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Comparison of Carbon-impregnated and Standard ePTFE Prostheses in Extra-anatomical Anterior Tibial Artery Bypass: A Prospective Randomized Multicenter Study

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Objectives. *The aim of this study was to find out whether carbon impregnated ePTFE vascular grafts have better long-term patency or limb salvage rates than Standard ePTFE vascular grafts in crural revascularization in patients with chronic critical ischemia.*
Design. *Prospective randomized multicenter trial. Study endpoints were 36 months follow-up, major amputation or death.*
Materials. *We used 6 mm carbon ePTFE (Carboflo®) and 6 mm standard ePTFE vascular grafts (both C.R. BARD Inc./IMPRA).*
Methods. *From June 1995 to November 1998, 283 patients were randomly assigned either to carbon (C) (n=140) or to standard (St) ePTFE (n=143) vascular grafts at 19 centres. A standard protocol was used with lateral extra-anatomic course of the graft to the anterior tibial artery and of a distal vein patch or cuff. More than 90% of the patients had rest pain or gangrene.*
Results. *Two hundred and sixty-five (C=130; St=135) patients could be analysed in the intention-to-treat (ITT) group. Primary patency, secondary patency and limb salvage rates after 36 months were 33, 43 and 67% in the carbon– and 30, 38 and 58% in the standard PTFE group, respectively, (log-rank test: p=0.20, 0.12 and 0.16). Additional analyses were made per protocol (PP) and as-treated (AT). The retrospective power of the study was calculated as 79 and 83%.*
Conclusion. *The ITT, PP and AT analysis, showed no statistically significant advantage of the carbon ePTFE vascular graft in terms of patency or limb salvage over the standard ePTFE vascular graft at 36 months.*

Keywords: Prospective randomized multicentric trial; Polytetrafluoroethylene; Crural bypass, extraanatomic; Biomaterials, Carbon; Anterior tibial artery; Peripheral arterial occlusive disease (pAOD); Chronic critical ischemia.

Introduction

The results of crural artery reconstruction in patients with critical ischemia of the lower limbs is often unsatisfactory.[1–4] The use of autologous great saphenous vein is recognized as gold standard.[5–7] If vein is unsuitable or absent, prosthetic material is generally used when there is danger that amputation will be necessary.[1,4] A technological approach to improve the patency rate is to reduce the thrombogenicity of the implant material. Use of carbon as addition to ePTFE is one possibility. The additive use of carbon with implants has been explored since the early 1960s.[8–10] Owing to its excellent biocompatibility, carbon is used in implant materials for various medical applications and has been associated with reduced thrombogenicity.[11–21] In animal studies carbon-coated vascular prostheses demonstrate better patency rates[18,22–25] but the coating of PTFE with carbon has proven impractical due to the detachment of carbon particles from the surface.[26,27]

The ePTFE carbon vascular prosthesis (Carboflo®) used in the present study is a modification of the standard ePTFE vascular prosthesis (both C.R. Bard Inc./IMPRA, USA). Carbon particles have been permanently integrated into ePTFE structure by means of a special manufacturing process based on co-extrusion. The carbon thus becomes an integral insoluble constituent of approximately 25% of the ePTFE structure.[27–29] Several animal experiments have been carried out with this new ePTFE carbon vascular prosthesis.[27,30–32] The results of

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Tsuchida *et al.*[27] and of Babatasi *et al.*[31] revealed a significantly reduced thrombogenicity in the early post-operative phase. However, Akers *et al.* (1993)[30] and Ao *et al.*(2000)[32] did not detect a difference.

Up to the beginning of the present study, one prospective randomized trial of distal bypass and two in vascular access had been reported utilising Carboflo®.[33–36] Bacourt *et al.* reported encouraging results of the patency and limb salvage rates for the ePTFE carbon vascular prosthesis, however, a statistically significant difference could not be shown.[33,34] Trials of Carboflo® in vascular access have not found a difference in outcome.[35,36]

The objective of the present study was to test whether the carbon prosthesis has a clinical advantage with regard to cumulative primary and secondary patency or limb salvage rates in a larger very homogenous patient population with peripheral arterial disease (pAOD) and chronic critical ischemia.

Materials and Methods

Participating centers of various sizes from Germany and Austria were chosen (ranging from university to county hospitals) in order to ensure a representative cross section (Table 1). To include a homogenous patient population, special care was taken to standardize the outflow tract exclusively via the anterior tibial artery and to standardize operation technique by restricting to lateral extra-anatomic course of the bypass only,[37,38] with obligatory application of a distal vein patch/cuff.

Inclusion criteria

- Age over 18 years (adults only).
- Critical ischemia with rest pain and or necroses/gangrene (Fontaine stage III and IV) or severe claudication (Fontaine stage IIb) after unsuccessful conservative treatment over at least 2 months.
- Indication for femoro-crural bypass with anterior tibial artery as only or best suitable distal vessel.
- No suitable veins available to perform a venous bypass (unsufficient length, diameter less than 3 mm or varicose).
- Arterial vascular inflow tract without hemodynamically relevant stenoses.

The following further technical inclusion criteria and post-operative anticoagulation regime has been defined for both groups:

- Use of Carbon or Standard ePTFE vascular grafts (Carboflo®/Standard C.R. Bard Inc./IMPRA) to eliminate any other technical difference but the carbon impregnation.
- Proximal anastomosis to either: the limb of an aorto-femoral or cross-over prosthetic bypass, external iliac artery, common femoral artery, superficial femoral artery or deep femoral artery.
- Lateral extra-anatomical course of the bypass.[37,38]
- Distal anastomosis to the anterior tibial artery.
- Obligatory vein patch technique at the distal anastomosis with the following techniques: Linton patch,[39] Miller cuff,[40] Taylor patch[41] or St Mary's boot.[42]
- Intraoperative or post-operative angiogram for quality control.

