LOWER LIMB REVASCULARIZATION WITH A NEW BIOACTIVE PROSTHETIC GRAFT: EARLY AND LATE RESULTS

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Lower Limb Revascularization with a New Bioactive Prosthetic Graft: Early and Late Results

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The aim of the study was to evaluate the immediate and long-term results of femoropopliteal bypasses performed with a new bioactive heparin-treated expanded polytetrafluoroethylene (ePTFE) graft in a single-center experience. From March 2002 to April 2006, 51 patients underwent lower limb revascularization with a new bioactive ePTFE prosthetic graft with covalent end-point attachment of heparin to the graft surface. Data concerning preoperative assessment, intraoperative strategy, drug administration, and follow-up surveillance program were prospectively collected in a dedicated database; early results were analyzed in terms of graft patency, amputation rate, and deaths. Follow-up consisted of clinical and duplex scan examination at 1, 6, and 12 months and yearly thereafter. Midterm results in terms of primary and secondary patency, limb salvage, and survival were analyzed. Patients were predominantly male (35 patients, 71%), with a mean age of 71 years (SD = 9.05). Indications for surgical revascularization were critical limb ischemia in 36 patients and severe intermittent claudication in 15 patients. Interventions were performed for occlusion of a native vessel in 35 cases, whereas 12 patients had late thrombosis of a femoropopliteal bypass; the remaining four patients were operated on for an occluded popliteal artery aneurysm. Intervention consisted of below-knee bypass in 34 patients, while the other 17 had an above-knee revascularization. No perioperative deaths occurred. Cumulative 30-day graft patency was 88%, with an amputation rate of 4% (two cases). Results were similar in above- and below-knee revascularizatons. Mean duration of follow-up was 18 months (SD = 7). Cumulative estimated 24-month survival and primary patency rates were 97% and 80.2%, respectively; the corresponding limb salvage rate was 85.7%. Long-term results did not significantly differ in above- and below-knee revascularizatons. In our experience, the use of a modified ePTFE graft with covalent end-point linkage of heparin molecules on the graft surface provides good early and midterm results, with low rates of graft thrombosis and amputation.

INTRODUCTION

Early and late graft occlusion is the main unsolved problem in lower limb revascularizations, despite attempts to develop an ''ideal'' small-diameter prosthetic vascular graft that is highly biocompatible and thrombosis-resistant.

Several studies and international consensus[1] have demonstrated that vein has better long-term patency than prosthetic grafts in the infrainguinal region. Prosthetic materials, particularly polytetrafluoroethylene (PTFE), provide near equivalent results in above-knee sites, while in below-knee revascularizations[2] mid- and long-term results of PTFE grafts are still poor, with <50% 2-year primary patency rates.

In low-flow and high-resistance situations, no synthetic graft has shown enough resistance to thrombosis to enable routine adoption in more demanding clinical applications such as below-knee bypass, particulary when autologous veins are not suitable.[3]

If one excludes technical errors and the progression of atherosclerosis in inflow and outflow vessels,

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the main cause of early graft thrombosis is an intrinsic graft thrombogenicity, whereas anastomotic myointimal hyperplasia in most cases leads to late failure of the revascularization.[4]

As a consequence, the reduction of graft thrombogenicity and the inhibition of neointimal formation seems to represent a logical strategy to prevent early and late graft thrombosis.

In recent years, several modified prosthetic vascular grafts have been developed and studied, with particular chemical, physical, and mechanical properties aimed at improving intrinsic thromboresistance; particularly, the use of heparin-bonded grafts has been proposed as an alternative to autologous vein to reduce both early thrombotic risk and late myointimal hyperplasia development, due to anti-inflammatory properties of this antithrombotic drug.[5]

Recently, a new bioactive PTFE graft with covalent end-point attachment of heparin to the graft surface, enabling maintenance of functional heparin bioactivity, has been developed; and its effectiveness in terms of improvement of early graft patency has been demonstrated in an experimental study;[6] recently, data from a multicenter study[7] demonstrated promising results in terms of early patency and limb salvage, even if follow-up was limited to 1 year. Moreover, we reported in a previous experience[8] initial satisfactory results with this modified graft in below-knee revascularizations compared with those obtained with standard expanded PTFE (ePTFE).

The aim of this study was to retrospectively evaluate the immediate and long-term results of above- and below-knee femoropopliteal bypasses performed with this new bioactive heparin-treated ePTFE graft in our experience.

