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ORIGINAL STUDIES

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Individual patient data meta-analysis of patients treated with a heparin-bonded Viabahn in the femoropopliteal artery for chronic limb-threatening ischemia

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Abstract

Objectives: The aim of the study was to analyze available data on patients treated for chronic limb-threatening ischemia (CLTI) with the heparin-bonded Viabahn endoprosthesis.

Background: The patency of self-expanding covered stents in patients with complex femoropopliteal lesions is encouraging. However, data were mostly derived in patients with intermittent claudication. Patients with CLTI often have more advanced disease and worse outcome.

Methods: After the abstract screening, full-text papers were checked. Authors were approached to consider joining the consortium. Data were sent anonymously, databases were merged and an individual patient data meta-analysis was performed. Kaplan–Meier curves were used to calculate the freedom from amputations, the amputation-free survival, and patency rates.

Results: Seven studies were enrolled, representing 161 limbs that were treated for CLTI. Median lesion length was 28.0 cm (interquartile range 25.0–33.0 cm) and 82.7% were chronic total occlusions. The technical success rate was 98.1% and the 30-day mortality 1.9%. Through 2-year follow-up, the freedom-from-major-amputations was 99.3%, with an amputation-free survival of 78.8%. The freedom-from-loss-of primary, primary-assisted, and secondary patency was 70.4%, 71.8%, and 88.2%, respectively, at 1-year and 59.5%, 62.7%, and 86.1% at 2-year follow-up, respectively. The reintervention-free survival was 62.2% at a 2-year follow-up.

Conclusions: Treatment of femoropopliteal disease in CLTI patients with the use of the heparin-bonded Viabahn is safe and effective with favorable clinical outcomes and low amputation rates. Reinterventions are needed in a subset of the population

to maintain endoprosthesis patency. Close follow-up using duplex is recommended to detect potential edge stenosis, allowing treatment before device occlusion.

KEYWORDS

amputation, chronic limb-threatening ischemia, covered stent, critical limb ischemia, endoprosthesis, femoropopliteal, heparin-bonded Viabahn

1 | INTRODUCTION

Endovascular treatment is becoming the prevalent treatment modality for most femoropopliteal lesions.[1] The latest Global Vascular Guidelines on the Management of chronic limb-threatening ischemia (CLTI) recommended considering adjuncts to plain balloon angioplasty for example with nitinol stents, covered stents, or drug-eluting technologies when there is residual stenosis, a flow-limiting dissection, or in the setting of advanced lesion complexity.[2] The use of drug-eluting technology was hampered in recent years, related to the publication of a meta-analysis reporting increased mortality in patients treated with paclitaxel-based devices.[3] Self-expanding covered stents have been available for quite some years. The latest generation Viabahn (W.L. Gore and Associates, Flagstaff), including the heparin-bonding technology, is one of the most commonly used self-expanding covered stents for the femoropopliteal artery. The case series showed promising results with 3-year primary and secondary patency rates of 73%–76% and 89%–92%, respectively, in patients with complex lesions.[4,5] The number of patients with CLTI in these studies, however, was limited to only 13%–30% of cases. In the Viabahn-25cm trial, only patients with intermittent claudication or ischemic rest pain were included.[6] The latter consisted of only 9% of the cohort. Additionally, in the randomized Viastar trial the number of patients with CLTI treated with the Viabahn was limited to 3% of patients having Rutherford 4% and 11% Rutherford 5.[7] In the randomized SuperB trial, comparing the outcomes of treatment with this particular device with femoropopliteal bypass surgery, the number of patients with CLTI was already higher with 38% of cases.[8] The low absolute numbers, however, made a subgroup analysis impossible.

Consequently, the available evidence on the outcomes of treatment with self-expanding covered stents in patients with CLTI is still limited, but clinically of utmost importance. As these patients have generally more advanced disease, also in their outflow vessels, therefore the patency results may differ from those treated for intermittent claudication (IC). Furthermore, an active infection is more common in CLTI patients, this could cause a higher risk for stent graft infection, in turn limiting patency results. In addition, the impact of overstenting collateral arteries could have a different clinical impact in this subgroup in case of acute occlusion of the endoprosthesis. Moreover, the clinical outcome measures in these patients differ from those treated for intermittent claudication, as the most relevant clinical parameter is the avoidance of major amputations. To date, no studies have been published that focused on the CLTI subgroup treated with this specific device, and in all of the performed studies, the subgroups were too small to draw relevant conclusions on this group. Some, however, have suggested that the use of endoprosthesis in CLTI should be avoided.[9]

The aim of the current study was to assess the outcomes of treatment with a heparin-bonded Viabahn in patients with CLTI using an individual patient data meta-analysis of the published studies.