Table 1. Participating centers and number of randomized patients (*n*)

Name	City	Clinic	*n*
Nestlé, Salzmann	Bad Nauheim	William Harvey Klinik	19
Albiker, Stockmann	Berlin	Franziskus Krankenhaus	60
Kindl, Schwilden	Esslingen	Städtische Kliniken Esslingen	23
Altstädt	Gütersloh	Städtisches Krankenhaus Gütersloh	3
Schröder, Riepe, Imig	Hamburg–Harburg	Allgemeines Krankenhaus Harburg	5
Dragojevic	Hannover	Klinikum Hannover Heidehaus	1
Bruckschlegl	Heidenheim	Klinikum Heidenheim	14
Müller–Reinartz, Husfeldt	Karlsruhe	Diakonissenkrankenhaus Karlsruhe	7
Hiemer, Uy, Gruß	Kassel	Diakonissen-Krankenhaus	5
Baumann, Mangold	Lahr	Klinikum Lahr-Ettenheim	16
Munteanu, Hamann	Leonberg	Kreiskrankenhaus Leonberg	15
Naundorf, Maurer	Munich	Klinikum rechts der Isar	4
Teßarek, Torsello	Münster	St Franziskus Hospital	14
Grögler, Reinhuber	Ravensburg	Krankenhaus St Elisabeth	24
Haug	Remscheid	Sana Klinikum Remscheid	25
Djibey, Glücklich	Rendsburg	Kreiskrankenhaus Rendsburg	17
Schareck	Rostock	Klinikum der Universität Rostock	1
Kapfer, Orend, Sunder-Plassmann	Ulm	Klinikum der Universität Ulm	21
Straßegger, Hagmüller	Vienna	Wilhelminen Spital	9
		Total	283

- Anticoagulation regime: perioperatively (primary) with heparin, afterwards with warfarin or, when contraindicated, Acetylsalicylacid (ASA).

Exclusion criteria

- Proximal anastomosis to an axillo-femoral bypass.
- Acute ischemia.
- Life expectancy less than 3 years.

Exclusively ePTFE vascular prosthesis of 6 mm diameter and thin-walled were chosen. The choice of using prosthesis with or without external spiral reinforcement was left to the operating surgeon due to the extra-anatomic course of the bypass.

The randomization sequence was generated as a block randomization (block size 2) using an SAS macro generated by a contract biometric institute (METRONOMIA GmbH, Munich). The randomization to either a carbon or standard PTFE vascular graft was carried out directly in the operating theatre by the surgeon just before the operation who opened the double-sealed, numbered envelopes in ascending order.

Post-operative follow-up examinations were made at the time of discharge from hospital and after 3, 6, 12, 18, 24 and 36 months.

The following study endpoints of post-operative follow-up were defined:

- Follow-up at 36 months,
- A major amputation or
- Death of the patient.

Additional follow-up examinations could be carried out at any time following adverse events and at the discretion of the managing physician. Furthermore, details on revision operations were documented. The data were entered on a triplicate print-through form and sent at regular intervals to an external independent contract biometric institute (METRONOMIA GmbH, Munich). This contract institute fulfils the quality norm ISO 9002 and works in accordance with the usual GCP guidelines. Data input was in a data bank environment with entry masks specifically adapted to the documentation forms. The data were entered twice by two members of staff independently of each other, to rule out typing errors. Discrepancies detected by tests of plausibility were clarified by written queries to the investigators. The data analysis was made by an experienced biometrician using the SAS system (version 8) under WINDOWS 2000.

Investigators and patients were not blinded to treatment assignment after the sealed envelopes have been opened for the further duration of the study. The external independent study statisticians/biometrician saw unblinded data.

The number of cases needed was calculated on the basis of the following assumptions:

In view of the encouraging results with carbon-impregnated prostheses reported in the studies of Bacourt, Tsuchida und Babatasi,[27,31,34] a one-sided hypothesis was formulated: '*carbon-impregnated prostheses have better patency rates and attain better limb salvage rates than standard ePTFE prosthesis*'. Data reported in the literature[1,3–6,34,37,38] indicate that the primary patency rate of the standard ePTFE grafts to crural arteries is about 40% after 36 months. A difference of 15% was considered to be clinically relevant with regard to the main parameter 'primary patency rate'. A power of 80% (β-error = 0.2) and an α-error of 5% enabled an evaluation of 135 patients per group. The loss to follow-up rate that was assumed with 10% per year. It was therefore, planned to recruit a total of 330 patients in two groups of 165 patients. The study protocol was approved by ethics committees and informed consent was delegated to the participating centres. An interim analysis at 1 year did not show a significant difference, thus the study was continued.

Differences between groups for nominal data were tested with the chi-square test or Fisher's exact test. Continuous variables were investigated for group differences using the *t*-Test for equality of means or with the Mann–Whitney-*U* test. The primary outcome measure primary and secondary patency and the limb salvage rates of the groups were compared on a univariate basis using life-table analysis and the log-rank test. The primary analysis was made on an intention-to-treat (ITT) basis. A per protocol (PP) and an as-treated (AT/or treatment received) analysis were also calculated. The ITT, AT and PP-analysis sets included only patients who comply with the inclusion criteria and have received one of the two graft types evaluated (Fig. 1).[43] A retrospective power analysis of the final study has been performed.

The reporting standard according to Rutherford *et al.*[44] and the CONSORT statement[45,46] were followed.

Results

Randomization, study flow, treatment groups

In the period from June 1995 to November 1998, 283 patients in 19 centres were allocated on a random basis to bypass with either Carbon PTFE (n = 140 C) or Standard PTFE (n = 143 St) prosthesis. Eight patients

