days) results were assessed, including all-cause mortality; major adverse cardiovascular events; and major adverse limb events, including major amputation (above-ankle amputation of the index limb), major graft reintervention with placement of a new graft or an interposition graft, open or percutaneous graft thrombectomy, pharmacologic thrombolysis, or graft infection.22

Follow-up Schedule and Definitions
Assessment was performed at baseline, and at 1, 3, 6, and 12 months after surgery, and at least every 6 months thereafter. Adverse events and wound complications were assessed at

| Table 1. Studies on AKb Using Bioactive HB-ePTFE Grafts |
| Authors | Year | Study type | No. limbs | Diabetes (%) | HD (%) | Prior treatment (%) | Rutherford classification |
|---------|------|------------|-----------|--------------|--------|---------------------|-------------------------|
|         |      |            |           |              |        | 2,3 (%)             | 4–6 (%)                 |
|         |      |            |           |              |        | 1 year (%)          | 2 years (%)             | 3 years (%) | 4 years (%) | 5 years (%) |
| Piffaretti et al13 | 2018 | Retrospective, multicenter | 364 | 39 | 2 | 16.7 | 55 | 45 | 82 | 77.5 | 74 | 71 | 64 |
| Samson et al12 | 2016 | Retrospective, single-center | 85 | NSR | NSR | NSR | NSR | NSR | 91.8 | 85.2 | 85.2 | 85.2 | 85.2 |
| Pulii et al11 | 2010 | Retrospective, multicenter | 101 | NSR | NSR | NSR | 0 | 100 | 80 | 72 | 72 | NA | NA |
| Daenens et al14 | 2009 | Retrospective, single-center | 86 | NSR | NSR | NSR | NSR | NSR | 92 | 83 | NA | NA | NA |
| Hugl et al15 | 2009 | Prospective, multicenter | 87 | NSR | NSR | NSR | NSR | NSR | 82.7 | NA | NA | NA | NA |
| Bosiers et al16 | 2006 | Prospective, multicenter | 55 | NSR | NSR | NSR | 69 | 31 | 84 | NA | NA | NA | NA |

AKb, above-the-knee femoropopliteal bypass; HB-ePTFE, heparin-bonded expanded polytetrafluoroethylene; HD, hemodialysis; NA, not available; NSR, not specifically reported; PP, primary patency.
Statistical Analysis

All data were analyzed according to the intention-to-treat principle. For the baseline variables, summary statistics are presented as n (%) for categorical data and as mean±SD for continuous variables. Primary endpoint analysis was performed using a Cox proportional hazards model with prognostic factors as covariates. Kaplan-Meier curves were generated to display event distributions over time. All P-values were two-sided. P<0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Clinical and Lesion Characteristics

The demographic data and baseline characteristics are listed in Table 2. The age of the 113 patients who underwent AKb using HB-ePTFE grafts ranged from 44 to 89 years (mean, 72.7±8.1 years), with 34.5% of the patients being female. There were 45 limbs (37.5%) with critical limb ischemia (CLI) of Rutherford classification 4, 5, or 6. Mean ABI was 0.45±0.27. The most common comorbidities were hypertension (76.1%), diabetes mellitus (54.0%), hyperlipidemia (47.8%), and smoking history (76.1% overall; 25.7% current smoker). There were 17 patients (15.0%) on hemodialysis (HD). Mean length of the SFA lesion was 26.2±5.7 cm (median, 26.0 cm). At preoperative imaging, according to the Trans-Atlantic Inter-Society Consensus (TASC) II classification,7 16.7% of SFA lesions were classified as type C and 78.3% as type D; and 29.2% of limbs had 3 patent tibial vessels, and 34.2% had 2 patent tibial vessels with direct inflow to the foot as distal run-off.

In 31 limbs (25.8%), AKb using HB-ePTFE grafts was performed after failure of a previous ipsilateral revascularization by EVT. Medical treatment at discharge consisted of single antiplatelet therapy in 57 patients (50.4%), double antiplatelet therapy in 51 (45.1%), and oral anticoagulants in 22 (19.5%).