2 | MATERIALS AND METHODS

2.1 | Data sources

A search query was executed to identify all papers published after the latest release of the heparin-bonded Viabahn stent in 2009 when the contoured proximal edge was launched. This resulted in a time window between January 1, 2020 and December 15, 2020, using the Scopus database with the search terms being Viabahn OR heparin-bonded OR heparin-coated for the title, abstract, and keywords. The individual participant data (IPD) methods were set up and executed according to the guidelines from the Preferred Items for Systematic Reviews and Meta-Analysis of IPD (PRISMA-IPD).[10] Papers were identified regarding studies that included patients with Rutherford classification 4–6 and were treated in the superficial femoral artery with the heparin-bonded Viabahn endoprosthesis. The search query identified 1236 articles. After title and abstract screening, 1212 papers did not meet the inclusion criteria and were rejected, resulting in 24 papers being eligible for full-text screening. After full-text screening, another 11 papers were rejected. The remaining 13 studies were eligible for IPD analysis and the authors were invited for participation by electronic mail. A communication log was kept to review all responses. If the authors did not respond, after a second email, the study was excluded. Seven authors responded positively and agreed to join and signed clinical investigation and data transfer agreements.[5,6,8,11–14] Six authors did not respond to either the first or second email. The contributing authors supplied anonymized databases for patients that were treated for CLTI (Figure 1). The original principal investigators had obtained ethics approval before inclusion in the IPD consortium; the Medical Ethics Committee Nijmegen (file number 2018-4043) and the local institutional board (file number 2017-1135) approved the analysis itself.

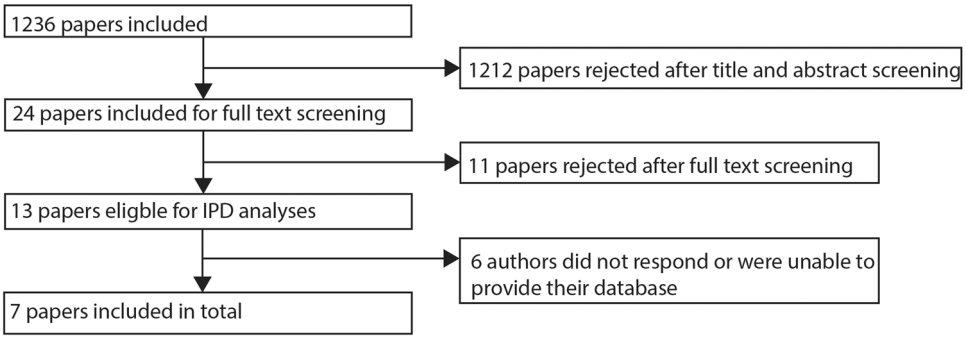


FIGURE 1 Flow chart of study selection

2.2 | Data merge

A database was created using SPSS software (version 25; IBM Corporation) before merging the individual data sets. Fields of every original study database were mapped to a prebuilt database and a conversion log was maintained. When applicable, a conversion scheme was also saved in the log, based on the value label defined for the original field and the IPD field. After initial mapping and conversion, the conversion log and data copying per study cohort were checked. Discrepancies were resolved by discussion with the author. A copy of the IPD database was saved for each database conversion; all copies were thereafter merged into one final data set. Empty fields in the prebuilt IPD database were culled.

2.3 | Definitions

Definitions were based on the reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease.[15] Units for length, diameter, blood pressure, and so on were predefined, and conversion was applied if needed. If no standard definition was available, labels per database were added if not yet available in the IPD database. Technical success was defined as successful implantation of the endoprosthesis. Definitions of patency were used as specified by the authors for their original studies. Clinical improvement was defined as an increase of the ankle-brachial index (ABI) by at least 0.1 and a 1-level improvement in the Rutherford category between baseline and the first postoperative measurement and subsequent follow-up visits.