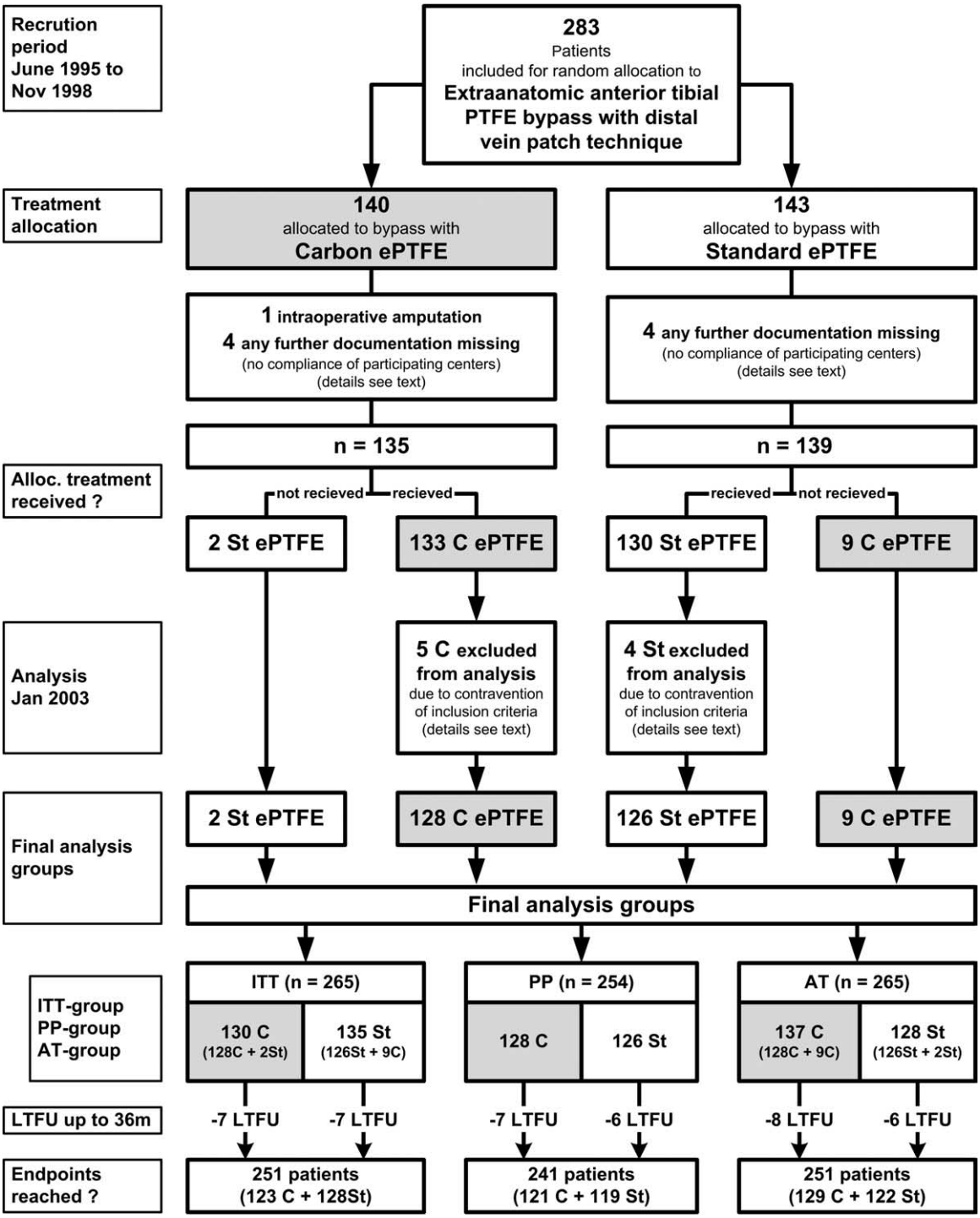


Fig. 1. Flow diagram of the study acc. to CONSORT statement: randomization and analysis groups (C, carbon PTFE; St, standard PTFE; ITT, intention-to-treat; PP, per protocol; AT, as-treated; m, month; LTFU, lost-to-follow-up/did not reach defined study endpoints).

were not further documented due to lack of compliance of the participating centers (six for unknown hospital-internal reasons, two received an ePTFE prosthesis of another brand), one patient underwent an amputation intra-operatively before receiving the prosthesis.

Eleven patients (C=2/St=9) did not receive the prosthesis assigned by the randomization due to

Table 2. Baseline demographics and vascular risk factors of the intention-to treat (ITT) groups at the date of operation. Pre-operative Fontaine stage, pain-free walking distance and ankle-brachial-index

	Carbon ($n=130$)	Standard ($n=135$)	p-value	d.f.
Gender: n (%)				
Male	60 (46%)	54 (40%)	0.32*	1
Female	70 (54%)	81 (60%)		
Median age: (years) (range)	73 (37–91)	75 (49–90)	0.14†	1
Height: (cm) mean ± SD	168 ± 9	167 ± 9	0.33†	1
Weight: (kg) mean ± SD	70 ± 12	67 ± 13	0.05†	1
BMI: (kg/m^2) mean ± SD	24.6 ± 3.7	23.7 ± 4.0	0.07†	1
Vascular risk factors: n (%)				
CHD	80 (63%)	84 (62%)	1.00‡	1
Hypertension	85 (65%)	89 (63%)	1.00‡	1
Hyperlipidemia	61 (47%)	52 (39%)	0.17‡	1
Diabetes mellitus	60 (46%)	63 (47%)	1.00‡	1
Smoking (acc. to Rutherford[44]): n (%)				
None	86 (66%)	93 (69%)	0.91‡	3
Not current	6 (5%)	7 (5%)		
Current	37 (29%)	34 (25%)		
No data	1 (1%)	1 (1%)		
pAOD stage acc. to Fontaine: n (%)				
IIb (severe claudication)	11 (8.5%)	7 (5.2%)	0.55‡	2
III (rest pain)	43 (33.1%)	44 (32.4%)		
IV (necrosis/gangrene)	76 (58.5%)	84 (62.2%)		
Pain-free walking distance: (m) median (range) ($n=205$)	10 (0–115)	10 (0–160)	0.73§	1
ABI index¶:				
ABI treated limb ($n=239$) median (IQR)	0.36 (0.13–0.50) ($n=114$)	0.35 (0.14–0.53) ($n=125$)	0.68§	1
ABI untreated limb ($n=206$) median (IQR)	0.75 (0.59–1.00) ($n=100$)	0.70 (0.53–0.93) ($n=106$)	0.06§	1

(BMI, body-mass-index; CHD, coronary heart disease; ABI, ankle-brachial-index; SD, standard deviation; IQR, inter quartil range; d.f., degrees of freedom.
* Pearson chi-square test.
† t-test for equality of means.
‡ Fisher's exact test.
§ Mann–Whitney-U test.
¶ Only ABI indices below 1.5 included.

surgeon preference ($n=7$) or availability of the assigned graft ($n=4$).

A further nine patients were excluded from all analyses of the principal parameters owing to contraventions of the inclusion criteria (C = 5: proximal anastomosis at an axillo-femoral bypass $n=1$, patients already with contralateral extremity in study $n=4$; St = 5: no vein patch at distal anastomosis $n=2$, patch technique with PTFE $n=1$, a priori candidate for amputation $n=1$). A complete flow diagram of the study according to the CONSORT statement[45,46] is shown in Fig. 1.