Data given as n (%) or mean±SD. Additional procedures included endovascular therapy for iliac artery or tibial artery, femoral crossover bypass, or endarterectomy of ipsilateral common femoral artery.
Surgery
Surgery details are listed in Table 3. Prosthetic graft diameters were 6mm (60.0%), 7mm (23.3%), and 8mm (16.7%). There were 93 limbs (77.5%) with cuffed distal anastomoses. Intraoperative completion angiography was performed in 79 patients (65.8%). Concomitant EVT of the iliac artery, femoral cross-over bypass, or endarterectomy of the ipsilateral common femoral artery was performed in 30.8% of patients to achieve adequate inflow, and concomitant EVT of the tibial artery was performed in 7.5% of patients to achieve adequate run-off. There were no concomitant ilio-femoral or tibial bypasses performed in this series. The mean operative time was 201±86 min, and the mean intraoperative bleeding volume was 279.8±290.2mL.

Efficacy Endpoints
Median duration of follow-up was 16 months (range, 1–36 months). Estimated 1- and 2-year primary, primary assisted,
and secondary graft patency rates were 89.4% (95% CI: 81.2–94.2%) and 82.7% (95% CI: 71.9–89.6%), 89.4% (95% CI: 81.2–94.2%) and 87.2% (95% CI: 77.5–92.9%), and 94.7% (95% CI: 87.6–97.8%) and 92.5% (95% CI: 83.2–96.7%), respectively (Figures 1–3). On univariate analysis, number of run-off vessels, cuffed distal anastomoses, coronary artery disease (CAD), and chronic kidney disease (CKD) on HD were significantly associated with 2-year primary patency (Table 4). Mean postoperative ABI across the entire cohort was 0.96±0.15.

**Safety Endpoints**

One patient (0.9%) died perioperatively in the hospital due to takotsubo cardiomyopathy. There were no early thromboses of the treated vessels and none of the patients required a major amputation perioperatively. Reinterven-

| Variable | HR | 95% CI | P-value |
|----------|----|--------|---------|
| Gender (male vs. female) | 0.460 | 0.501–4.258 | 0.488 |
| Age (≥75 vs. <75 years) | 0.805 | 0.281–2.301 | 0.685 |
| BMI (≥25 vs. <25 kg/m²) | 1.477 | 0.427–5.109 | 0.537 |
| Clinical status (intermittent claudication vs. CLI) | 2.338 | 0.838–6.524 | 0.1047 |
| No. run-off vessels (3 vs. ≤2) | 6.209 | 1.086–35.51 | 0.040 |
| Arterial hypertension (yes vs. no) | 0.613 | 0.151–2.479 | 0.492 |
| Diabetes mellitus (yes vs. no) | 1.096 | 0.350–3.036 | 0.860 |
| Dyslipidemia (yes vs. no) | 0.661 | 0.236–1.855 | 0.432 |
| Hemodialysis (yes vs. no) | 0.199 | 0.067–0.592 | 0.004 |
| Prior coronary disease (yes vs. no) | 0.225 | 0.076–0.672 | 0.008 |
| Prior cerebrovascular disease (yes vs. no) | 0.448 | 0.153–1.309 | 0.142 |
| Prior PAD treatment (yes vs. no) | 0.620 | 0.187–2.055 | 0.434 |
| Smoking history (never vs. former) | 2.023 | 0.327–12.51 | 0.448 |
| Smoking history (never vs. current) | 0.855 | 0.100–7.331 | 0.886 |
| Smoking history (former vs. current) | 0.423 | 0.098–1.823 | 0.248 |
| Operator (senior vs. resident) | 2.448 | 0.719–8.338 | 0.152 |
| Cuffed anastomosis (yes vs. no) | 3.759 | 1.300–10.870 | 0.014 |
| Postoperative medical treatment (single antiplatelet vs. double or more antiplatelet) | 2.040 | 0.668–6.227 | 0.210 |
| Oral anticoagulants (yes vs. no) | 0.498 | 0.158–1.577 | 0.236 |