2.4 | Outcomes

The primary study outcome was the freedom from major amputations at 1-year follow-up. Secondary outcomes included the primary, primary-assisted, and secondary patency rates, amputation-free survival, freedom from reinterventions, survival rate, and clinical improvement at 1- and 2-years follow-up.

2.5 | Statistical analysis

The normality of the data was inspected by graphs and tested by Kolmogorov–Smirnov or Shapiro Wilk in case of many missing values. Continuous variables are presented as mean and *SD*, since the majority of the data were normally distributed. Categorical variables are presented as numbers (percentage). Kaplan–Meier analysis was used to evaluate amputation-free survival, overall survival, patency rates (primary, primary assisted, and secondary), and freedom from reintervention rate. For pre- and postprocedure comparisons and changes in continuous variables at follow-up intervals (30-days, 12-months, and 24-months), log transformation and quadrate of the variables were applied if continuous variables were not normally distributed to determine if analysis of variance (ANOVA) for repeated measures could be used in case of nonnormally distributed data. Since all of these variables violated the assumption to perform ANOVA for repeated measures, the Wilcoxon Signed-Rank test was used for paired samples. Dichotomous variables were compared with a Fisher exact test, and the χ^2 test was used to compare nominal categorical variables. p values < 0.05 were considered to represent a significant difference. Statistical analyses were performed using IBM SPSS Statistics (SPSS version 25.0 for windows, IBM Corporation).

3 | RESULTS

3.1 | Study population

Eight databases were included for analysis in the study, representing 958 cases of which 155 patients with 161 (16.8%) limbs were treated for CLTI). Fifty-nine limbs (36.6%) were treated for Rutherford category 4, 86 (53.4%) for Rutherford 5, and 16 patients (9.9%) for Rutherford 6. The mean ipsilateral ABI before treatment was 0.51 ± 0.22. The below-the-knee vessel runoff was 3-vessels in 25.5% (n = 41), 2-vessels in 27.3% (n = 44), 1-vessel in 31.1% (n = 50), and all outflow vessels were stenosed in 4.3% (n = 7) of cases (11.8% (n = 19) missing data. Other baseline patients and lesion characteristics are depicted in Table 1. Overall, these characteristics reflect the usual appearances of patients with the peripheral arterial disease (PAD). The median length of the treated segment was 28.0 cm

TABLE 1 Patient and lesion characteristics

Characteristics	N	Mean (±SD) or N/%
Age (years)	146	74.5 (±9.4)
Male gender	146	93 (63.7)
Body Mass Index (kg/m^2)	112	23.1 (±4.2)
Hypertension	161	128 (79.5)
Diabetes mellitus	161	103 (64.0)
Hyperlipidemia	161	87 (54.0)
Statin use	43	34 (79.1)
Smoking	158	53 (33.5)
Coronary artery disease	161	80 (49.7)
Cardiovascular disease	114	27 (23.7)
Renal insufficiency	141	50 (35.5)
ASA usage	43	38 (88.4)
Clopidogrel usage	42	3 (7.1)
TASC 2 classification	128	
A		2 (1.6)
B		7 (5.5)
C		44 (34.4)
D		75 (58.6)
Median length treated segment (cm)	161	28 (IQR: 25.0–33)
Chronic total occlusions	156	129 (82.7)

Abbreviations: ASA, acetylsalicylic acid; *SD*, standard deviation; TASC 2, Trans-Atlantic Inter-Society Consensus II for the management of a peripheral arterial disease.

(interquartile range [IQR] 25.0–33.0 cm) and 82.7% were chronic total occlusions and 93% ($n = 119$) were classified as TASC-2 C and D lesions. Previous PAD treatment information was available on 33.5% ($n = 54$), of which 18 underwent previous interventions for PAD, including one patients with minor amputations. Information on the presence of healing of ulcerations was only available for five patients, and therefore not further analyzed.