A total of 265 patients entered the ITT (C = 130/St = 135) and AT (C = 137/St = 128) population. Fourteen patients were lost to follow-up (LTFU). Thus two hundred and fifty-one patients reached the defined study endpoints in the ITT and AT analysis groups. The per protocol (PP) population comprised 254 patients. Thirteen patients were LTFU in the PP population, so that 241 patients reached the defined evaluation endpoints in this group.

Demographic and clinical data

Table 2 show the demographic and clinical data of the ITT population. More than 90% of the patients were in Fontaine stages III (33%) and IV (60%) with rest pain and/or necroses/gangrene. The parameter 'walking distance' was not evaluated in 58 patients. This was due to the patient being bedridden, requiring wheelchairs or because of a pre-existing contralateral amputation ($n=15$). The ankle-brachial-index (ABI) according to the American Heart Association (AHA) standards[47] could be calculated for the affected side in 239 patients and for the unaffected side in 206 patients. Pseudohypertensive values of more than 1.5 (e.g. media sclerosis) were not considered[48,49] (Table 2).

Previous ipsilateral arterial operations were reported in 150 patients (57%), 69 of these in the carbon group and 81 in the standard group (Fisher's exact test, $p=0.27$). More than one-third of patients ($n=99$/37%, C = 44/St = 55) had undergone previous infrainguinal bypass. An aorto-iliac operation had been previously carried out in 23 (9%, C = 10/St = 13)

Table 3. Run-off: overview of all patients in the ITT group ($n=265$)

Distal anterior tibial artery		Plantar arch			
	Total *n* (%)	Complete *n* (%)	Incomplete *n* (%)	Not assessed/no assessment possible *n* (%)	No data *n* (%)
Patent, without stenosis	169 (63.8%)	60 (22.6%)	65 (24.5%)	38 (14.3%)	6 (2,3%)
Patent, but stenosed	89 (33.6%)	6 (2.3%)	68 (25.7%)	12 (4.5%)	3 (1.1%)
Occluded	5 (1.9%)		2 (0.8%)	3 (1.1%)	
No complete data	2 (0.8%)		1 (0.4%)		1 (0.4%)
Total	265 (100.0%)	66 (24.9%)	136 (51.3%)	53 (20.0%)	10 (3.8%)

Results of pre-operative angiographic assessment of the distal anterior tibial artery and the plantar arch.

patients. Seventeen patients (7%, C=10/St=7) had undergone aorto-iliac and infrainguinal reconstructions previously. No location has been specified in 11 (4%, C=5/St=6) of the cases. (Fisher's exact test, 4 d.f., $p=0.64$). Bypass implantation ($n=102$) including combinations with angioplasty/Stent and endarterectomy were the most frequent form of previous ipsilateral therapy. The remaining 48 patients had angioplasty ($n=24$), stents ($n=3$) or endarterectomy ($n=12$) or non-specified procedures ($n=9$), (Fisher's exact test, 5 d.f., $p=0.28$).

Outflow tract

Table 3 shows a complete overview on the run-off status of the overall patient population, a more detailed description of the outflow tract for the two groups is shown in Fig. 2. The prognostic favourable situation with distal patent anterior tibial artery and simultaneous complete plantar arch was found in only 60 patients (23%). There was no difference in run-off between the two groups in any of the four subgroups shown in Fig. 2. (Fisher exact test, $p>0.05$ for the groups and subgroups).

Operation data and post-operative anticoagulation/thromobocyte aggregation regime

There were no significant differences with regard to the data of the surgical technique, such as operation time, external spiral reinforcement used, location of the proximal anastomosis, the kind of distal vein patch

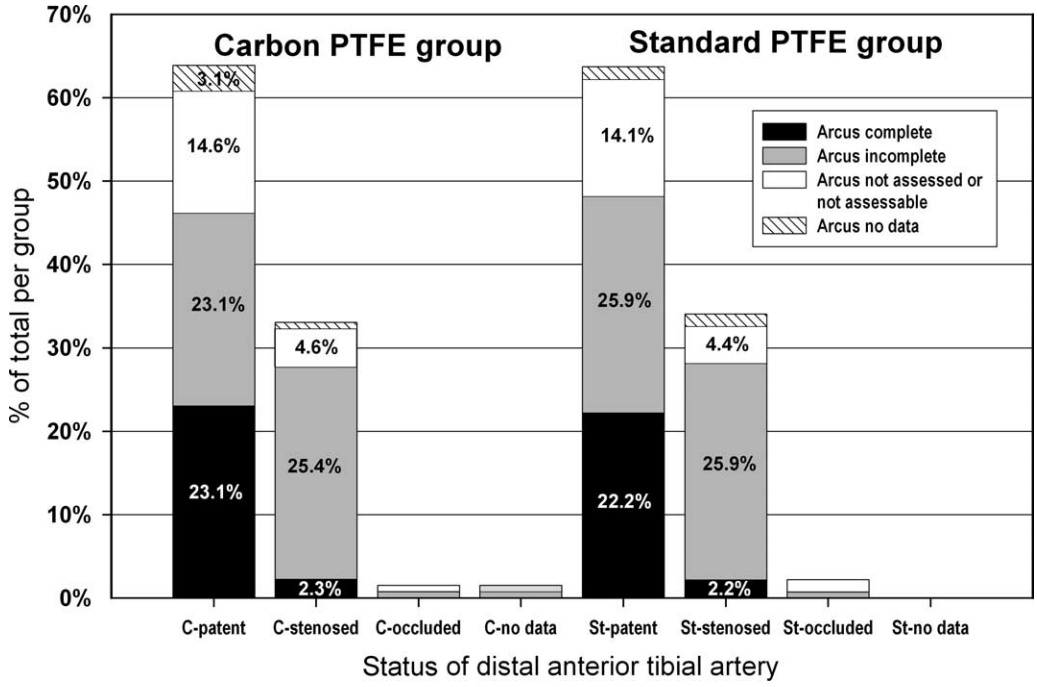


Fig. 2. Pre-operative angiographic run-off status of the anterior tibial artery and plantar arch in the carbon and standard PTFE group ($n=265$; ITT-analysis; Arcus, plantar arch; patent, patent-no relevant stenosis; stenosed, patent-but relevant stenosed; occluded, distal occlusion; values below 2% not numbered; Fisher's exact test $p>0.05$ for all groups and subgroups).