BMI, body mass index; intermittent claudication, Rutherford class 2 or 3; CLI, critical limb ischemia (Rutherford class 4, 5 or 6); PAD, peripheral artery disease.
tion was performed in 11 (9%) of the 120 limbs during the follow-up period. Three limbs required secondary EVT for stenosis of the proximal anastomosis. In 2 of these 3 limbs, only balloon angioplasty was performed, and a covered stent with a heparin bioactive surface (GORE Viabahn Endoprosthesis; W. L. Gore & Associates) was placed in the remaining case. However, no significant restenosis of the distal anastomosis was found in the patent bypass grafts during the follow-up period. In 8 of the 11 limbs, a secondary intervention to treat graft thrombosis was required through open thrombectomy (n=5), open thrombectomy with patch or angioplasty of the proximal anastomosis (n=2), or redo bypass surgery using HB-ePTFE graft (n=1). A total of 12 graft occlusions were observed during the follow-up period. At the onset of graft occlusion, 3 patients had mild-to-moderate intermittent claudication, which was treated using anti-thrombotic medication only. One patient with graft occlusion and deterioration of general condition due to heart failure died after major amputation without any vascular reconstruction.

Major amputation was performed in 2 patients (1.8%) in the follow-up period, and 8 patients (7.0%) died. Cause of death was cardiac event in 4 patients, fatal sepsis in 3, and cancer in 1. There were 2 patients (1.8%) with wound infection and 2 (1.8%) with sepsis. Prosthetic graft infection occurred in 1 patient (0.9%). In that patient, fluid collection was detected around the implanted graft and the anastomotic site, and methicillin-resistant Staphylococcus aureus was detected in both the proximal and peripheral areas of the wound 2 weeks after bypass surgery. The infection was controlled by tube drainage, daily irrigation, and antibiotic treatment without graft excision.

**Discussion**

This is a Japanese multicenter prospective study involving 120 limbs of AKb patients using HB-ePTFE grafts. In this study, using HB-ePTFE grafts for AKb yielded acceptable midterm results when compared with previous reports (Table 1). This is despite the present cohort having relatively severe comorbidities, including failure of a previous ipsilateral revascularization in 25.8% of patients and CKD on HD in 15.0%. The 2-year primary patency rate of 82.7% seems to be better than that of most reports of prosthetic AKb using Dacron or ePTFE, which reported outcomes ranging from 57% to 73% and is similar to the 78–84% rate reported for saphenous vein grafting. Patients with 3 run-off vessels, cuffed distal anastomoses, without CAD, or without CKD on HD had significantly more favorable primary patency outcomes on univariate analysis. Multivariate analysis was not performed, however, because of the insufficient number of events in the present cohort.

Recently, excellent results have been reported for intraluminal bypass using HB-ePTFE stent grafts for long SFA lesions. In a multicenter, randomized, controlled trial analyzing AKb with HB-ePTFE endografts, Reijnen et al found that there were no significant differences in primary (endoluminal, 64.8%; surgical, 63.6%), primary assisted (endoluminal, 78.1%; surgical, 79.8%), or secondary patency (endoluminal, 85.9%; surgical, 83.3%) rates at 1 year between endoluminal and surgical bypasses. In the present study, however, the patency rate was better than in that study (1-year primary patency rate, 89.4% vs. 63.6%).

We have previously reported the safety, low invasiveness, excellent 1-year primary graft patency rate (92%) and freedom from TLR using HB-ePTFE stent grafts to treat Japanese patients with long SFA lesions. The 1-year patency rate in the previous study and in the current one were equivalent, but the target lesions were much longer (26.2±5.7 cm vs. 21.8±5.8 cm) and more severe lesions were included (TASC II D: 78% vs. 2%) in the current study. Furthermore, patients with more severe comorbidities, such as CLI, HD, or previous failure of ipsilateral revascularization, were included, unlike in the 3 studies.