3.2 | Procedural data

The technical success rate was 98.1%. Technical success was not achieved in three cases: in one patient the procedure was converted to an above-the-knee surgical bypass using a prosthetic graft, as no suitable vein was available, and in two patients residual stenosis was >30%. Details on the used Viabahn endoprosthesis with regard to lengths and diameters were only available for one-third of the total number of cases (113 missing data and one patient no endoprosthesis was used). In 19 cases one single endoprosthesis was used (11.8%), in 22 two endoprostheses (13.7.0%), and in seven cases three endoprosthesis (4.3%). The most frequently used diameters were 6 mm (38.5%), 5 mm (13%), and 7 mm (11.8%).

The median hospital stay was 3 days (IQR 2–7), with a range from 1 to 24 days. ABI before discharge was available for 114 cases, with a mean of 0.85 (IQR 0.73–0.97) ($p < 0.001$ compared with baseline).

3.3 | Follow-up

The freedom from major amputation at both 1- and 2-year follow-up was 99.3%. Minor amputations were performed in four patients through 2-year follow-up; one scheduled minor amputation was performed before 30-days follow-up, two minor amputations were reported at 18-months, and the last one at 24-months follow-up, rendering the 2-year freedom from minor amputations 94.5% (Figure 2A). The amputation-free survival at 1-year follow-up was 85.7% after 2-year follow-up this declined to 78.8% (Figure 2B).

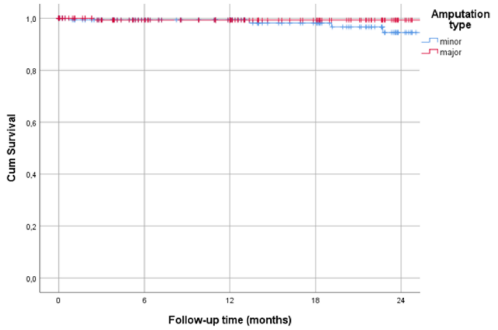
Data on primary, primary assisted, and secondary patency was available for 160, 76, and 75 cases, respectively. The primary, primary-assisted, and secondary patency rates were 70.4%, 71.8%, and 88.2% rates at 1-year follow-up and 59.5%, 62.7%, and 86.1% at 2-year follow-up, respectively (Figure 2C). The majority of failures occurred during the first year after intervention. There were no significant differences in patency rates between patients with Rutherford 4, 5, or 6. When stratified for the number of patent below-the-knee outflow vessels, no differences in outcomes were observed in primary, primary-assisted, nor secondary patency rates.

In total 27 (16.8%) patients died through 2-years follow-up. The freedom from all-cause mortality at 1- and 2-year follow-up was 86.3% and 78.4%, respectively (Figure 2D) with a mean time to death of 13.1 ± 2.4 months. Three patients (1.9%) died within 30-days after the procedure and 20 (12.4%) within 1-year after the procedure.

The reintervention-free survival was 74.0% and 62.2% at 12- and 24-months, respectively (Figure 2E). Reinterventions were required in 23 cases through 24-months follow-up. The median time to the first reintervention was 13.6 months (IQR 4.7–22.4 months). The majority of first reinterventions occurred during the first 6 months of follow-up. One patient required three reinterventions, six needed two, and 17 needed one reintervention through 24-months follow-up. An overview of all reinterventions is depicted in Table 2.

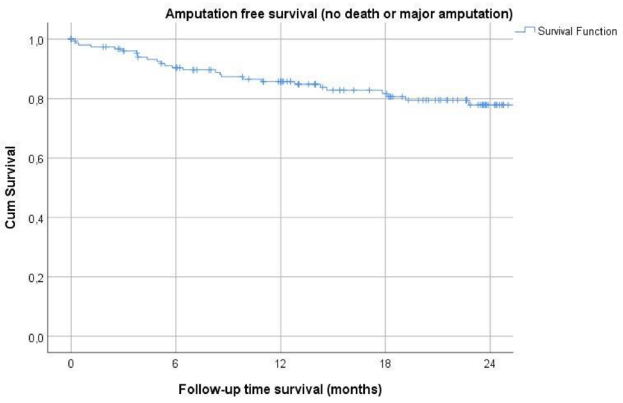
Rutherford classification was available for 31.1% of cases at 30-days follow-up, 26.1% at 6-months, 23% at 1-year, 17.4% at 18-months, and 19.3% at 1-years. In these patients, there was a significant clinical improvement (≥ 1 category Rutherford) at all postprocedural time-points compared with baseline ($p < .05$, Figure 3). Improvement in Rutherford was determined comparing last known with baseline category ($n = 50$). At latest follow-up, 1 patient