Table 4. Surgical technique, operative data, hospital stay–ITT

	Carbon ($n=130$)	Standard ($n=135$)	p-value	d.f.
Operation time: (min) median (IQR)	140 (115–185)	140 (106–180)	0.79*	1
Prosthesis with external spiral reinforcement: n (%)				
Yes	79 (61%)	78 (58%)	0.71†	1
No	51 (39%)	57 (42%)		
Location of proximal anastomosis: n (%)				
Limb of aorto-femoral prosthesis	14 (11%)	15 (11%)	0.94†	5
External iliac artery	8 (6%)	7 (5%)		
Common femoral artery	87 (70%)	94 (70%)		
Superficial femoral artery	11 (9%)	13 (10%)		
Deep femoral artery	9 (7%)	5 (4%)		
No data	1 (1%)	1 (1%)		
Type of distal vein patch technique: n (%)				
Taylor patch	78 (60%)	80 (59%)	0.85†	3
Linton patch	45 (35%)	49 (36%)		
St Mary's boot	6 (5%)	4 (3%)		
Miller cuff	1 (1%)	2 (2%)		
Intraoperative Heparin, admin.: n (%)				
Systemic	52 (40%)	57 (42%)	0.81†	3
Local	19 (15%)	23 (17%)		
Systemic and local	57 (44%)	54 (40%)		
No data	2 (2%)	1 (1%)		
Intraoperative Heparin, dosage: I.U. median (IQR)	5.000 (5.000–7.500)	5.000 (5.000–7.500)	0.93*	1
Intraoperative angiogram: n (%)	86 (66%)	93 (69%)	0.60†	1
Immediate bypass occlusion (<24 h): n (%)	10 (8%)	14 (10%)	0.67†	1
Hospital stay, post op: (days), median (IQR) ($n=204$); (C=26, St=35 no data)	26 (16–35)	24 (17–41)	0.12‡	1

d.f., degrees of freedom.
* Mann–Whitney-U test.
† Fisher's exact test.
‡ t-test for equality of means.

technique, intraoperative administration of Heparin, intraoperative angiogram, immediate bypass occlusion and hospital stay (Table 4). Simultaneous procedures on the inflow tract in the iliac region and the bifurcation of the femoral artery were performed in 18 patients (7%). This involved 11 endarterectomies, three bypasses, one endarterectomy and bypass, two angioplasties and one type not specified. In nine patients (C=3/St=6), 11 intraoperative complications were documented. These included five venous injuries, three dissections, two perforations and one plaque disruption. The two treatment groups did not differ with regard to the occurrence of simultaneous procedures (Fishers exact test, 4 d.f., $p=0.66$) and intraoperative complications (Fisher's-exact test, 3 d.f., $p=0.33$).

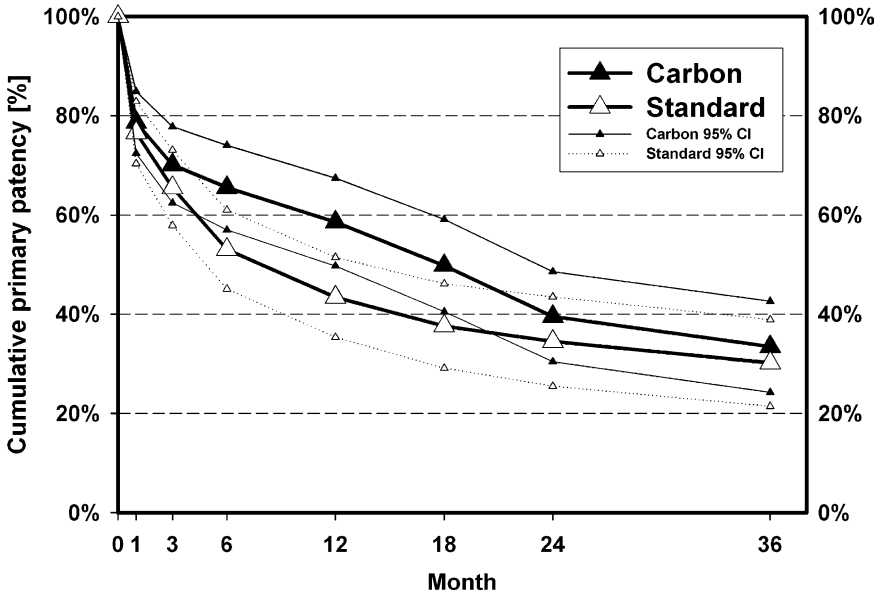
The status of the post-operative anticoagulation was evaluated in 253 patients at the time of discharge from hospital to check for group differences (five patients were already deceased and seven had prior major amputations within the hospital). In 55% ($n=138$) patients were receiving warfarin, 30% ($n=75$) of the patients were on Acetysalicylacid (ASA) and 11% ($n=27$) on heparin at this time. Five patients have received ASA in combination with other anticoagulation drugs (two ASA+Heparin, three ASA+Tiplopidin). Five received other types of anticoagulation (one LMWH, one Clopidogrel, one Danaparanoid-Natrium, two Ticlopidin). No data on the applied anticoagulation regime has been recorded for three patients. There were no differences between the groups (Fisher's exact test, 10 d.f., $p=0.44$).

Redo procedure, infections, 30-days mortality rate:

Redo procedures were performed in 15 cases (nine bypass explantations (2<30d/7>30d), six new bypasses) (Fisher's exact test, 2 d.f., $p=0.62$). These patients were rated as secondary occluded at the time of the redo operation, even if the redo procedure was successful.[44] Thirteen (4.9%) bypass infections of which 3 (1.1%) have been before 30 days and five (1.9%) seroma formations were recorded during the follow-up period. 30-days mortality rate was 3.4% ($n=9$).

