

Will heparin-bonded PTFE replace autologous venous conduits in infrapopliteal bypass?

P. PEETERS¹, J. VERBIST¹, K. DELOOSE², M. BOSIERS²

Aim. Expanded polytetrafluoroethylene (ePTFE) grafts are commonly used for treatment of infrainguinal arterial occlusive disease. Especially in below-knee (BK) reconstructions, patency is often inferior to the outcome in patients eligible for venous bypass grafting. This study assesses whether the Carmeda® BioActive Surface (CBAS), which employs covalent end-point linkage to retain heparin on the device surface, as it is used on the GORE-TEX® Propaten Vascular Graft (W.L. Gore & Associates, Flagstaff, Arizona) successfully can prolong patency.

Methods. From June 2002 to December 2005, 138 patients (97 men and 41 women; mean age, 73 years) received the Propaten Vascular Graft for 153 infrainguinal bypass procedures. Seventy-five above-knee (AK) and 78 BK (including 37 femoro-crural [FC]) procedures were performed. Follow-up evaluations consisted of clinical examinations, color-flow duplex ultrasound control and distal pulse assessments. Patency and limb salvage rates were assessed by using life-table analyses.

Results. The overall primary and secondary 3-year patency rates were 72.1% and 77.3%, respectively. Three-year primary patency rates for BK bypasses were 74.7% for BK femoropopliteal and 60.4% for femoro-crural bypasses. The corresponding secondary patency rates were 80.2% and 61.6%. The 3-year limb salvage rate in patients with CLI was 85.9%.

Conclusion. These findings show that CBAS-ePTFE bypass grafts appear to give prolonged patency and perform quite well, also in BK application. However, a large prospective randomized trial is mandatory to provide more definitive information about the graft's patency and limb salvage performance.

KEY WORDS: Polytetrafluoroethylene - Arterial occlusive diseases - Lower extremities - Heparin.

¹Department of Cardiovascular and Thoracic Surgery
Imelda Hospital, Bonheiden, Belgium
²Department Vascular Surgery
A.Z. Sint-Blasius, Dendermonde, Belgium

One of the most common manifestations of atherosclerosis is infrainguinal arterial occlusive disease. Symptomatic clinical presentation of patients affected by this disease includes intermittent claudication (Rutherford 1-4) and critical limb ischemia (CLI) (Rutherford 5 or 6). Claudication generally involves a benign natural evolution with a low risk of amputation, whereas the presence of CLI implies a much more extensive underlying arterial disease with much more serious short and long-term consequences.¹ Revascularization is often necessary in order to alleviate symptoms and to obtain limb salvage.² The method of revascularization will, amongst others, be influenced by patient co-morbidity, life expectancy and the lesion distribution. The optimal treatment of the femoropopliteal segment has given rise to much debate, be it surgical or endovascular, as outlined by numerous and often conflicting publications in the last decade.³⁻⁵

Contemporary general recommendations for an evidence based approach for patients with peripheral artery disease (PAD), have recently been described in the Inter-Society Consensus for the Management of Peripheral Arterial Disease TASC II document,⁶ which contains the TASC femoro-popliteal lesion classifi-

Corresponding author: P. Peeters, MD, Department of Cardiovascular and Thoracic Surgery, Imelda Hospital, Bonheiden, Belgium.
E-mail: patrick.peeters@imelda.be

TABLE I.—TASC classification categories.

-
- Endovascular therapy is the treatment of choice: TASC type A lesions
 - Endovascular therapy is the preferred treatment, after consideration of the patient's co-morbidities, fully informed patient preference and the local operator's long-term success rates: TASC type B lesions
 - Surgery is the preferred treatment for good-risk patients, after consideration of the patient's co-morbidities, fully informed patient preference and the local operator's long-term success rates: TASC type C lesions
 - Surgery is the treatment of choice: TASC type D lesions
-

cation. This classification is based upon response to intervention, independent of technology and techniques. The goal of this system is to indicate the best form of treatment, endovascular (TASC A) or surgical (TASC D). The lesions without strongly supportive evidence, but that are more likely to respond better to endovascular therapy (TASC B) or surgery (TASC C), need more evidence (Table I).

The TASC II 2007 femoro-popliteal lesion classification defines surgery as preferred treatment for good risk patients (TASC C) for: 1) multiple stenoses or occlusion totalling at least 15cm in length, with or without heavy calcification, 2) recurrent stenoses or occlusions that need treatment after two endovascular interventions. The classification indicates surgery is the treatment of choice (TASC D) for: 1) chronic total occlusion of the common femoral artery or superficial femoral artery above 20 cm in length, involving the popliteal artery, 2) chronic total occlusion of the popliteal artery and proximal trifurcation vessels.

