Clinical Investigation

JOURNAL OF ENDOVASCULAR THERAPY
A SAGE Publication
An official publication of the ISEVS

Journal of Endovascular Therapy
1–13

DOI: 10.1177/15266028241231520
www.jevt.org
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Five-Year Outcomes of the SuperB Trial: A Multicenter Randomized Controlled Trial Comparing Heparin-Bonded Endograft to Surgical Femoropopliteal Bypass

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Abstract

Objective: This study aims to compare the 5-year outcomes of endoluminal bypass (EB) using heparin-bonded self-expanding covered stents versus bypass surgery for extensive femoropopliteal disease, including technical and clinical outcomes and health status. **Background:** The surgical femoropopliteal bypass was the gold standard to treat peripheral arterial disease (PAD) for decades; however, endovascular treatment modalities are now recommended for most femoropopliteal lesions. One-year data of a randomized controlled trial comparing EB with surgical bypass (SB) have shown a faster recovery, less morbidity, and comparable patency rates between the two techniques. To date, long-term randomized controlled data regarding both techniques are lacking. **Methods:** Five-year results of a multicenter randomized controlled trial comparing EB with SB in patients with femoropopliteal artery disease were evaluated based on intention-to-treat and per-protocol analyses. **Results:** At 5-year follow-up, primary, primary-assisted, and secondary patency rates were 36.2%, 52.4%, and 68.1% for EB and 49.4%, 72.2%, and 77.8% for SB, respectively (p=0.608). Freedom from target lesion revascularization (fTLR) was 34.1% for EB and 57.6% for SB (p=0.365). In both groups, the ankle-brachial index, Rutherford classification, and walking distance significantly improved compared with baseline without differences between groups at follow-up. Freedom from major amputation rate was 92.6% in the EB group and 96.2% in the SB group (p=0.361). The 36-Item Short-Form Health Survey showed no significant differences between groups. **Conclusion:** Treatment of extensive femoropopliteal disease with self-expanding covered stents provides comparable clinical-related and health-related questionnaire outcomes when compared with SB through 5 years of follow-up. However, the EB is related to a higher number of reinterventions.

Clinical Impact

This present study is the first to report five-year outcomes comparing an endoluminal (EB) using heparin-bonded self-expanding covered stents with surgical bypass (SB) for long and complex femoropopliteal disease. Although the advantages of treatment with EB are mostly seen in the early period after treatment, the outcomes support the use of EB for this indication and seems to be a valid and safe alternative for bypass surgery. Future trials comparing various endovascular strategies may provide further guidance for the development of an evidence-based treatment algorithm.

Keywords

endoluminal bypass, Viabahn endoprosthesis, self-expanding covered stent, surgical bypass, femoropopliteal bypass, peripheral arterial disease, femoropopliteal artery, superficial femoral artery

Introduction

The incidence of peripheral arterial disease (PAD) is increasing globally, driven by an increased prevalence of cardiovascular risk factors and an aging population.[1] In the guidelines of the European Society of Cardiology and European Society for Vascular Surgery on PAD, the autologous venous bypass remains the gold standard for lesions longer than 25 cm, provided the patient is not at high operative risk. Nevertheless, an autologous vein is not always available and, in these patients, either a prosthetic bypass is used, or endovascular therapy may be considered.[2,3] In femoropopliteal lesions

shorter than 25 cm, an endovascular-first strategy is recommended (class I, level C).[3] A recent meta-analysis of randomized trials, including 639 patients, showed that at 2 years of follow-up, there were no significant differences regarding major adverse limb events (MALEs), including amputation between patients treated endovascularly (bare metal, drug eluting, and covered stents) or with a femoropopliteal bypass. The endovascular approach was related with significantly lower rates of early complications and a shorter hospital stay. Primary patency, however, was lower in the endovascular group.[4]

Nowadays, various modes of endovascular treatment are available when treating long and complex lesions in the femoropopliteal artery, including drug-eluting-based technology, atherectomy, and variations in stent design, including balloon-expandable and self-expandable bare metal and covered stents, or endoprosthesis. We previously reported on the 1-year outcome of a randomized trial comparing the use of a heparin-bonded endoprosthesis (Viabahn®, W.L. Gore and associates, Flagstaff, AZ, USA) with femoropopliteal bypass surgery, preferably with a venous conduit. It was shown that the endoluminal strategy was related to comparable patency rates, albeit with a faster recovery in health status, less morbidity, and a shorter hospital stay.[5] Long-term prospective data on this treatment modality is, however, scarce.[6] Retrospective analyses of the endoprosthesis have shown primary patency rates ranging from 38.5% to 47.5% after 5-year follow-up.[7,8] Although these studies provide a long-term overall picture, large randomized trials will still be needed to define which of both treatment modalities is superior to one another.

The aim of this study was to evaluate clinical outcomes and health status after treatment with heparin-bonded endograft compared with surgical bypass (SB) in patients with extensive femoropopliteal artery disease through 5-year follow-up.

Materials and Methods

Design of the Study

Subjects from 6 vascular centers in the Netherlands were recruited and, after signing informed consent, randomized with stratification per site. The design of this study and the 1-year outcomes have been previously published.[9] In summary, this was a multicenter prospective randomized controlled trial comparing the heparin-bonded endograft (Viabahn®, W.L. Gore and associates) with the surgical femoropopliteal bypass, when possible, with a venous conduit, with 2 primary endpoints: the primary patency rate at 1 year and health status at 30 days. Subjects with stenotic or occlusive lesions in the femoropopliteal artery, with a minimum lesion length of 100 mm, and a clinical indication for intervention, were included. The study was approved by the Medical Ethics committee of Nijmegen (CMO-2010-089) and the local institutional review board of each participating center.

All procedures were performed by surgeons who had ample experience in both techniques, to prevent a learning curve bias. Due to the study design, post-procedural assessment was non-blinded. Follow-up was performed at 1, 3, 6, 12, 18, and 24 months and annually thereafter until 5-year follow-up. Follow-up consisted of clinical evaluation, including duplex ultrasound, ankle-brachial index (ABI) assessments, the Short-Form 36 Questionnaire (SF-36), and the Walking Impairment Questionnaire (WIQ).

The hypothesis of the current analysis was that the EB provides comparable clinical outcomes and health status when compared with the SB through 5-year follow-up.

Endpoints and Definitions

Primary outcomes were patency rates and freedom from target lesion revascularization (fTLR) rates, and the health status, assessed by the SF-36, at 5-year follow-up. Secondary outcomes included reintervention free survival, amputation-free survival, and overall patient survival after 5-year follow-up. In addition, ABI, Rutherford classification, and WIQ at 5 years were evaluated.

Data Collection

Data were prospectively collected by case report forms and were entered in a central online database with audit trail (ResearchManager, Deventer, the Netherlands). Data were monitored annually by independent monitors from the Trial Bureau from the sponsor of the trial. Adverse events were adjudicated by a data safety monitoring board and reported to the Central Committee on Research involving Human Subject.