Patency and limb salvage rates analysis

The detailed data of the life table analysis of the primary (PrimPat), secondary patency rates (SecPat) and the limb salvage rate (LSalv) for the two groups are shown in the figures (Figs. 3–5) and tables (Tables 5–7). At 36 months, 33% of grafts were still primary



Month	0	1	3	6	12	18	24	36
Carbon (*n*)	130	96	78	70	55	44	34	26
Standard (*n*)	135	99	80	63	47	37	32	28

Fig. 3. Life table curves for primary patency rate acc. to Rutherford *et al.*[44], carbon- *vs.* standard-PTFE vascular grafts; ITT analysis (log-rank test $\chi^2=1.65$, 1 d.f.; $p=0.20$); standard-error $<5\%$ at all times; table indicates number of patients (n) at risk at begin of each intervall.

patent in the carbon group and 30% in the standard group. The SecPat at 36 months was 43% in the carbon group and 38% in the standard group. The LSalv was 67% in the carbon group and 58% in the standard group. The 95% confidence intervals (95% CI) of both groups did not overlap in SecPat between 6 and 12 months. During all other intervals for SecPat and in all intervals for PrimPat and LSalv the 95% CI did overlap (Tables 5–7 and Figs. 3–5). The obvious nominal differences between 6 and 18 months in favour of the carbon group did not lead to a statistically significant difference. In our life table analysis results have been curtained at 36 months as the number of remaining patients at risk have reached only 20% ($n=54$) of the original patient population ($n=265$). Results in these later intervals are also biased by the high degree of loss to follow-up.

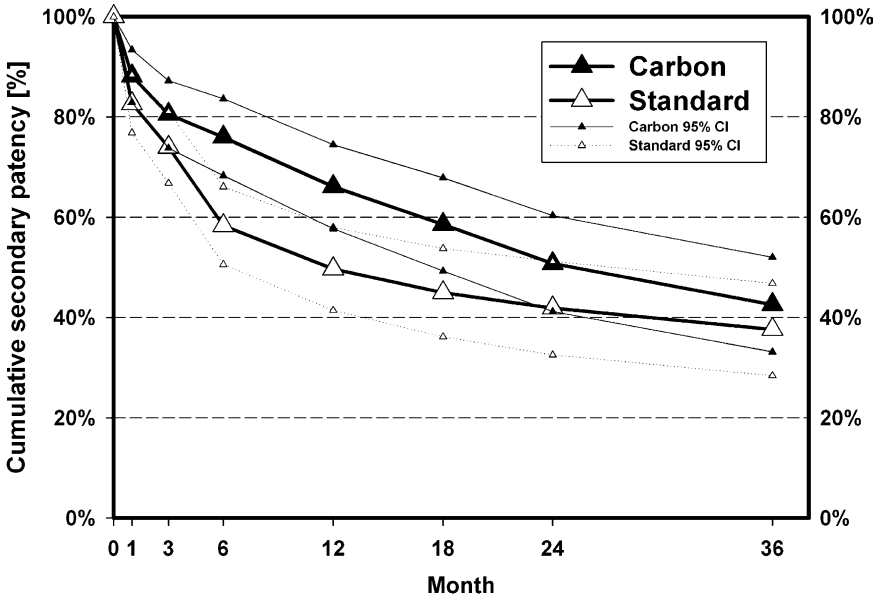
Comparison of the group evaluations and power analysis

The PP and AT analysis did not show any qualitative difference from the ITT analysis (Table 8). The alternative hypothesis according to which 'carbon-impregnated prosthesis have better patency or limb salvage rates than standard ePTFE prostheses' hence could not be accepted. The null hypothesis ('carbon-impregnated prostheses do not have better patency or limb salvage rates') is valid for all three analysis groups.

The retrospective power analysis of the ITT set showed a power of 79%. For this computation the sample size 265 patients (C=130, St=135) and the observed lost-to-follow-up rate (5.3%, 14/265) was used. That means that a study with 135 patients in the control group and 130 in the treatment group has a chance of 79% (=power) to show a difference between a patency rate of 40% in the Standard PTFE group and a patency rate of 55% in the Carbon PTFE group, using a one-sided log-rank test with alpha equals 5%; given a lost-to follow-up rate of 5.3%. When using the final patency rate of 30.7% for the Standard group with a 15% difference for the Carbon group a power of 83% was calculated for the ITT set. This means that the study was large enough in order to detect a difference of 15% points between carbon and standard PTFE grafts in case this difference is true (but unknown). The power analysis computations were performed with *n* Query Advisor Version 5.0.

Discussion

One of the main problems in crural bypass surgery is choice or availability of suitable bypass material. The autologous great saphenous vein (GSV) is the material



Month	0	1	3	6	12	18	24	36
Carbon (*n*)	130	108	91	81	63	53	45	35
Standard (*n*)	135	107	91	70	55	45	40	34

Fig. 4. Life table curves for secondary patency rate acc. to Rutherford *et al.*[44], carbon- *vs.* standard-PTFE vascular grafts; ITT analysis (log-rank test $\chi^2 = 2.46$, 1 d.f.; $p = 0.12$); standard-error < 5% at all times; table indicates number of patients (*n*) at risk at begin of each interval.

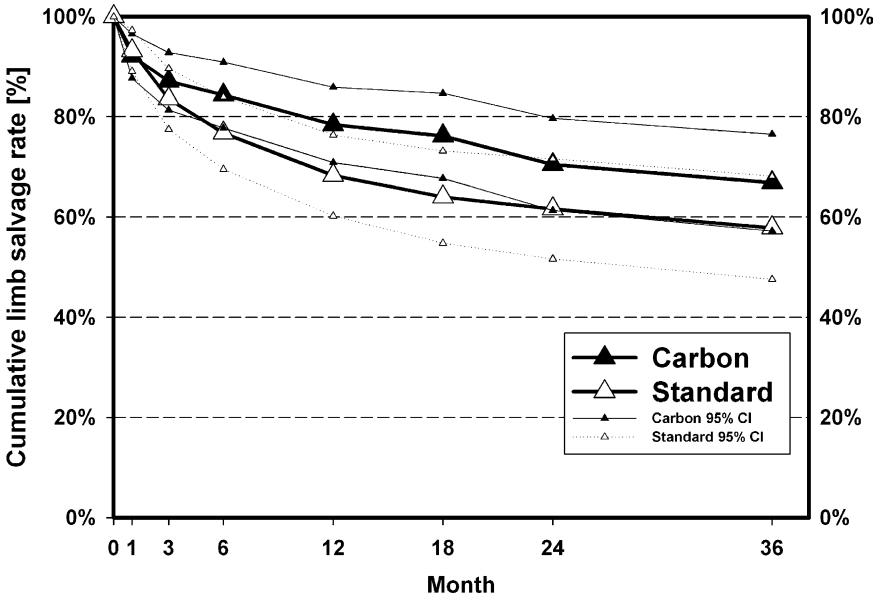
of first choice, but is unavailable in up to 28% of patients owing to prior coronary bypass surgery, varicose veins surgery, prior arterial reconstructions, insufficient vein calibre and prior thrombophlebitis.[50]