MATERIALS AND METHODS

From March 2002 to April 2006, a new bioactive prosthetic graft (Propaten Gore-Tex®; W. L. Gore, Flagstaff, AZ), which consists of an ePTFE prosthetic graft with covalent end-point attachment of heparin to the graft surface, was implanted in 51 patients undergoing lower limb revascularization; the covalent end-point linkages maintain the catalytic bioactivity of the antithrombin sites of the bound heparin.[9]

Data concerning these patients were prospectively collected in a dedicated database containing main pre-, intra-, and postoperative parameters.

Early results were analyzed in terms of graft patency, amputation rate, and deaths. Differences in subgroups were assessed by the χ^2 test. Clinical and ultrasonographic follow-up was performed at 1, 6, and 12 months and then once a year. All studies were performed using the Acuson Sequoia 512 Ultrasound System (Acuson, Mountain View, CA). An 8L5 linear array probe with an operating frequency of 8.0-5.0 MHz was used in all cases.

Long-term results were analyzed by Kaplan-Meier curves, and differences in subgroups were assessed by the log-rank test.

Table I. Comorbidities and common risk factors for atherosclerosis

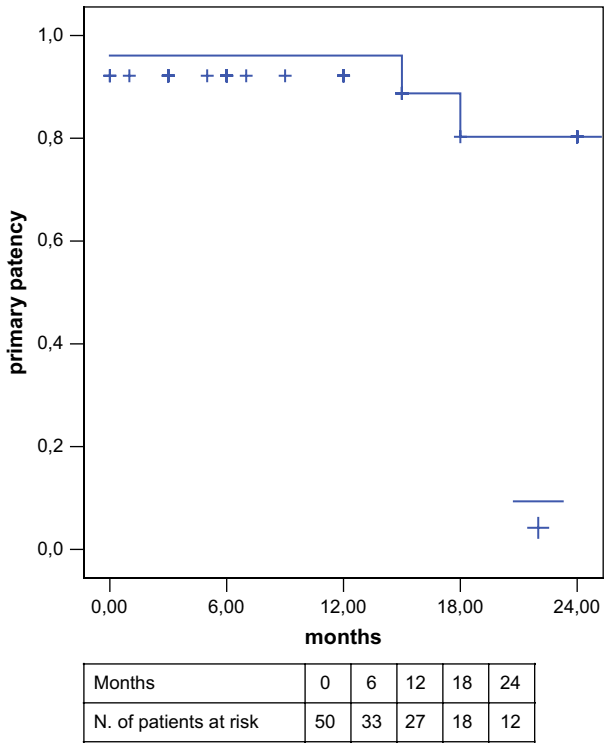
Arterial hypertension	39 (76.5%)
Smoking	37 (72.5%)
Diabetes	13 (25.5%)
Hyperlipemia	33 (64.7%)
Coronary artery disease	22 (43.1%)

RESULTS

Patients were predominantly males (35 patients, 71%), with a mean age of 71 years (standard deviation [SD] = 9.05). Comorbidities and main risk factors for atherosclerosis are summarized in Table I. Indications for surgical intervention were the presence of critical limb ischemia in 36 patients (Rutherford class 4 in 19 patients, class 5 in 14 patients, and class 6 in the remaining three); in 15 patients severe intermittent claudication (IIb degree according to the Fontaine classification and Rutherford class 3) was present (Table II). Interventions were performed in 35 cases for occlusion of a native vessel and in 12 patients for an occluded femoropopliteal bypass; four patients were operated on for an occluded popliteal artery aneurysm. In all patients undergoing below-knee bypass, preoperative duplex scanning of superficial veins of the limbs was performed, showing unsuitable autologous saphenous vein due to small diameter (<3 mm), valvular incompetence with varicose veins, previous phlebitis, and previous surgical harvesting. Mean preoperative ankle-brachial index in the affected limb was 0.42 (SD = 18). All patients were preoperatively treated with antiplatelet drugs. Intervention consisted of a below-knee bypass in 34 patients, and the remaining 17 had an above-knee revascularization. Distal targeted vessels are reported in Table II. Associated interventions were performed in 26 patients and consisted of proximal or distal patching in five patients, endovascular treatment of inflow or outflow vessel disease in four patients, and distal surgical thrombectomy in 17 patients. Intraoperative stop-flow thrombolysis[10,11] was used in 14 patients.