(A)



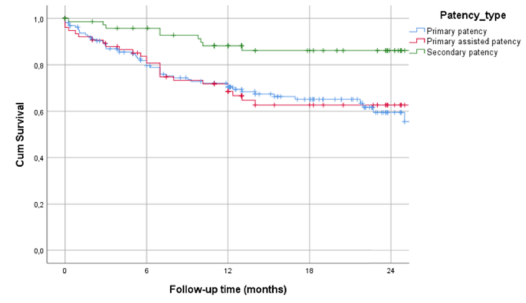
Minor amputation	**0**	**6**	**12**	**18**	**24**
No. At Risk	160	122	101	70	32
Amputation-free (%)	100	99.3	99.3	98.2	94.5
SE	-	0.007	0.007	0.013	0.029
Major amputation					
No. At Risk	153	115	95	64	29
Amputation-free (%)	100	99.3	99.3	99.3	99.3
SE	-	0.007	0.007	0.007	0.007

(B)



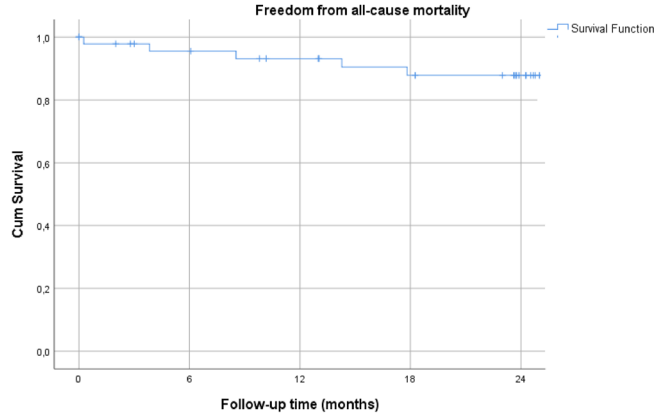
Survival	**0**	**6**	**12**	**18**	**24**
No. At Risk	**155**	**127**	**105**	**75**	**38**
Freedom from mortality and amputation(%)	**100**	**90.4**	**85.7**	**81.7**	**78.8**
SE	-	**0.025**	**0.030**	**0.034**	**0.040**

(C)



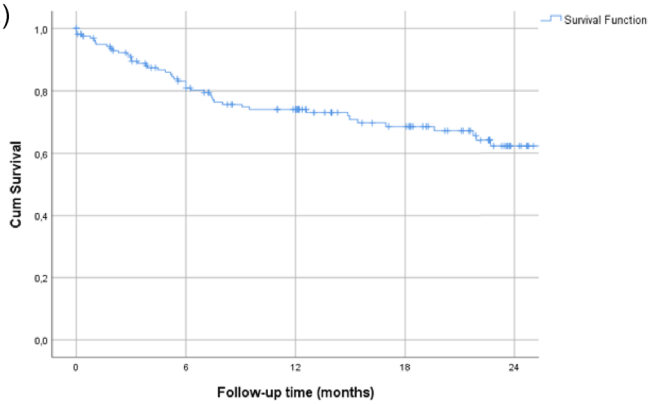
Primary	**0**	**6**	**12**	**18**	**24**
No. At Risk	160	108	86	52	18
Patency (%)	100	79.7	70.4	65.1	59.5
SE	-	0.033	0.039	0.042	0.050
Primary-assisted					
No. At Risk	76	55	36	27	16
Patency (%)	100	80.7	71.8	62.7	62.7
SE	-	0.047	0.057	0.061	0.061
Secondary					
No. At Risk	75	64	50	38	26
Patency (%)	100	95.7	88.2	86.1	86.1
SE	-	0.024	0.039	0.043	0.043

(D)



Survival	**0**	**6**	**12**	**18**	**24**
No. At Risk	**154**	**126**	**104**	**73**	**37**
Freedom from mortality(%)	**100**	**91.0**	**86.3**	**81.2**	**78.4**
SE	-	**0.024**	**0.029**	**0.036**	**0.040**