Although it is difficult to compare the present study directly with previously published reports, the current study suggests that bypass surgery using HB-ePTFE grafts could be an option for patients with long or complex SFA lesions, at least in Japanese patients. Bypass surgery is definitely more invasive than EVT, requiring general anesthesia and long-term hospitalization. Moreover, patients undergoing bypass surgery are at risk of several morbidities, such as wound infection, graft infection, and postoperative bleeding. In the present study, however, these complications were rare. This, together with the high effectiveness of AKb using HB-ePTFE grafts, suggests that the benefits outweigh the risks. Therefore, AKb using HB-ePTFE grafts could be an option for patients with long or complex SFA lesions, those in whom EVT is not indicated, or those with severe conditions.

Occlusion of a bypass graft can happen due to several reasons, including thrombotic occlusion after bypass surgery, obstruction by run-off deficiency due to peripheral arteriosclerosis progression, and anastomotic stenosis due to intimal hyperplasia. In the current study, we observed graft occlusion due to the first 2 reasons, but there was no case of intimal proliferation, such as distal anastomotic stenosis, at the midterm follow-up point. Inoue et al reported that the use of a cuffed anastomosis in AKb with an ePTFE stretch prosthesis appears to increase graft patency rates (2-year primary graft patency rate, 90%). They reported that the anastomotic shape produced by tailoring a stretch ePTFE graft has the advantage of allowing adjustments to the native arterial diameter. Additionally, precluding below-the-knee femoropopliteal grafts has been shown to achieve similar patency rates to vein-cuff interposition at the distal anastomosis. This suggests that peripheral anastomotic forms may play a role in achieving an acceptable patency rate.

Various factors associated with favorable graft patency after AKb have been reported, such as claudication rather than CLI; larger graft diameter; adequate popliteal artery diameter; ideal anastomotic angle; previously failed endovascular procedure in the SFA; pre- and postoperative antiplatelet therapy; statin therapy independent from lipid values after AKb revascularization; and vascular surgeon experience. In the present study, we identified the presence of 3 run-off vessels, cuffed distal anastomosis, absence of CAD, and absence of CKD on HD as additional factors associated with favorable patency. Therefore, in long or complex SFA lesions for which EVT is not appropriate, performing AKb using an HB-ePTFE graft with a cuffed distal anastomosis is also justified, especially in patients with good run-off vessels.

**Study Limitations**
The present study had several limitations. First, this study...
was a non-randomized analysis and had a relatively small sample size. Second, although this cohort included 20 institutions, there is a bias in the number of cases depending on the facility. Third, the surgical bypass procedure was performed according to each institution’s standard approach, with no unified surgical procedure or perioperative management protocol. Fourth, we analyzed only the 2-year follow-up results. A longer follow-up period is necessary to fully assess the efficacy of AKb using HB-ePTFE graft.

Finally, given that all of the patients in this study were Japanese, it is unknown whether the present results can be generalized to patients from other countries.

Conclusions

The HB-ePTFE graft offers satisfactory mid-term patency even in patients with complex anatomy. AKb using HB-ePTFE grafts may be a useful alternative to EVT in patients with long/complicated lesions of the SFA when a ePTFE grafts may be a useful alternative to EVT in patients with complex anatomy. HB using HB-ePTFE grafts offers the advantage of preserving patients’ autologous vein in case it is required for any subsequent peripheral or cardiac revascularizations. These issues should be taken into consideration, particularly when the candidates are young.

Author Contributions

S.S., H. Obara, N.F., T.O. conceived of and designed the study. S.S., H. Obara, T.O. obtained funding. S.S., H. Obara, Y.S., T.O. carried out analysis and interpretation. S.S., H. Obara, K.M., N.T., N.I., H. Ogino, S.W., A.A., T.K., Y.K., N.F., H.H., H.U., Y.S., T.O. carried out data collection. Y.S., S.S., H. Obara carried out statistical analysis. S.S., H. Obara, T.O. wrote the paper. S.S., H. Obara, K.M., N.T., N.I., H. Ogino, S.W., A.A., T.K., Y.K., N.F., H.H., H.U., Y.S., T.O. carried out critical revision of the paper and gave final approval. H. Obara has overall responsibility.

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Conflicts of Interest

T.O. has received a consulting fee from W.L. Gore and Associates and Endovascular Japan, and S.S., H. Obara, T.O. are on the speakers bureau for W. L. Gore. The other authors declare no conflicts of interest.

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