Table II. Clinical features (Fontaine and Rutherford classifications), run-off score, kind of intervention, and site of distal anastomosis

	n (%)
Severe claudication (IIB)	15 (29.5%)
Critical ischemia	
Rest pain	19 (37.3%)
Ulcers	17 (33.3%)
Rutherford class 3	15 (29.5%)
Rutherford class 4	19 (37.3%)
Rutherford class 5	14 (27.4%)
Rutherford class 6	3 (5.8%)
Run-off score	
0-1 vessels	34 (66.7%)
2-3 vessels	17 (33.3%)
Redo surgery	12 (23.5%)
Distal anastomosis	
Above-knee popliteal artery	17 (33.3%)
Below-knee popliteal artery	29 (56.7%)
Tibioperoneal trunk	5 (10%)



Months	0	6	12	18	24
N. of patients at risk	50	33	27	18	12

Fig. 1. Cumulative primary patency during follow-up.

All patients had intraoperative administration of 2,000 IU of i.v. heparin at arterial clamping; in all patients the postoperative drug protocol consisted of i.v. heparin administration (800-1,000 IU/hr) followed by oral anticoagulants in patients who had undergone below-knee bypass, to maintain the international normalized ratio (INR) range 2.0-3.0,[12] and double antiplatelet therapy in patients with above-knee revascularization.

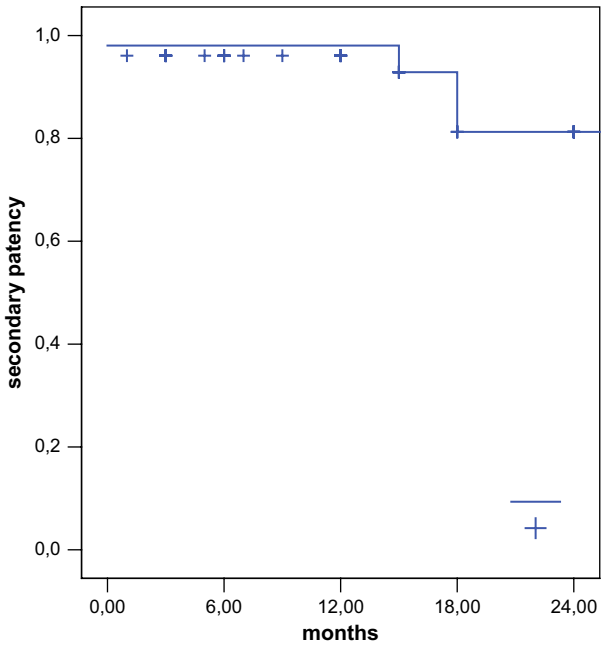
There were neither perioperative deaths nor severe bleeding; early (<30 days) graft thrombosis occurred in six patients (cumulative graft patency was 88%). All these patients were immediately reoperated on, and the intervention was successful in four cases. In two cases surgical revascularization was impossible and major amputation was performed, with a 30-day amputation rate of 4%. Results in terms of thrombosis and amputation rates were similar in above- and below-knee revascularizations; in fact, there were one (5.8%) thrombosis in the above-knee group and five (14.5%, p = non-significant [n.s.]) in the below-knee group and no amputations in the above-knee group and two (5.5%, p = n.s.) in the below-knee group.

Mean duration of follow-up was 18 months (range 1-60); all patiens had at least one postoperative clinical and ultrasonographic examination. During follow-up, one death, seven new graft thomboses, and four amputations occurred.

All graft thromboses during follow-up occurred in patients without significant lesions detected at follow-up duplex scanning examinations. Only two patients showed 60% stenoses at distal anastomoses; one patient had a <60% stenosis at distal anastomosis, and in three cases no significant lesions were found. The remaining patient had graft thrombosis due to occlusion of ipsilateral external iliac and common femoral arteries.