In this prospective, randomized and multicenter study, the effect of a physically and chemically insoluble carbon impregnation of ePTFE prosthesis on clinical outcome was investigated by comparison with standard ePTFE prosthesis of the same kind. The principal parameters evaluated were the primary (PrimPat) and secondary patency rate (SecPat) and the limb salvage rate (LSalv). Important factors affecting these parameters are the outflow tract and the kind of bypass procedure, which were tightly controlled. Use of a vein patch technique at the distal anastomosis[39–42,51,52] was an indispensable prerequisite in the present study, but the technical implementation was left to the surgeon's discretion in order to rule out additional sources of technical error. With these restrictions we have compared two very homogeneous patient groups.

As suggested by Meichelböck in 2002,[53] the outflow tract was described in terms of the condition of the anterior tibial artery and the hollow of the foot (Fig. 2). Descriptive angiographic data enable a differentiated evaluation of the outflow tract. Schweiger *et al.*[3] also point to the crucial significance of the outflow tract for the prognosis of bypass extending beyond the knee joint. The method suggested by Meichelboeck[53] appeared to us to be more effective for practical clinical use than the well-known appraisal of the outflow tract according to Rutherford.[44]

By using a material with a reduced thrombogenicity we would have expected differences in the early post-operative phase up to 30 days. But we did not see any difference in the immediate occlusion up the 24 h (Table 4) and in the further early course up to 30 days. In total 39% of all occlusions in the Carbon and 36% of all occlusions in the Standard grafts occurred in the early period up to 30 days, suggesting that a significant number of graft failures could be related to technical problems. Less occlusions in favour of the carbon prosthesis were recorded in the period between one and 6 months. In the interval between 6 and 18 months the life table curves of both groups run almost parallel, while the standard PTFE prosthesis seems to have a quantitative advantage later than 18 months (Figs. 3–5).

The life tables for PrimPat, SecPat and LSalv presented are shown consistently in accordance with the revised Rutherford recommendations.[44] All cumulative patency calculations were made not at the beginning of an interval, but at the end. This leads to a formal worsening of the results, but gives a more precise picture of the actual course. Consequently, our results cannot be compared directly with 'former' literature, which has been calculated according the



Month	0	1	3	6	12	18	24	36
Carbon (*n*)	130	114	99	90	74	67	61	53
Standard (*n*)	135	120	101	87	67	56	51	44

Fig. 5. Life table curves for limb salvage rate acc. to Rutherford *et al.*[44], carbon- *vs.* standard-PTFE vascular grafts; ITT analysis (log-rank test $\chi^2 = 1.96$, 1 d.f.; $p = 0.16$); standard-error < 5.3% at all times; table indicates number of patients (*n*) at risk at begin of each interval.

recommended standards of Rutherford 1986[54] at the beginning of each interval.

In a meta-analysis, Albers *et al.*[55] showed pooled results for PTFE bypass to infrapopliteal arteries for primary patency ($n = 40$ studies), secondary patency ($n = 35$ studies) and limb salvage ($n = 31$ studies). The results at 36 months were 41, 51 and 66%, respectively. However, it was shown that there is a marked difference in the results for PrimPat, SecPat and LSalv between 'qualitatively good' and 'qualitatively less good' studies. In a total of 43 publications investigated, only ten reported on a patient number in excess of 100. Of these, only five[3,56–59] attained a rating of more than 10 points in quality scoring used (maximum 14 points).

Table 5. Life tables primary patency rate according to Rutherford *et al.*[44], carbon *vs.* standard PTFE vascular grafts, ITT (log-rank test $\chi^2 = 1.65$, 1 d.f.; $p = 0.20$) (LTFU, lost-to-follow-up; CI, confidence interval)

Interval (month)	No. at risk at start of interval (*n*)	No. failed during interval (*n*)	Withdrawn during interval (*n*) due to			Interval failure rate	Cumulative patency rate, (95% CI%)	Standard error (%)
			Death	LTFU	Duration			
Carbon PTFE								
0–1	130	27	5	2	0	0.2134	78.7% (72.4–84.9)	3.2
1–3	96	10	6	2	0	0.1087	70.1% (62.4–77.8)	3.9
3–6	78	5	1	2	0	0.0654	65.5% (57.0–74.1)	4.4
6–12	70	7	7	1	0	0.1061	58.6% (49.8–67.4)	4.5
12–18	55	8	3	0	0	0.1495	49.8% (40.5–59.1)	4.8
18–24	44	9	1	0	0	0.2069	39.5% (30.4–48.6)	4.6
24–36	34	5	3	0	0	0.1538	33.4% (24.3–42.6)	4.7
Total		71	26	7	0			
Standard PTFE								
0–1	135	31	2	3	0	0.2340	76.6% (70.3–82.6)	3.2
1–3	99	14	4	1	0	0.1451	65.5% (57.9–73.1)	3.9
3–6	80	15	2	0	0	0.1899	53.1% (45.1–61.0)	4.1
6–12	63	11	5	0	0	0.1818	43.4% (35.4–51.5)	4.1
12–18	47	6	2	2	0	0.1333	37.6% (29.1–46.1)	4.3
18–24	37	3	1	1	0	0.0833	34.5% (25.5–43.5)	4.6
24–36	32	4	0	0	0	0.1250	30.2% (21.4–38.9)	4.5
Total		84	16	7	0			

Table 6. Life tables secondary patency rate, according to Rutherford *et al.*[44], carbon *vs.* standard PTFE vascular grafts, ITT (log-rank test $\chi^2=2.46$, 1 d.f.; $p=0.12$) (LTFU, lost-to-follow-up; CI, confidence interval)