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Statistical Analyses

Categorical variables were expressed as number followed by percentage and differences between groups were tested using chi-square analysis. Distribution of continuous variables was determined based on visual inspection of normality graphs and using Kolmogorov-Smirnov tests. Continuous variables were expressed as mean ± standard deviation or as median with interquartile ranges when skewed distributed. Differences were tested using a Student's *t* test for normal distribution or Mann-Whitney *U* test for skewed distribution. Intention to treat analyses was performed, as well as per-protocol analyses.

Cumulative patency rates (primary, primary-assisted, and secondary), overall patient survival, freedom from amputation, and fTLR were analyzed using Kaplan-Meier analyses and included censoring for patients lost to follow-up. Differences were tested using log-rank test if curves did not cross and Breslow test if curves did cross. The Wilcoxon signed-rank test was used to analyze differences between baseline and 5-year follow-up for Rutherford classification, SF-36, and WIQ. The data were not eligible for repeated measures analysis of variance (ANOVA) and differences between groups for these outcomes were tested using the Mann-Whitney *U* test. Repeated measures ANOVA was used to analyze differences for ABI at baseline and after 5 years. Differences between the 2 groups for ABI at these time points were tested using the independent sample *t* test. Binary logistic regression analyses were performed to identify possible factors that predict failure of the EB and SB. Overall correlations for definite failure, primary patency, primary-assisted patency, secondary patency, and fTLR with baseline variables were tested. Variables with a significance level of ≤0.3 in univariate regression analysis were entered in a multivariate model. Statistical analyses were performed using IBM SPSS Statistics (SPSS version 25.0 for Windows, IBM Corporation, Armonk, NY, USA).

Results

Between November 2010 and June 2015, 129 subjects were randomized: 64 limbs in the EB group and 65 limbs in the SB group. There were 6 technical failures in the EB group, including 4 conversions to surgical treatment. In the SB group, 42 patients (69.2%) were treated with a venous bypass and 20 patients (30.8%) were treated with a prosthetic conduit. Concomitant endarterectomy of the common femoral artery was performed in 37.1% of the patients in the EB group. One patient in the EB group was excluded for the intension-to-treat (ITT) analysis (other treatment) resulting in 63 limbs and 3 patients were excluded in the SB group (other treatment, no treatment, and withdrawn consent) resulting in 62 limbs. In total, 57 patients were included in the EB group and 43 in the SB group for additional per-protocol analysis (Figure 1). Follow-up compliance at 5-year follow-up was 49.2% in the EB group and 58.1% in the SB group.

Baseline Characteristics

When looking at the ITT cohorts, baseline and target lesion characteristics were similar in both groups, except for the popliteal diameter that was larger in the SB group.[5] In the EB group, 38.1% and in the SB group, 32.2% was treated for chronic limb-threatening ischemia (CLTI) (p=0.551). When looking at the PP cohorts, the baseline data were comparable with the ITT cohorts, except for a slight significant difference in the prevalence of pulmonary disease (14.0% in the EB group and 30.2% in the SB group, p=0.049). The distal landing zone in the EB group was in most patients the distal superficial femoral artery (SFA) or P1 segment (n=14; 22.8% and n=33; 54.4%, respectively). In 11 patients (18%), this was at the level of P2 and in 3 patients (4.9%) at P3. In the SB group, the majority of distal anastomosis was at P1 or P2 level (n=42; 67.7% and n=12 19.4%, respectively). In 6 patients (9.7%), this was at the level of P3.

Patency, Reintervention, and Amputation Rates

In the ITT analysis, the primary, primary-assisted, and secondary patency rates at 5-year follow-up were 30.7%, 46.7%, and 68.4% for the EB group and 48.7%, 69.2%, and 77.6% for the SB group, respectively (p=0.608, p=0.372, p=0.973, respectively; Figures 2A, 3A, 4A). There were 16 (26.2%) definitive failures in the EB group and 15 (24.2%) in the SB group. The median time to definitive failure was 20.6 (IQR=10.0–35.5) months in the EB group and 7.3 months (IQR=2.1–14.2) in the SB group (p=0.034). The fTLR was 34.1% for the EB group and 57.6% for the SB group (p=0.365; Figure 5).

Through 5-year follow-up, a total of 59 reinterventions were performed in 32 patients in the EB group and 37 reinterventions in 22 patients in the SB group (p=0.050). In the EB group, 16 subjects underwent 1 reintervention, 6 subjects 2, 9 subjects 3, and 1 subject underwent 4 reinterventions. In the SB group, 11 subjects underwent 1, 8 subjects 2, 2 subjects 3, and 1 subject underwent 4 reinterventions. The most frequently performed interventions in both groups were plain balloon angioplasty with or without additional stent placement or adjunctive drug-coated balloon (DCB) treatment (EB group, n=32; SB group, n=21). Chemical thrombolysis was significantly more often performed in the EB group (11 vs 3 times, p=0.02). There was no difference between groups in the median time to first reintervention 18.1 (IQR=6.6–39.8) months for the EB group and 33.1 (IQR=6.0–60.4) months for the SB group (p=0.312). During follow-up, one major amputation was required in the EB