(E)



	0	**6**	**12**	**18**	**24**
No. At Risk	160	111	88	58	22
Freedom from reintervention (%)	100	80.9	74.0	68.6	62.2
SE	-	0.033	0.037	0.042	0.049

FIGURE 2 (A) Freedom from major and minor amputation through 24-months follow-up. (B) Amputation-free survival through 24-months follow-up. (C) Patency through 24-months follow-up. (D) Freedom from all-cause mortality through 24-months follow-up. (E) Reintervention free survival through 24-months follow-up [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Overview of reinterventions

# Reinterventionsper patient (N = 23)[a]	First reintervention Type (months[b])	Second reintervention Type (months[b])	Third reintervention Type (months[b])
3	Thrombolysis (6)	PBA target lesion (12)	Thrombolysis (24)
2	Thrombolysis (6)	Thrombolysis (12)	
2	Thrombolysis (6)	Surgical bypass (12)	
2	Surgical bypass (6)	Second open bypass (12)	
2	PBA target lesion (6)	PBA target lesion (24)	
2	Thrombolysis (1)	PBA target lesion (6)	
2	Additional endograft (12)	PBA target lesion (18)	
1	PBA target lesion (24)		
1	Thrombectomy (18)		
1	Surgical bypass (18)		
1	Surgical bypass (12)		
1	PBA target lesion (12)		
1	PBA target lesion (12)		
1	Surgical bypass (6)		
1	Surgical bypass (12)		

Abbreviation: PBA, plain balloon angioplasty.

[a]Reintervention details from nine patients, who underwent one reintervention was not available.

[b]Time in months since index procedure.

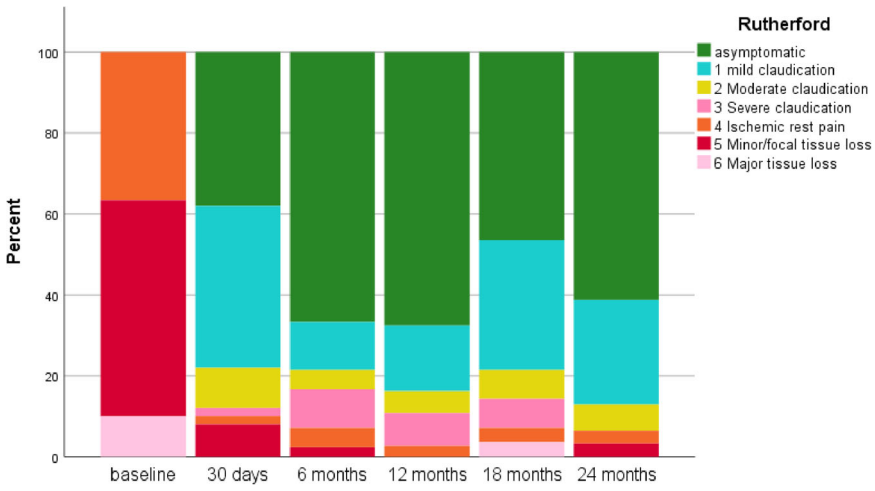


FIGURE 3 Overview of the Rutherford category distribution through 24-months follow-up [Color figure can be viewed at wileyonlinelibrary.com]

had a worse, 3, equal, and 46 had an improved Rutherford. The majority of cases showed ≥3 grades improvement.

Changes over time in the ABI are depicted in Figure 4. For the majority of cases, ABI at discharge was the last available measure. Comparing the difference in ABI between last measured and baseline showed a mean improvement of 0.41 ± 0.26. Through 2-year follow-up the median ABI was significantly increased ($p < 0.05$) from baseline for all time points. At 30-days the improvement was significantly improved from discharge ($p < 0.05$).