Interval (month)	No. at risk at start of interval (*n*)	No. failed during interval (*n*)	Withdrawn during interval (*n*) due to			Interval failure rate	Cumulative patency rate, (95% CI%)	Standard error (%)
			Death	LTFU	Duration			
Carbon PTFE								
0–1	130	15	5	2	0	0.1186	88.1% (82.9–93.4)	2.7
1–3	108	9	6	2	0	0.0865	80.5% (73.8–87.2)	3.4
3–6	91	5	3	2	0	0.0565	76.0% (68.3–83.6)	3.9
6–12	81	10	7	1	0	0.1299	66.1% (57.7–74.5)	4.3
12–18	63	7	3	0	0	0.1138	58.6% (49.3–67.9)	4.8
18–24	53	7	1	0	0	0.1333	50.8% (41.2–60.4)	4.9
24–36	45	7	3	0	0	0.1609	42.6% (33.2–52.0)	4.8
Total		60	28	7	0			
Standard PTFE								
0–1	135	23	2	3	0	0.1736	82.6% (76.8–88.5)	3.0
1–3	107	11	4	1	0	0.1053	73.9% (66.8–81.1)	3.7
3–6	91	19	2	0	0	0.2111	58.3% (50.6–66.1)	4.0
6–12	70	10	5	0	0	0.1481	49.7% (41.4–58.0)	4.2
12–18	55	5	3	2	0	0.0952	45.0% (36.1–53.8)	4.5
18–24	45	3	1	1	0	0.0682	41.9% (32.6–51.2)	4.8
24–36	40	4	2	0	0	0.1026	37.6% (28.4–46.8)	4.7
Total		75	19	7	0			

In their extensive retrospective study of 1993, Schweiger *et al.*[3] were able to demonstrate a cumulative PrimPat and SecPat of 37 and 45%, respectively, at 3 years. If these calculations are considered in terms of the latest Rutherford criteria,[44] they would be reduced to 31 and 38%, respectively, comparable with our own results. The cumulative LSalv was 63% after 2 years and 51% after 5 years.

The results of Bacourt[33,34] for Carbon *vs.* Standard PTFE at 24 months were 45 *vs.* 35% (PrimPat), 53 *vs.* 36% (SecPat) and 57 *vs.* 47% (LSalv). These results compare with our 24 months data with 40 (C) *vs.* 35% (St), 51 *vs.* 42% and 71 *vs.* 62%.

In 2001 Lang *et al.*[60] presented results of a prospective randomized study with more than 200 patients of Carbon PTFE *vs.* Standard PTFE bypass, but confined exclusively to the below knee popliteal segment. No statistically significant difference could be found in the per protocol analysis in this study. The results for PrimPat, SecPat and LSalv for carbon *vs.*

Table 7. Life tables limb salvage rate according to Rutherford *et al.*[44], carbon *vs.* standard PTFE vascular grafts, ITT (log-rank test $\chi^2=1.96$, 1 d.f.; $p=0.16$) (LTFU, lost-to-follow-up; CI, confidence interval)

Interval (month)	No. at risk at start of interval (*n*)	No. failed during interval (*n*)	Withdrawn during interval (*n*) due to			Interval failure rate	Cumulative patency rate, (95% CI%)	Standard error (%)
			Death	LTFU	Duration			
Carbon PTFE								
0–1	130	10	5	1	0	0.0787	92.1% (87.7–96.6)	2.3
1–3	114	6	6	3	0	0.0548	87.1% (81.3–90.9)	2.9
3–6	99	3	5	1	0	0.0313	84.4% (77.8–90.8)	3.4
6–12	90	6	9	1	0	0.0706	78.4% (70.9–85.9)	3.8
12–18	74	2	4	1	0	0.0280	76.2% (67.7–84.7)	4.3
18–24	67	5	1	0	0	0.0752	70.5% (61.3–79.7)	4.7
24–36	61	3	5	0	0	0.0513	66.7% (57.2–76.5)	4.9
Total		35	35	7	0			
Standard PTFE								
0–1	135	9	3	3	0	0.0682	93.2% (89.1–97.3)	2.1
1–3	120	12	7	0	0	0.1030	83.6% (77.6–89.6)	3.1
3–6	101	8	5	1	0	0.0816	76.8% (69.5–84.0)	3.7
6–12	87	9	11	0	0	0.1104	68.3% (60.2–76.4)	4.1
12–18	67	4	5	2	0	0.0630	64.0% (54.8–73.2)	4.7
18–24	56	2	2	1	0	0.0367	61.6% (51.6–71.6)	5.1
24–36	51	3	4	0	0	0.0612	57.9% (47.6–68.2)	5.3
Total		47	37	7	0			

Table 8. Log-rank test analysis at 36 months of the life table curves for the three different analysis groups. (ITT, intention-to-treat; PP, per protocol und; AT, as-treated)

Analysis group	Primary patency *p*-value	Secondary patency *p*-value	Limb salvage *p*-value
ITT ($n=265$)	0.20	0.12	0.16
PP ($n=254$)	0.23	0.18	0.23
AT ($n=265$)	0.29	0.28	0.34

standard PTFE at 36 months were 36 *vs.* 35%, 46 *vs.* 45% and 60 *vs.* 63%, respectively. The detailed final results are currently being prepared for publication.[61]

While the coating with Carbon in mechanical heart valves is standard today as surface treatment to achieve higher mechanical stability, it did also not lead to clinical improved results in other implants with blood contact such as stents,[62–64] although the results for carbon coating were encouraging in terms of biocompatibility, hemocompatibility and decreased thrombogenicity evaluated *in vitro*, in animal trials and in non-randomized clinical settings.[65–69]

The apparent advantage in the carbon group in our study in the period from six to 18 months is noteworthy and might be of clinical importance for individual patients, but seems to be a temporary effect. However, any single point on a survival curve is not a particularly reliable representation of survival at that time; it is the entire curve which is a reliable representation of survival, thus the entire curves should be compared, not a single point on the curve.

Our hypothesis that PrimPat, SecPat and the LSalv rate are better for the Carbon prosthesis was refuted. At 36 months, Carbon PTFE prosthesis and Standard PTFE prosthesis had similar outcomes. This finding was confirmed with additional calculations based on the 'per protocol' (PP) and 'as-treated' (AT) groups, with reasonable power to show an effect (79 and 83%, respectively). Overall this suggests that reduction of graft thrombogenicity with a non-pharmacological method will not result in a crucial clinical advance in treatment of this group of patients evaluated in the long term without further additional measures. Alternative mechanisms and conduits needed to be evaluated in proper prospective randomized studies for the group of patients with no autologous vein available.

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