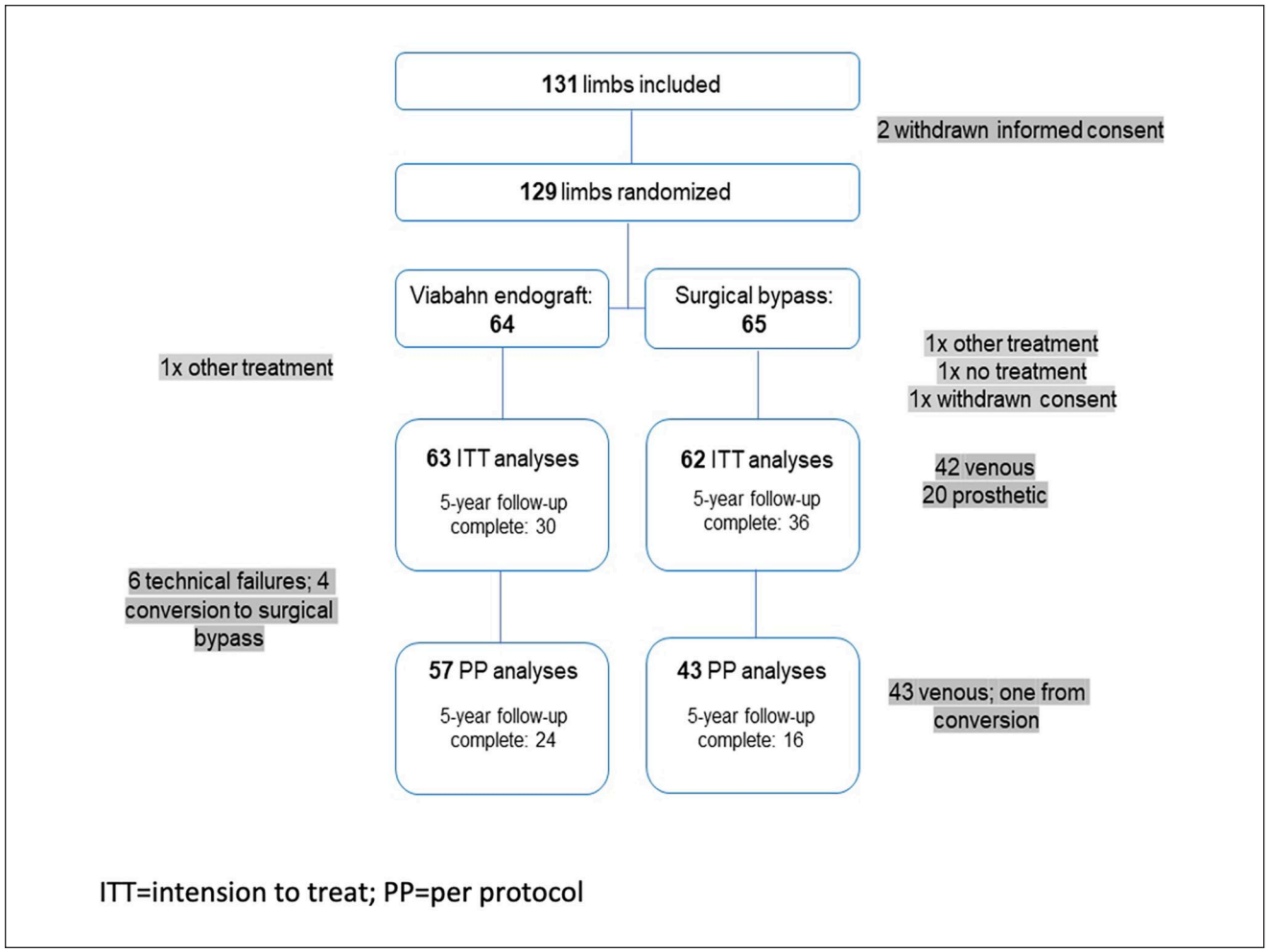


Figure 1. Inclusion flow chart. ITT, intension-to-treat; PP, per protocol.

group and one in the SB group. Consequently, the freedom from major amputation rate after 5-year follow-up was 92.6% in the EB group and 96.2% in the SB group, respectively (p=0.361). Both patients were originally treated for CLTI. The patient in the EB group underwent a below-the-knee amputation related to an occlusion after 3-year follow-up, whereas the patient in the SB group underwent a below-the-knee amputation due to an ongoing infection of the foot after 4-year follow-up. Six minor amputations in 4 patients were performed in the EB group and 3 minor amputations in 2 patients in the SB group.

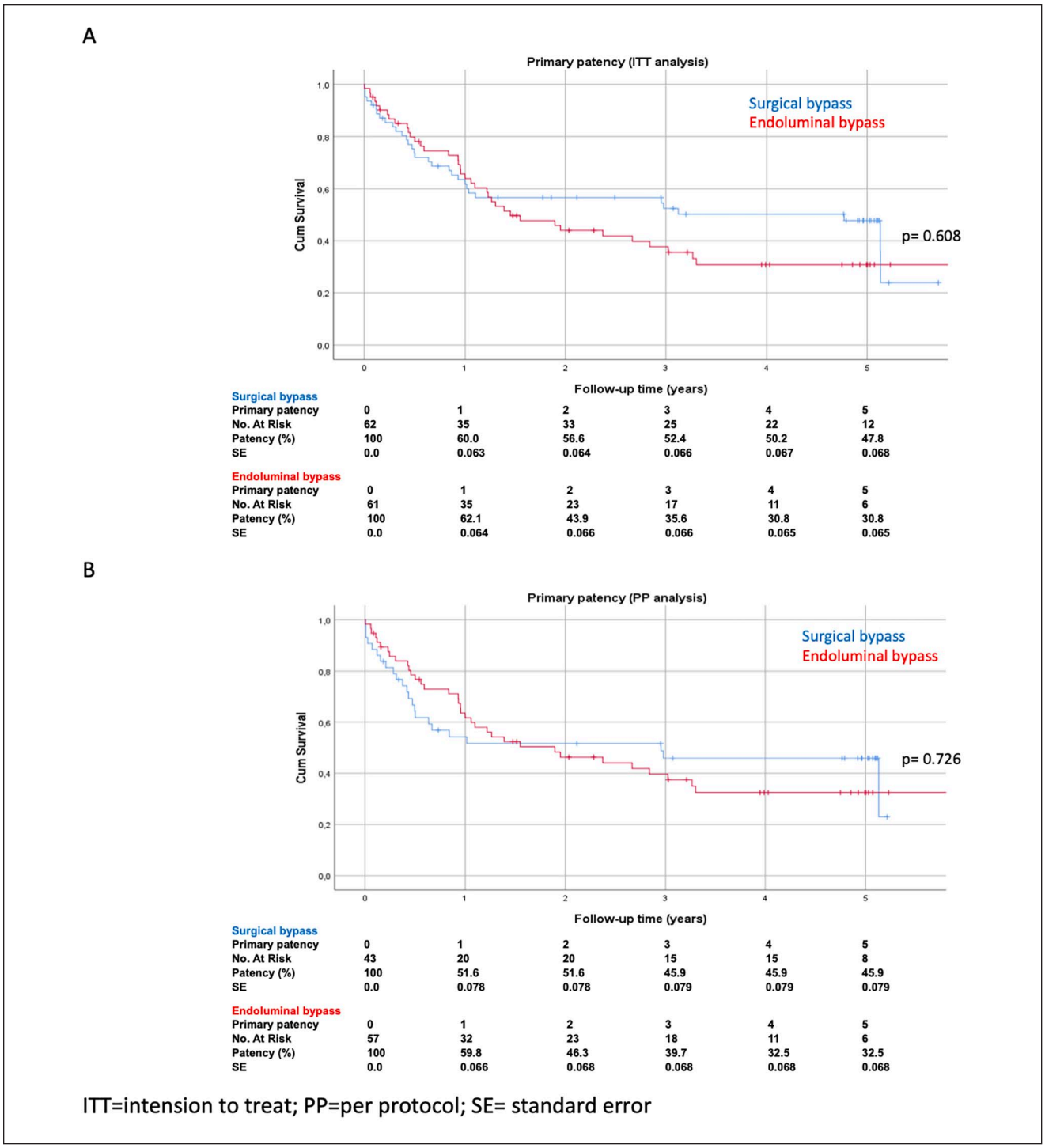
When analyzing the data in the PP cohorts (Figures 2B, 3B, 4B), the results were in line with the ITT analysis.