4 | DISCUSSION

In the present study, we have demonstrated that the use of the heparin-bonded Viabahn for long femoropopliteal lesions is associated with favorable clinical outcomes, with a clinical improvement in the majority of patients and limited major amputations through 24-months follow-up. The primary and assisted-primary patency rates, however, seem to be on the lower end of the spectrum when compared to date achieved in mixed IC/CLTI cohorts. Noteworthy are the

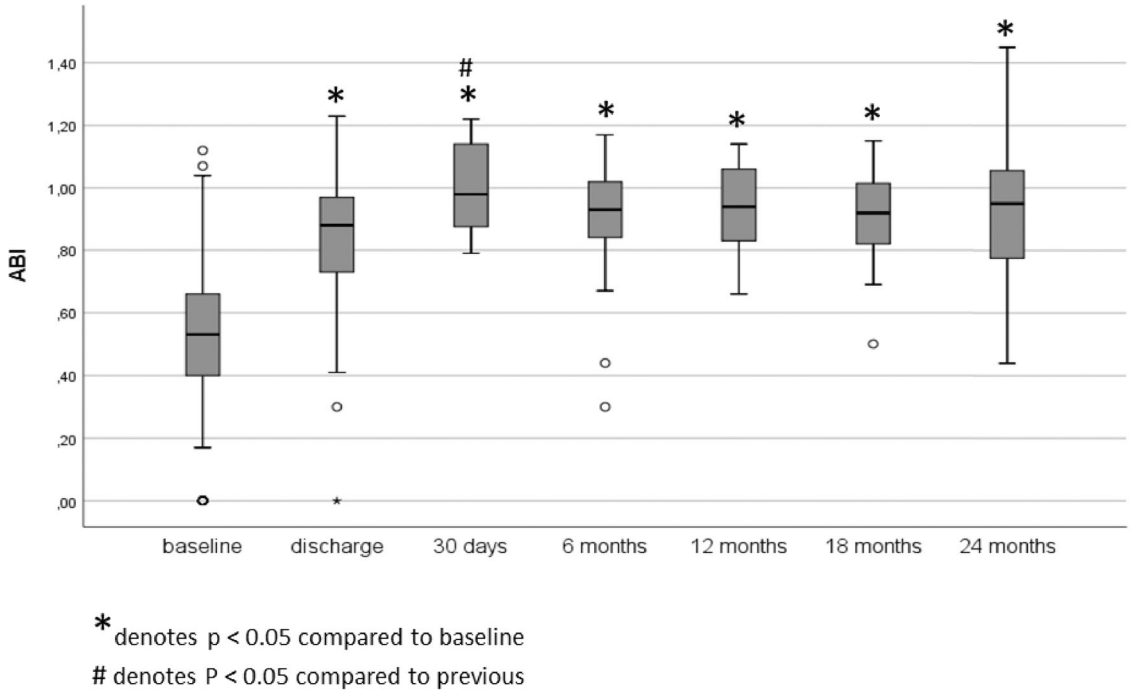


FIGURE 4 Ankle-brachial indices (ABI) through 24-months follow-up

secondary patency rates, 86.1% at 2-year follow-up. Consequently, the reintervention-free-survival was relatively low at 62.2% at 2 years, with the majority of reinterventions performed during the first year after treatment.

The need for reinterventions remains a drawback of endovascular therapy in general, and when using a Viabahn in particular, periodical ultrasound is recommended to detect restenosis and prevent subsequent occlusions. In a randomized controlled trial, the use of the heparin-bonded Viabahn yielded similar patency rates compared to the femoropopliteal bypass at 1-year, with a primary, primary-assisted, and secondary patency rate of 65%, 78%, and 86%, respectively, in a mixed cohort of patients with intermittent claudication (68%) and CLTI (32%).[8] The one-year data from the current meta-analysis are roughly in line with these results, suggesting that patients with CLTI might be treated with similar results compared with patients with intermittent claudication. The low incidence of major amputations is encouraging. It needs to be emphasized, however, that the current population is still on the relatively benign spectrum of the CLTI population, with only 9.2% treated for Rutherford 6. Therefore, the current data need to be interpreted with caution. This phenomenon has been observed before in studies on patients suffering from CLTI due to femoropopliteal lesions. Data derived from the IN.PACT Global Study, on the IN.PACT™ Admiral™ DCB (Medtronic), also showed good clinical results with freedom from major target limb amputation of 98.6% at 12-months and a clinical improvement of 89.0%.[16] The treated lesion length in that study was, however, significantly shorter, with an average of 16.1 cm compared with 28.0 cm in the current study, rendering comparisons untrustworthy. In another study, focusing on the outcomes of another DCB, the Passeo-18 Lux (Biotronik), in patients with CLTI the amputation rate at 12-months was 5.4%.[17] In that study, there were no differences in clinical outcomes of patients that were treated for femoropopliteal lesions or for below-the-knee pathology, although a nonsignificant trend was observed towards more amputations in the latter group.