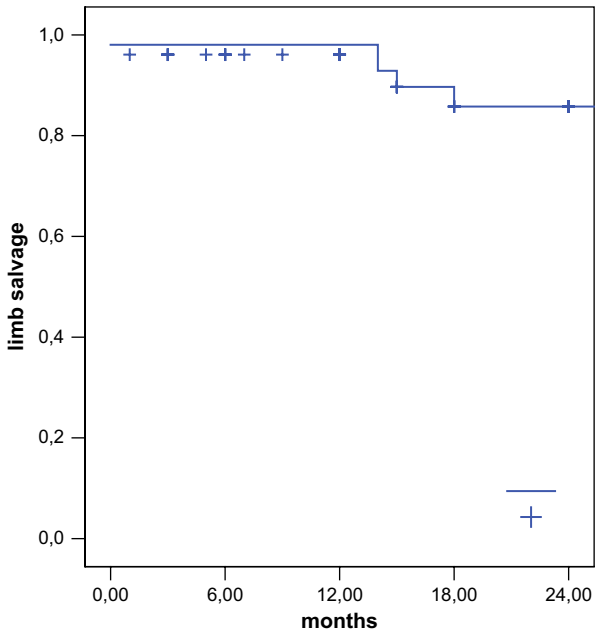
There were five reinterventions, in all cases due to graft thrombosis. In these patients intraoperative findings showed distal intimal hyperplasia causing graft occlusion in all but one patient, who had progression of atherosclerosis in his inflow vessels. In two cases the graft occluded without signs and symptoms of limb ischemia and the patients were medically treated. Cumulative estimated 24-month survival as well as primary and secondary patency rates were 97%, 80.2%, and 81.2% (Figs. 1 and 2), respectively. The corresponding limb savage rate was 85.7% (Fig. 3).

Follow-up results were similar in above- and below-knee revascularizations in terms of primary patency (78.6% and 80.6%, respectively; p = n.s.; log rank 4.1), secondary patency (80.6% and 81.3%, respectively; p = n.s.; log rank 1.1), and limb savage (90.1% and 83.6%, respectively; p = n.s.; log rank 10.5). Primary patency and limb savage rates were not affected by the need for reintervention, the level of revascularization, and preoperative clinical status, analyzed with both the Fontaine and Rutherford classifications.



Months	0	6	12	18	24
N. of patients at risk	50	37	30	18	12

Fig. 2. Secondary patency during follow-up.



Months	0	6	12	18	24
N. of patients at risk	50	37	30	18	12

Fig. 3. Cumulative limb salvage.

DISCUSSION

The main problem in lower limb revascularization is the not negligible rate of early and late failure, defined as the impossibility of maintaining graft patency, away from clinical manifestations of graft occlusion.

Data from meta-analysis and main mono- and multicentric series showed that the rate of graft failure, independently from preoperative clinical status, kind of graft, and site of distal anastomosis, ranges 25-35% at 2 years.[13,14] Most graft occlusions occur during the early postoperative period: when considering synthetic vascular graft, the rate of occlusions is 53 cases/1,000 patients/month in the first 3 postoperative months; the corresponding figures at 6 and 12 months are 21 cases/1,000 patients/month, whereas in following years the rate decreases to 10 cases/1,000 patients/month.[15]

Starting from these data, several studies have tried to identify the ideal vascular graft for peripheral revascularizations that is highly biocompatible and thrombosis-resistant.

Whereas the superiority of autologous veins over prosthetic grafts has been clearly demonstrated in below-knee revascularizations,[16] there is no consensus concerning the best synthetic vascular graft to be used when autologous veins are not suitable. In these situations, several authors have proposed the use of distal artery adjunct procedures, such as vein interposition of cuffs; however, results, even if promising, are limited by the small number of patients and the absence of comparison trials.[1]

For these reasons, in recent years, several attempts have been made to develop new prosthetic materials with increased intrinsic thrombosis resistance due to modifications of chemical and physical graft properties.

Particularly, the use of heparin bonded to biomaterial surfaces[17] has been proposed both to reduce graft thrombogenicity, which represents the main cause of early graft failure, and to inhibit the formation of myointimal hyperplasia at anastomotic sites, which usually leads to late graft occlusion.

Heparin not only provides a specific antithrombotic effect, due to its interaction with the thrombin–antithrombin system, but also shows intrinsic anti-inflammatory properties and can potentially lead in vivo to inhibition of the proliferation and migration of smooth muscle cells, which represents the main pathophysiological mechanism of neointimal hyperplasia.[18]

Several studies were published in the last decade concerning the use of heparin-coated synthetic

Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
,00	,00			1	50
,00	,00			2	49
,00	,00			3	48
,00	,00	,9216	,0376	4	47
,00	1,00			4	46
,00	1,00			4	45
1,00	1,00			4	44
3,00	1,00			4	43
3,00	1,00			4	42
3,00	1,00			4	41
3,00	1,00			4	40
3,00	1,00			4	39
5,00	1,00			4	38
6,00	1,00			4	37
6,00	1,00			4	36
6,00	1,00			4	35
6,00	1,00			4	34
6,00	1,00			4	33
7,00	1,00			4	32
9,00	1,00			4	31
12,00	1,00			4	30
12,00	1,00			4	29
12,00	1,00			4	28
12,00	1,00			4	27
15,00	,00	,8874	,0494	5	26
15,00	1,00			5	25
15,00	1,00			5	24
15,00	1,00			5	23
15,00	1,00			5	22
15,00	1,00			5	21
18,00	,00			6	20
18,00	,00	,8029	,0723	7	19
18,00	1,00			7	18
24,00	1,00			7	17
24,00	1,00			7	16
24,00	1,00			7	15
24,00	1,00			7	14
24,00	1,00			7	13
24,00	1,00			7	12
26,00	,00	,7360	,0922	8	11
26,00	1,00			8	10
28,00	,00			9	9
28,00	,00	,5888	,1188	10	8
28,00	1,00			10	7
30,00	,00	,5047	,1282	11	6
30,00	1,00			11	5
32,00	,00	,4038	,1366	12	4
36,00	,00	,3028	,1347	13	3
36,00	1,00			13	2
36,00	1,00			13	1
60,00	1,00			13	0

Life-table for figure 1

vascular grafts in lower limb revascularizations,[19-23] with great expectations but often conflicting results.

Particularly, there are few data in the literature[5,17,24] concerning the results of heparin-bonded ePTFE grafts.

The modified ePTFE graft we studied could represent an evolution in the development of bioactive synthetic vascular grafts; in fact, heparin does not simply cover the graft surface, as in most bonded grafts, but it is immobilized on the graft, producing a surface microstructure having stable, covalently bound heparin. The covalent end-point linkages maintain the catalytic bioactivity on the antithrombin sites of the bound heparin.[9] This peculiarity should lead to uniform surface heparinization and sustained in vivo heparin bioactivity; in other words, heparin would persist on the graft surface for a longer time, increasing its antithrombotic and anti-inflammatory properties.

A recent experimental study conducted on a canine carotid interposition model[6] demonstrated

Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
,00	,00			1	50
,00	,00	,9608	,0272	2	49
1,00	1,00			2	48
3,00	1,00			2	47
3,00	1,00			2	46
3,00	1,00			2	45
3,00	1,00			2	44
3,00	1,00			2	43
5,00	1,00			2	42
6,00	1,00			2	41
6,00	1,00			2	40
6,00	1,00			2	39
6,00	1,00			2	38
6,00	1,00			2	37
7,00	1,00			2	36
9,00	1,00			2	35
12,00	1,00			2	34
12,00	1,00			2	33
12,00	1,00			2	32
12,00	1,00			2	31
12,00	1,00			2	30
15,00	,00	,9288	,0410	3	29
15,00	1,00			3	28
15,00	1,00			3	27
15,00	1,00			3	26
15,00	1,00			3	25
15,00	1,00			3	24
18,00	,00			4	23
18,00	,00			5	22
18,00	,00	,8127	,0722	6	21
18,00	1,00			6	20
18,00	1,00			6	19
18,00	1,00			6	18
24,00	1,00			6	17
24,00	1,00			6	16
24,00	1,00			6	15
24,00	1,00			6	14
24,00	1,00			6	13
24,00	1,00			6	12
26,00	1,00			6	11
26,00	1,00			6	10
28,00	,00			7	9
28,00	,00	,6501	,1179	8	8
28,00	1,00			8	7
30,00	1,00			8	6
30,00	1,00			8	5
36,00	1,00			8	4
36,00	1,00			8	3
36,00	1,00			8	2
48,00	,00	,3251	,2373	9	1
60,00	1,00			9	0

Life-table for figure 2

that this modified bioactive ePTFE graft improved patency compared to untreated control ePTFE grafts; the patency difference, which was apparent early in the postimplant period and was sustained out to the 6-month end point, likely was attributable to inhibition of thrombus formation conferred by the immobilized heparin.

Our data confirm the results of experimental studies showing a satisfactorily low rate of early graft thrombosis; this study also confirms the fair results described in our previous report,[8] where this modified graft, used in below-knee revascularizations, was compared with autologous saphenous vein and standard ePTFE and was found to have poorer early and late results than autologous vein, as expected, but significantly better early and midterm primary patency rates than standard ePTFE.