Clinical Outcomes and Health Status

In the ITT analysis, the ABI was significantly higher at 5-year follow-up in both groups when compared with baseline (EB group: 0.85 vs 0.59, p<0.001; SB group: 0.90 vs 0.58 p<0.001), without differences between groups (p=0.162). The Rutherford classification had significantly improved in both groups at 5-year follow-up, when compared with baseline (p<0.001), but with a significantly better overall Rutherford classification in favor of the EB group (p=0.022). In the EB group, 68% was asymptomatic after 5 years, whereas 24% suffered from mild cognitive impairment (CI), in contrast with the SB group where 46% was asymptomatic and 18% suffered from mild CI (Figure 6).

When analyzing the data in the PP cohorts, there were no differences observed compared with the ITT analysis.

Five years after the index procedure, there were no significant differences in health status between groups in the ITT analysis. At baseline, the EB group scored significantly higher for health change and the SB group for emotional well-being (Table 2). At 5-year follow-up, both groups improved in the physical role function dimension when compared with baseline. The SB group experienced a significantly better physical functioning at 5-year follow-up when compared with baseline (p=0.045). Both groups scored significantly better on pain perception at 5-year



Surgical bypass						
Primary patency	0	1	2	3	4	5
No. At Risk	62	35	33	25	22	12
Patency (%)	100	60.0	56.6	52.4	50.2	47.8
SE	0.0	0.063	0.064	0.066	0.067	0.068
Endoluminal bypass						
Primary patency	0	1	2	3	4	5
No. At Risk	61	35	23	17	11	6
Patency (%)	100	62.1	43.9	35.6	30.8	30.8
SE	0.0	0.064	0.066	0.066	0.065	0.065

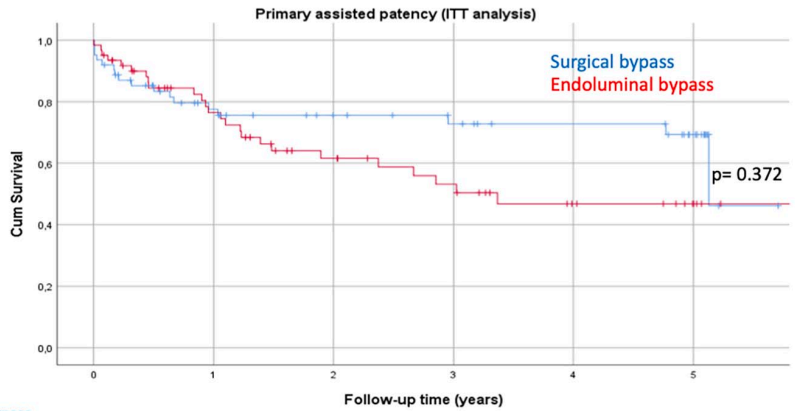
Surgical bypass						
Primary patency	0	1	2	3	4	5
No. At Risk	43	20	20	15	15	8
Patency (%)	100	51.6	51.6	45.9	45.9	45.9
SE	0.0	0.078	0.078	0.079	0.079	0.079
Endoluminal bypass						
Primary patency	0	1	2	3	4	5
No. At Risk	57	32	23	18	11	6
Patency (%)	100	59.8	46.3	39.7	32.5	32.5
SE	0.0	0.066	0.068	0.068	0.068	0.068

Figure 2. Kaplan-Meier curve presenting the primary patency for the surgical (blue) and the endoluminal (red) groups during 5-year follow-up according to ITT analysis (A) and per-protocol analysis (B). ITT, intension-to-treat; PP, per protocol; SE, standard error.

follow-up (EB group, p=0.001; SB group, p=0.047), compared with baseline.

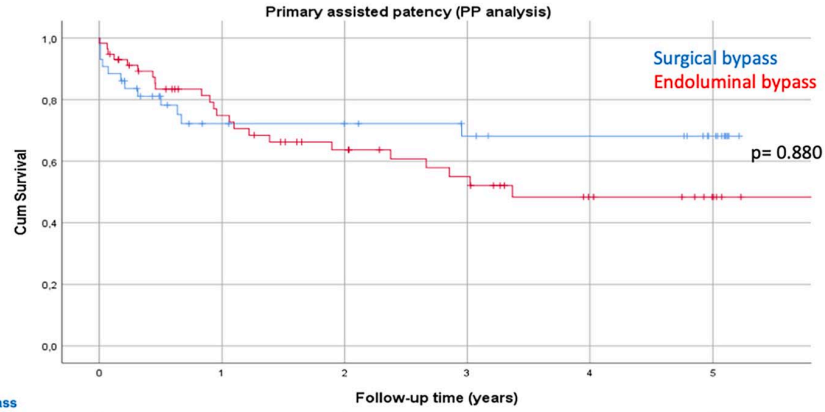
There were no differences between groups in the WIQ dimensions at both baseline and 5-year follow-up. The walking distance significantly improved in both groups at 5 years of follow-up when compared with baseline (p=0.001 and p=0.002 for the EB and SB, respectively). In addition, the SB group also showed a significant improvement for

A



Surgical bypass						
Primary assisted patency	0	1	2	3	4	5
No. At Risk	62	37	30	26	22	12
Patency (%)	100	75.5	75.5	72.7	72.7	69.2
SE	0.0	0.055	0.055	0.062	0.062	0.068
Endoluminal bypass						
Primary assisted patency	0	1	2	3	4	5
No. At Risk	61	37	25	19	11	6
Patency (%)	100	74.4	61.5	53.1	46.7	46.7
SE	0.0	0.060	0.069	0.075	0.078	0.078

B



Surgical bypass						
Prim. assisted patency	0	1	2	3	4	5
No. At Risk	43	22	20	17	15	8
Patency (%)	100	72.1	72.1	68.1	68.1	68.1
SE	0.0	0.072	0.072	0.079	0.079	0.079
Endoluminal bypass						
Prim. assisted patency	0	1	2	3	4	5
No. At Risk	57	35	25	18	11	6
Patency (%)	100	74.8	63.7	52.1	48.4	48.4
SE	0.0	0.061	0.070	0.077	0.080	0.080

ITT=intension to treat; PP=per protocol; SE= standard error

Figure 3. Kaplan-Meier curve presenting the primary-assisted patency for the surgical (blue) and the endoluminal (red) groups during 5-year follow-up according to ITT analysis (A) and per-protocol analysis (B). ITT, intension-to-treat; PP, per protocol; SE, standard error.

climbing stairs (p=0.009). The total WIQ significantly improved in the SB group at 5 years (p=0.005) and showed a similar trend as in the EB group (p=0.076) (Table 3).

In the PP analysis of the SF-36, the EB group experienced a significantly better emotional functioning at baseline, which is in contrast with the ITT analysis. There was no significant better physical functioning in the SB group after 5-year follow-up (p=0.072), in contrast to the ITT analysis. The EB group still had a significantly better pain relief (p=0.001) after 5-year follow-up, whereas this improvement was not observed in the SB group (p=0.367).