The major advantage of an endovascular strategy over bypass surgery is related to its minimally invasive character, leading to fewer early complications, a shorter hospital stay, and earlier recovery in a patient cohort that is often frail.[8,18] In patients, undergoing bypass surgery for CLTI increased frailty is related to more complications, higher mortality, and more nonhome destination.[19] Frailty also correlates with the 2-year amputation-free survival rates.[20] The observed low 30-day mortality rate, in combination with the good clinical outcomes, further supports an endovascular first strategy in this subset of patients.

One of the commonly assumed drawbacks of the use of covered stents is the potential hazard of overstenting collateral arteries, particularly in patients with CLTI. In the case of an acute occlusion, this might worsen the clinical outcome, with more severely threatened limbs and subsequent amputations. In a previous study, it was shown that failure of the endoprosthesis in the femoropopliteal artery is not associated with a deterioration in clinical state and related to a low amputation rate,[21] challenging that assumption. In that study, the mean Rutherford category at the time of failure did not differ from the category as it was scored before the index procedure. The amputation rate after occlusion of the endoprosthesis was low at 4.1%, indicating that the clinical impact of overstenting collateral arteries might be limited. In another single-center study, however, it

was observed that reinterventions were common in the first year after placement of an endoprosthesis, in a group with 44% suffering from CLTI, with more than half of the events being a major adverse limb event (MALE).[21] In yet another study the same group concluded that failure modes of endoprosthesis may differ from bare-metal stents and that clinical consequences may not be benign, with more acute limb ischemia and a higher need for thrombolysis.[9] Since these publications, however, the endoprosthesis has been improved, incorporating the heparin-bonding technology and making the proximal edge contoured-shaped, preventing in-folding in case of oversizing. In addition, from the VIPER study it became apparent that excessive oversizing should be avoided to improve results.[5] In the current study, even though there were several patients with failures, the requirement of major amputation was low. In addition, no compartment syndromes were reported in any of the cases requiring thrombectomy or thrombolysis. It must be emphasized, though, that in the vast majority of patients the endoprosthesis did not extend below the P1 segment of the popliteal artery and therefore these statements cannot be generalized. It was previously described that about 19% of collaterals from the deep femoral artery and 72% of those deriving from the superficial femoral artery terminate in the most distal part of the SFA and the popliteal artery, emphasizing the potential importance of this artery in the collateral artery pathways.[22] Nevertheless, the estimated maximum collateral system flow of the SFA is only a fraction, with a range of 5%–20%, of the healthy SFA flow, indicating that other mechanisms are likely more decisive.[23]

The current study has limitations. First, not all available papers could be included in the analysis. Moreover, there were missing data on several variables in the datasets. Data on the clinical state at time of re-interventions could not be retrieved from the datasets of the various studies and as a consequence, the incidence of MALE at the time of thrombosis of the endoprosthesis could not be calculated in this study. In addition, the incidence of patients with Rutherford 6 was still low and therefore the current cohort may not be fully representative of real-world patient cohorts with CLTI. The results should therefore be interpreted with utmost care. In addition, no information was available on the time to wound healing, which is a key outcome in patients with CLTI. Finally, data for this particular analysis was limited to follow-up through 24 months, which is still relatively short. Longer follow-up in populations with Rutherford 4–6 are needed to draw robust conclusions for the efficacy of heparin-bonded covered stents in femoropopliteal lesions in patients with CLTI.

5 | CONCLUSION

Treatment of femoropopliteal disease in CLTI patients with the use of the heparin-bonded Viabahn is safe and effective with favorable clinical outcomes, low amputation rates, and technical outcomes that are in line with previously published literature in complex lesions. Reintervention is needed to maintain endoprosthesis patency, a close follow-up using duplex is recommended to detect potential edge stenosis.

CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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