Also, Bosiers and colleagues[7] reported good results in terms of early graft thrombosis and limb salvage with the examined graft, with a 30-day amputation rate of 4%, similar to the rate reported in our series.

Time	Status	Cumulative survival	Standard error.	Cumulative events	Number remaining
,000	1,00	.	.	1	50
,000	1,00	,961	,027	2	49
1,000	,00	.	.	2	48
3,000	,00	.	.	2	47
3,000	,00	.	.	2	46
3,000	,00	.	.	2	45
3,000	,00	.	.	2	44
3,000	,00	.	.	2	43
5,000	,00	.	.	2	42
6,000	,00	.	.	2	41
6,000	,00	.	.	2	40
6,000	,00	.	.	2	39
6,000	,00	.	.	2	38
6,000	,00	.	.	2	37
7,000	,00	.	.	2	36
9,000	,00	.	.	2	35
12,000	,00	.	.	2	34
12,000	,00	.	.	2	33
12,000	,00	.	.	2	32
12,000	,00	.	.	2	31
12,000	,00	.	.	2	30
14,000	1,00	,929	,041	3	29
15,000	1,00	,897	,051	4	28
15,000	,00	.	.	4	27
15,000	,00	.	.	4	26
15,000	,00	.	.	4	25
15,000	,00	.	.	4	24
15,000	,00	.	.	4	23
18,000	1,00	,857	,062	5	22
18,000	,00	.	.	5	21
18,000	,00	.	.	5	20
18,000	,00	.	.	5	19
18,000	,00	.	.	5	18
24,000	,00	.	.	5	17
24,000	,00	.	.	5	16
24,000	,00	.	.	5	15
24,000	,00	.	.	5	14
24,000	,00	.	.	5	13
24,000	,00	.	.	5	12
26,000	,00	.	.	5	11
26,000	,00	.	.	5	10
28,000	1,00	,772	,098	6	9
28,000	,00	.	.	6	8
28,000	,00	.	.	6	7
30,000	,00	.	.	6	6
30,000	,00	.	.	6	5
32,000	,00	.	.	6	4
36,000	,00	.	.	6	3
36,000	,00	.	.	6	2
36,000	,00	.	.	6	1
60,000	,00	.	.	6	0

Life table analysis for limb salvage

This modified graft seems to affect surface thrombotic processes, preventing graft thrombosis during the initial high-risk period for thrombotic failure; the mechanism of modulation of initial thrombus accumulation has been explained with a reduced platelet deposition on the graft surface, specifically correlated with the immobilized high antithrombin-affinity heparin fraction.[25] Moreover, the stable, long-lasting covalent linkage between the graft surface and heparin could influence not only the extrinsic, platelet-mediated pathways but also the intrinsic coagulation cascade. We did not find a significant difference in terms of early graft thrombosis between above- and below-knee bypasses; however, as expected, there was a higher percentage of graft thrombosis in below-knee revascularizations, and the difference, even if not statistically relevant, is likely clinically relevant.

Results at 24 months were satisfactory in our experience, with 2-year patency and limb salvage rates similar to those reported at 1-year follow-up by Bosiers et al.;[7] particularly in below-knee bypasses, our 24-month 80% primary patency compares favorably with the reported 24-month rate of 48.2% in a recent meta-analysis on infrainguinal ePTFE grafts.[2] It could be supposed that prolonged heparin bioactivity on the graft surface can somehow influence the formation of anastomotic myointimal hyperplasia; particularly, long-term patency rates may be significantly affected by reduced thrombus accumulation in the first several months after implant.[5] It could be hypothesized that sustained heparin activity may reduce thrombus accumulation, thereby decreasing the scaffold available for both midgraft and anastomotic remodeling events.

CONCLUSIONS

The development of a synthetic vascular graft with intrinsic high thromboresistance and low stimulus to intimal hyperplasia formation in lower limb revascularization is mandatory due to high failure rates of below-knee bypasses when an adequate autologous vein is not suitable. The modification of chemical properties of prosthetic grafts and their interaction with antithrombotic anti-inflammatory drugs seems, at the moment, a promising strategy.

In our experience, the use of a new modified ePTFE graft provides good early and midterm results, with low rates of graft thrombosis and amputation also in below-knee revascularizations, making it a potential alternative to autologous saphenous vein when it is absent, unsuitable, or of poor quality.

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