The total score of the WIQ was only just significant (p=0.050) for the SB group, which is in contrast with the ITT analysis (p=0.005). This may perhaps reflect the more

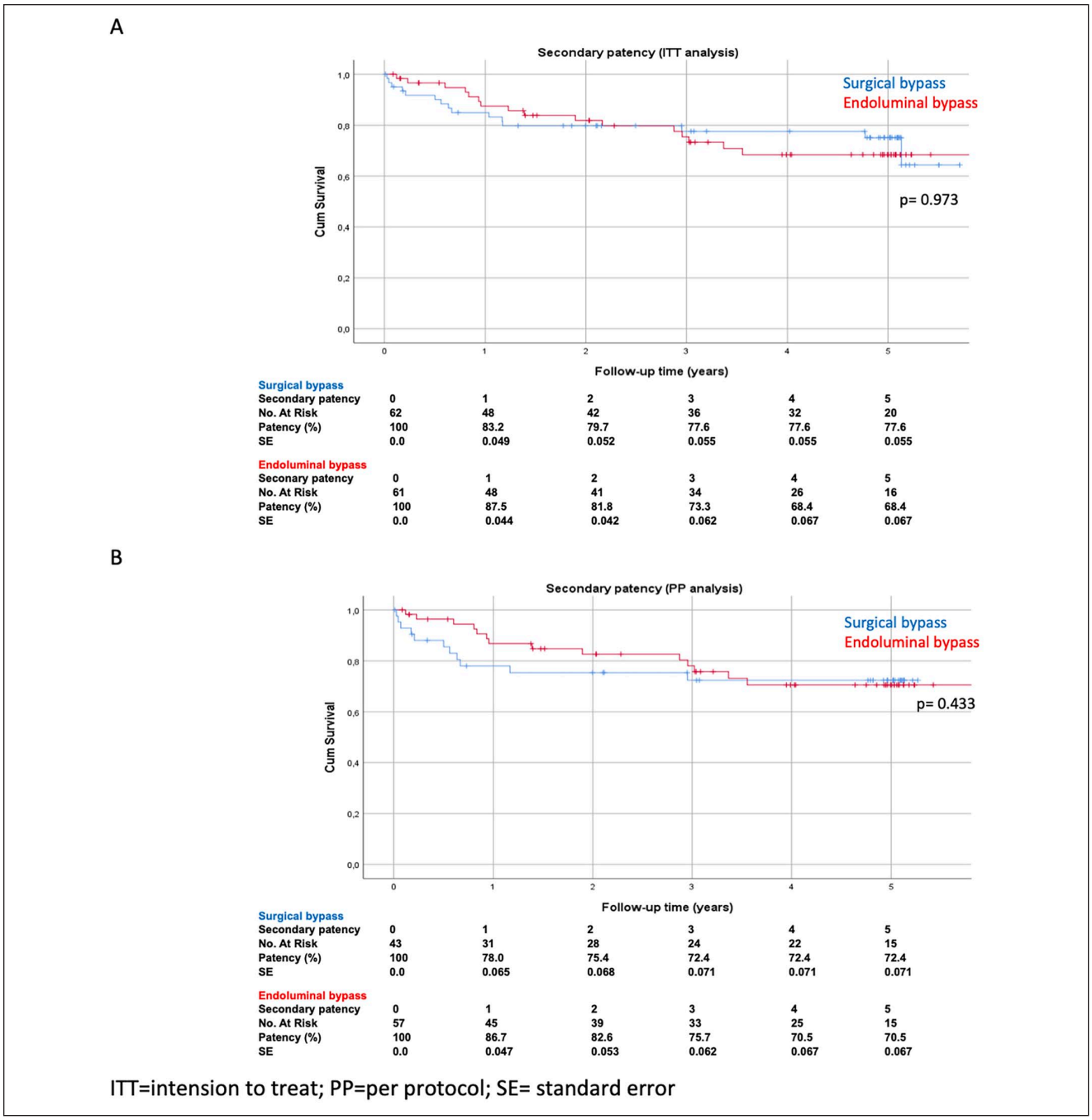


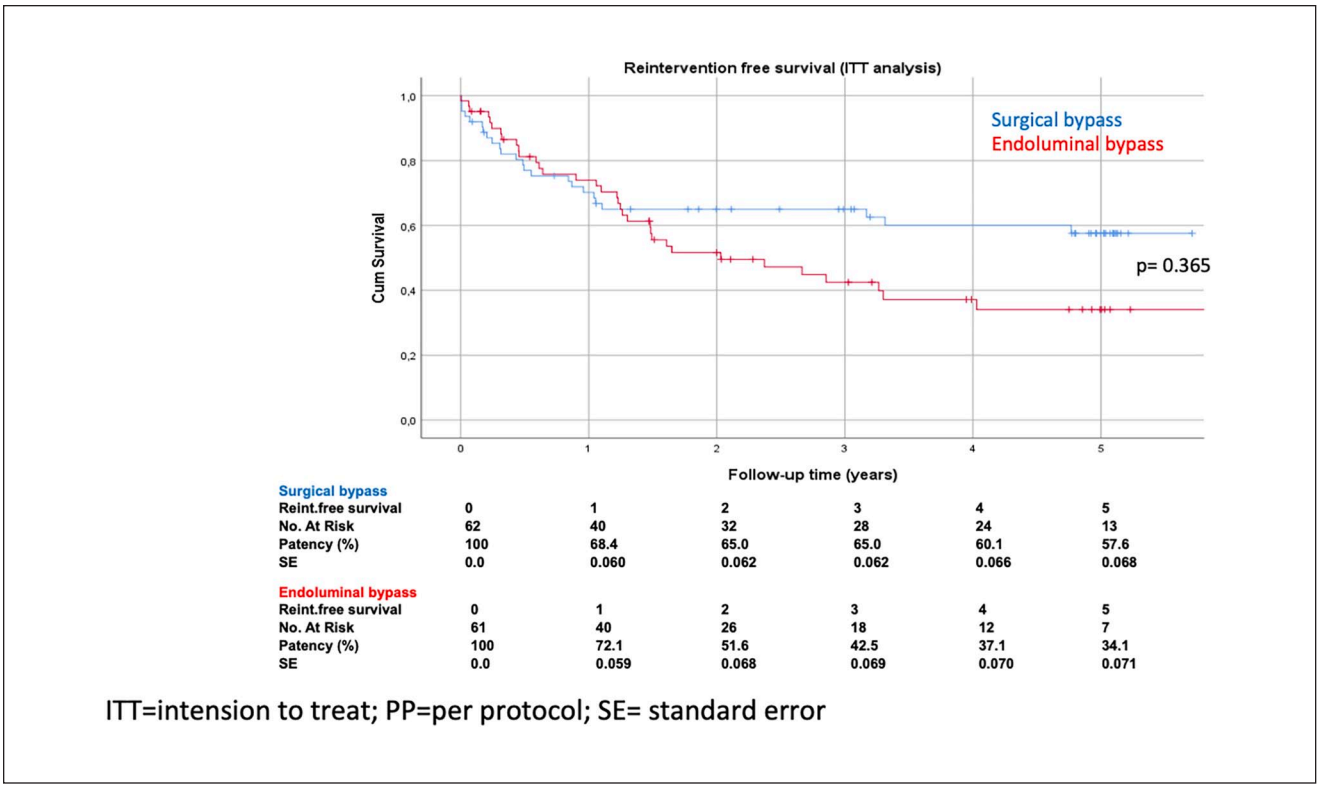
Figure 4. Kaplan-Meier curve presenting the secondary patency for the surgical (blue) and the endoluminal (red) groups during 5-year follow-up according to ITT analysis (A) and per-protocol analysis (B). ITT, intension-to-treat; PP, per protocol; SE, standard error.

invasive form of venous bypass surgery. There were no other differences compared with the ITT analysis between groups at baseline or at 5-year follow-up.

Mortality and Adverse Events

The overall survival rates in the ITT analysis were 72.5% for the EB bypass group and 73.0% for the SB group after 5-year follow-up (p=0.947). In total, 14 patients in the EB group and 16 patients in the SB group died. There were no procedure-related or treatment-related deaths, however, 1 patient in the SB group died after hospitalization for a wound infection after resection of the first metatarsal of the treated limb, which eventually led to a below-the-knee amputation.

The PP analysis showed no difference in survival between groups (71.0% in the EB group and 70.3% in the



Surgical bypass						
Reint.free survival	0	1	2	3	4	5
No. At Risk	62	40	32	28	24	13
Patency (%)	100	68.4	65.0	65.0	60.1	57.6
SE	0.0	0.060	0.062	0.062	0.066	0.068
Endoluminal bypass						
Reint.free survival	0	1	2	3	4	5
No. At Risk	61	40	26	18	12	7
Patency (%)	100	72.1	51.6	42.5	37.1	34.1
SE	0.0	0.059	0.068	0.069	0.070	0.071

ITT=intension to treat; PP=per protocol; SE= standard error

Figure 5. Kaplan-Meier curve presenting the 5-year freedom from clinically-driven reintervention during the 5-year follow-up according to intension-to-treat analysis. ITT, intension-to-treat; PP, per protocol; SE, standard error.

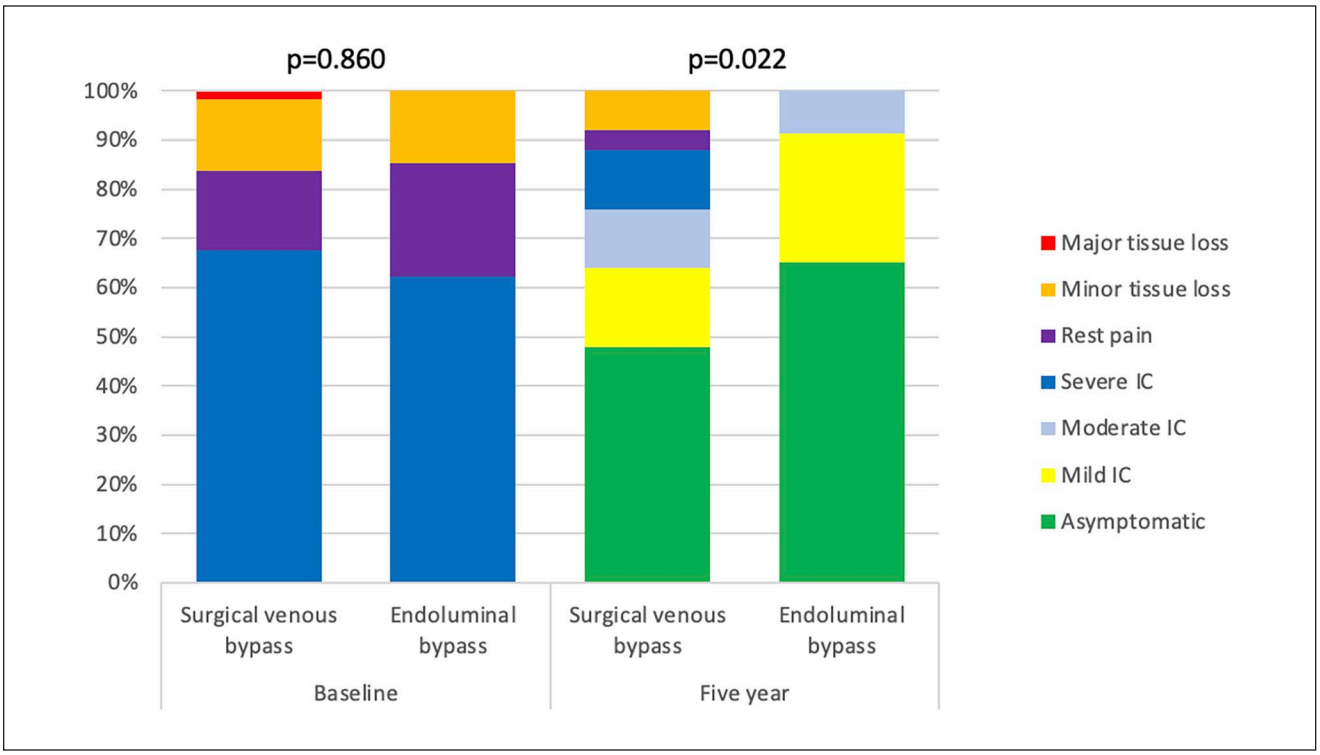


Figure 6. Bar chart presenting the Rutherford stages at baseline as well as at 5-year follow-up intension-to-treat analysis.

Table 1. Overview of Baseline Characteristics and Treated Lesion Characteristics for Both Study Groups.

	Surgical (n=62)	Endoluminal (n=63)	p Value
Age (years)	66±7.9	68.5±8.8	0.227
Male	80.6	73.0	0.312
Cardiovascular risk factors			
Tobacco use (current smoker)	51.6	49.2	0.788
Hypertension	74.2	68.3	0.463
Diabetes mellitus	33.9	34.9	0.902
Dyslipidemia	71.0	74.6	0.648
Cardiac disease	38.7	38.1	0.944
Pulmonary disease	27.4	17.5	0.182
Stroke	22.6	14.3	0.231
Renal insufficiency	16.1	9.5	0.269
Rutherford classification			
3	67.7	61.9	0.551
4	16.1	23.8	
5	14.5	14.3	
6	1.6	0.0	
TASC II classification			
B	5.0	3.3	0.458
C	13.3	21.7	
D	81.7	75.0	
Lesion length (cm)	23.6±7.1	23.3±8.3	0.857
Diameter of popliteal artery (mm)	5.6±1.0	5.2±0.8	0.012*

Values are % or mean±SD.
Abbreviation: TASC, Trans-Atlantic Inter-society Consensus.
*$p \leq 0.05$.

Table 2. Outcomes of the SF-36 Questionnaire, Depictured as a Percentage for the 2 Interventional Groups Over Time.

	N	Baseline	5 years	p value
Physical functioning				
Surgical bypass	23	42.3	53.8	0.045
Endoluminal bypass	20	43.6	50.9	0.556
Role functioning/physical				
Surgical bypass	27	38.1	58.9	0.011
Endoluminal bypass	21	30.8	64.1	0.010
Role functioning/emotional				
Surgical bypass	25	71.9	78.2	0.447
Endoluminal bypass	21	56.9	59.7	0.254
Energy/fatigue				
Surgical bypass	28	61.9	61.4	0.847
Endoluminal bypass	22	57.1	56.0	0.740
Emotional well-being				
Surgical bypass	28	78.9*	79.3	0.769
Endoluminal bypass	22	67.6	72.2	0.822
Social functioning				
Surgical bypass	27	67.2	71.4	0.349
Endoluminal bypass	21	66.3	75.5	0.732
Pain				
Surgical bypass	28	46.9	63.7	0.047
Endoluminal bypass	22	41.5	72.9	0.001
General health				
Surgical bypass	29	54.5	51.8	0.119
Endoluminal bypass	21	56.9	56.1	0.337
Health change				
Surgical bypass	29	37.3	41.7	0.311
Endoluminal bypass	22	45.5*	52.0	0.099

The p value represents the (*significant*) difference between the percentages at baseline versus 5-year follow-up for a single interventional group.
*Significant difference between different groups at given time points ($p < 0.05$).

SB group, p=0.774). An overview of the numbers of serious adverse events (SAEs) in both groups over 5 years are depicted in Table 4. Per-protocol analysis showed less adverse events in the SB group compared with the EB group, and the total number of events was lower than in the ITT analysis (136 ITT vs 87 PP), attributed to the group treated with a prosthetic conduit. The higher number of SAE in the EB group is mainly due to the number of reinterventions in this group.

Predictors of Failure

In Table 5, results of the regression analysis are depicted. The total number of failures was too small for each group to perform a multivariate analysis. Therefore, an analysis was performed on all failures in both groups combined. The baseline SFA diameter was the only predictor regarding loss off primary patency (p=0.006) and a predictor for reintervention (p=0.015); a larger diameter was associated with less failure of patency and less reinterventions.

A history of cardiovascular disease (CVD) was not only a predictor of loss off primary-assisted patency (p=0.027) and secondary patency (0.043), but also a predictor of definitive failure (p=0.043). Diabetes mellitus (DM) was a predictor for both loss of secondary patency (p=0.043) and definitive failure (p=0.025), and age was a predictor for reinterventions (p=0.030).

Discussion

This present study is the first to report 5-year randomized outcomes comparing treatment with an EB or with an SB for complex femoropopliteal disease. The outcomes support the use of EB for this indication and it seems to be a valid alternative for bypass surgery also at the long-term, albeit with more reinterventions during follow-up. The advantages of treatment with EB are mostly seen in the early period after treatment with a shorter hospital stay, a faster recovery in health status, and less complications. During follow-up, the

Table 3. Outcomes of the WIQ, Divided in the 3-Dimensions and the Total WIQ Score for the 2 Interventional Groups at Baseline and at 5-Year Follow-Up.

	N	Baseline	5 years	p value
Walking distance				
Surgical bypass	23	21.1	50.4	0.001
Endoluminal bypass	17	25.6	48.2	0.002
Walking speed				
Surgical bypass	20	29.2	44.1	0.070
Endoluminal bypass	20	34.2	42.3	0.052
Stairs climbing				
Surgical bypass	21	44.2	57.2	0.009
Endoluminal bypass	20	53.6	53.4	0.549
Total WIQ score				
Surgical bypass	19	31.8	50.1	0.005
Endoluminal bypass	17	37.5	47.3	0.076

The p value represents the (*significant)* difference between baseline and 5 years of follow-up for each interventional group.
Abbreviation: WIQ, Walking Impairment Questionnaire.

clinical endpoints were mostly comparable between both techniques with the EB group even having a better overall Rutherford category at 5-year follow-up.

Although we did not observe statistically significant differences in patency rates at both 1-year and 5-year follow-ups, there were some notable differences. The primary patency rate at 5 years was 18% lower in the EB group. The overall primary patency rates in both groups were lower than anticipated, and most reinterventions were performed during the first 2 years after intervention. Many of them were not clinically apparent, but per protocol driven as a restenosis with a peak systolic velocity ratio >2.5 was an indication for preemptive reintervention.[5,9] This also explains the higher number of reinterventions in the EB group, related to the occurrence of, often asymptomatic, edge stenosis, which remain to be the Achilles heel of EB. Our data of the EB group are in line with other studies providing long-term follow-up of EB,[7,8,10] but they were lower when compared with the long-term outcome of the Japanese Viabahn trial[11] in which an fTLR of 79.1% after 5 years was described. Although most of the SFA lesions were long and complex, with 84.5% TASC (Trans-Atlantic Inter-society Consensus) C/D lesions and 65.7% chronic total occlusions (CTOs), most patients (97.1%) in that study were treated for intermittent claudication (IC), which makes a comparison less reliable. All studies in which EB treatment was described for long complex lesions in the femoropopliteal artery show a wide variation of primary patency rates, but consistent high secondary patency rates.[6,11–13] The 68% secondary patency rate in the current EB group at 5 years can be considered in that range.

The 5-year patency rates of the SB group are not in line with the literature reporting 5-year primary patency rates of 75.5% and 76.6% for a venous above-the-knee SB.[14,15]

Table 4. Table Presenting the Number of Serious (Adverse) Events for Both Groups After 5 Years of Follow-up.

Serious (adverse) events	N
Peripheral artery disease-related events	
Surgical bypass	71
Endoluminal bypass	106
Cardiac-related events	
Surgical bypass	11
Endoluminal bypass	11
Neurologic-related and cerebrovascular-related events	
Surgical bypass	6
Endoluminal bypass	2
Oncologic-related events	
Surgical bypass	5
Endoluminal bypass	11
Respiratory-related events	
Surgical bypass	3
Endoluminal bypass	8
Infection-related events	
Surgical bypass	6
Endoluminal bypass	4
Urogenital-related events	
Surgical bypass	1
Endoluminal bypass	3
Gastrointestinal-related events	
Surgical bypass	9
Endoluminal bypass	2
Endocrine system-related events	
Surgical bypass	3
Endoluminal bypass	1
Renal disease-related events	
Surgical bypass	3
Endoluminal bypass	0
Hematologic-related events	
Surgical bypass	0
Endoluminal bypass	1
Other or multiple disease-related events	
Surgical bypass	8
Endoluminal bypass	4
Total number of events	
Surgical bypass	136
Endoluminal bypass	157

Comparison with those older publications is severely hampered by differences in follow-up protocol, imaging and definitions regarding patency.[4,14–16] However, the five-year primary patency rates in the SB group are in line with a recent publication on patients who received a venous bypass using the same definitions regarding follow-up, imaging and patency.[16] Unfortunately, the sample size in the surgical cohort is too low to perform a meaningful subgroup analysis on the type of conduit used for the surgical reconstruction.

The equality in long-term clinical and functional outcomes in this study, regardless of the higher reintervention rate, emphasize the need for incorporation of patient

Table 5. Final Models of the Multivariate Regression Analyses to Identify Predictors of Definitive Failure, Primary, Primary-Assisted, and Secondary Patency, and Reinterventions.

	Univariate regression	Multiple regression final model
	OR [95% CI], p value	OR [95% CI], p value
Definite failure		
Diabetes mellitus	2.257 [0.979–5.203], p=0.056	2.761 [1.138–6.703], p=0.025
History of CVD	1.907 [0.837–4.344], p=0.124	2.485 [1.030–5.996], p=0.043
≥2 patent outflow arteries	2.739 [0.755–9.940], p=0.125	
Primary patency		
Baseline SFA diameter	0.662 [0.492–0.890], p=0.006	0.659 [0.488–0.889], p=0.006
History of CVD	1.783 [0.847–3.753], p=0.128	
ASA category≥III	1.867 [0.890–3.917], p=0.099	
Diabetes mellitus	1.591 [0.738–3.426], p=0.236	
Primary-assisted patency		
History of CVD	2.561 [1.190–5.509], p=0.016	2.668 [1.119–6.360], p=0.027
Diabetes mellitus	1.781 [0.820–3.867], p=0.144	
Baseline SFA diameter	0.770 [0.578–1.026], p=0.074	
Secondary patency		
History of CVD	1.907 [0.837–4.344], p=0.124	2.485 [1.030–5.996], p=0.043
Diabetes mellitus	2.257 [0.979–5.203], p=0.056	2.761 [1.138–6.703], p=0.025
≥2 patent outflow arteries	2.739 [0.755–9.940], p=0.125	
Reintervention		
Baseline SFA diameter	0.685 [0.512–0.918], p=0.011	0.686 [0.507–0.928], p=0.015
Age	0.973 [0.932–1.016], p=0.215	2.633 [1.099–6.305], p=0.030
History of CVD	2.190 [1.050–4.570], p=0.037	
ASA category≥III	2.045 [0.960–4.356], p=0.064	

Abbreviations: ASA, American Society of Anesthesiologists' (ASA) classification of Physical Health; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; SFA, superficial femoral artery.

reported-outcome measures (PROMs) in clinical trials as it may help the interventionalist in shared decision-making choice of intervention in patients with PAD.[17]

After 5 years, the limb salvage in both groups was high and shows the safety of the EB, also in the group that presents with an occlusion, with only 1 major amputation in both groups. One of the potential drawbacks of the EB is the fear of overstenting of collateral arteries, which could have a negative outcome in case of occlusion, particularly in patients treated for CLTI that often have more concomitant below-the-knee pathology. The data show, in line with previous research, that this does not lead to limb loss after an occlusion of an EB also at long-term follow-up.[18,19]

In this study, DM was a predictor for loss of secondary patency and definitive failure. It is not clear whether the number of outflow vessels nor the quality of the vessels plays a role in this. The lack of correlation between the number of runoff vessels and functional outcome as described by Ohki et al[11] does not support this possible correlation often seen with DM patients. In this study, there was neither a correlation between patent outflow arteries regarding secondary patency or definitive failure in both groups.

The treatment of long and complex SFA lesions in clinical practice has mostly shifted to an endovascular approach first for most patients. Individual assessment, regarding symptoms, functional status, comorbidities, age, longevity have to be considered as lesion characteristics (CTO, calcium, flush occlusion, collaterals) forms no limitation in the use of a self-expanding covered stent regarding outcomes.[5,7] A smaller distal vessel diameter (<4 mm) increases the likelihood of excessive oversizing the endograft, due to the diameter of available stents, which is a proven predictor of failure and should therefore be avoided.[10] In the current trial, crossover was only observed from the endovascular to the surgical arm. Performing an endovascular procedure after SB, however, is feasible.[20]

The optimal treatment algorithm of complex femoropopliteal disease remains a topic for debate. The results of bare metal stents are limited due to the occurrence of in-stent restenosis and stent fractures.[21–23] The Viastar trial has shown superiority of EB over bare stents, particularly in long lesions. Nevertheless, in these lesions, there may also be a value of the use of atherectomy in combination with drug-based technology. For example, in a retrospective study, Tsujimura et al[24] found that treatment with a

drug-eluting stent was related to a lower rate of primary patency but a higher rate of freedom from stent thrombosis compared with EB. The ZILVERPASS Study, which was a study comparing the use of drug-eluting stents with bypass surgery, has shown that drug-eluting stents were non-inferior to bypass surgery using a prosthetic graft through 12 months.[25] Long-term outcomes of that study are lacking to date. Likely, advantages of the endovascular strategy are mostly in the early period after treatment, and femoropopliteal bypass surgery will always remain an important tool for the vascular community.

The data from all randomized controlled trials comparing endovascular stent implantation with bypass surgery were pooled and found no significant difference in MALEs and amputation-free survival, giving robust evidence on the comparison of both groups for these clinical endpoints.[4] Future trials might not be randomized anymore with an SB arm as comparative trials between various endovascular strategies will provide further evidence for the development of an evidence-based treatment algorithm. In a subset of patients of the EB group, a concomitant endarterectomy of the common femoral artery was performed. At present, less is known about the long-term outcomes of these hybrid procedures, but it may influence the outcomes compared with purely endovascular interventions. With the low sample size, this cannot be concluded from the current trial.

In addition, the trial was not designed to capture healthcare resource use and costs, nor it was powered to calculate cost effectiveness. This will certainly be an important addition, especially in endovascular future trials. As an alternative, a scenario resource consumption data analysis could be modeled, based on the current data.

Despite the randomized controlled design, the current study has limitations. First, the powered sample size for the primary patency rate at 1 year could not be achieved due to a lower than anticipated enrollment rate and the absolute number of patients at 5 years were low. A larger sample size with more venous bypasses in the surgical arm might lead to a significant difference in terms of primary patency. Second, the follow-up compliance was low, further decreasing the sample size at 5-year follow-up. For this reason, a non-inferiority for patency could not be claimed. Due to the smaller group sizes, subgroup analyses between IC and CLTI patients could not be performed. Finally, therapy compliance was not monitored and could have influenced the outcomes.

Conclusion

The current study shows that treatment of complex femoropopliteal disease with EB using a heparin-bonded endograft is related to similar clinical and functional outcomes, compared with bypass surgery, albeit with higher reintervention rates. Future studies should be focused on comparison of EB with alternative endovascular strategies.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This is an investigator-sponsored study supported in part by W.L. Gore and Associates. Dr Reijnen IS consulting for W.L. Gore and Associates. Dr van Walraven has received speakers fees from W.L. Gore and Associates. Dr Zeebregts recieved research grants from W.L.gore and Associates. All other authors have reported that they have no relationships relevant to the contents of the paper to disclose.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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