Femoro-popliteal venous bypass placement is the golden standard for surgical repair of symptomatic arterial TASC C and D lesions in the lower extremities. Autologous vein grafts are the surgeon's first choice in peripheral arterial bypass procedures because of superior patency rates in comparison to those of traditional prosthetic grafts. Veith *et al.*⁷ published 4-year results in a large prospective multi-center randomized comparison of autologous vein and expanded polytetrafluoroethylene (ePTFE) bypass. The authors reported 4-year primary patency rates of 61% for above-knee venous bypass, 38% for AK PTFE grafts, 76% for below-knee (BK) femoropopliteal vein conduits, 54% for BK femoropopliteal prostheses, 49% for BK infrapopliteal venous bypasses and 12% for BK infrapopliteal PTFE implants. These numbers indicate a tendency of superior patency for above-knee (AK)

venous bypasses over PTFE grafts. For below-knee (BK) femoropopliteal and BK infrapopliteal grafts, however, the difference in patency rates was statistically superior for venous conduits over prosthetic implants. It is currently generally accepted that great saphenous vein bypasses perform better than regular PTFE grafts and should be used whenever possible.

However, venous autologous graft placement is not possible in all patients. A first reason is absent or unsuitable venous material due to prior coronary or peripheral arterial bypass placement, or due to inadequate quality, diseased state or incompatible measurements of the vein available. Secondly, a prosthetic bypass placement decreases operative time and morbidity because of a more limited dissection, which may rule out venous bypass placement considering some patients' constitution. Finally, sometimes a prosthetic peripheral bypass is opted for as the vein needs to be preserved for future revascularisation. Therefore, Dacron and expanded polytetrafluoroethylene (ePTFE) have been introduced for infrainguinal bypass applications,^{3, 8-10} but give disappointing results especially for reconstructions below the knee.¹¹

Potential causes for prosthetic graft occlusion include technical failure at implantation, progression of vascular disease, thrombosis, and intimal hyperplasia at the anastomosis between the graft and vessel. The primary cause of early graft occlusion is, especially in small-caliber prostheses, thrombus deposition on the graft lumen.¹²⁻¹⁵ As the rate prosthetic graft occlusions is highest in the first months after surgery, manufacturers have been looking for technical improvements to reduce these early failures and hence improve patency results. Under the assumption that the solution for these early failures could lay in an improved thromboresistancy of the inner lumen, researchers began to investigate the effects of attaching heparin, an anticoagulant agent with a long history of safety and efficacy. The use of heparin coatings on several types of medical devices, including extracorporeal circuits for cardiopulmonary bypassing^{16, 17} and stents,¹⁸ has successfully enhanced hemocompatibility and improved patient outcome. The optimal method for attaching heparin to a prosthetic surface must provide long-term retention of the agent on that surface, as well as sustained heparin activity.¹²

The GORE-TEX[®] Propaten Vascular Graft (W.L. Gore & Associates, Flagstaff, Arizona) uses the Carmeda[®] BioActive Surface (CBAS; Carmeda AB, Uplands Väsby, Sweden), which employs covalent end-

point linkage to retain heparin on the device surface. It has been available for clinical use in Europe since 2002 and aspires to bridge the gap in patency results between venous and ePTFE grafts. The authors hereby describe the 3-year clinical outcome of all consecutive patients receiving this particular graft during an infrainguinal bypass procedure since its introduction in our service.

Materials and methods

Between June 2002 and December 2005, a prospective, non-randomized, multicenter study of the GORE-TEX[®] Propaten Vascular Graft was conducted at the Departments of Cardiovascular and Thoracic Surgery of the Imelda Hospital in Bonheiden, Belgium, and the Department of Vascular Surgery at the AZ Sint-Blasius in Dendermonde, Belgium. In total, 138 patients (97 men) and 153 diseased limbs were included. Mean age was 73 years. Clinically, all patients had to present with symptoms of intermittent claudication or CLI (Rutherford categories 2-6).

Standard surgical bypass techniques were used in all patients; no special implantation or handling methods were opted. Only straight, thin-walled, 6 mm diameter grafts with an external ring support system were selected. End-to-side anastomoses, without the use of patches or cuffs, were performed in all cases. Immediately after graft implantation, angiography was always performed to detect technical failures. Intraoperative antiplatelet or anticoagulant therapy, including administration of heparin, was given in accordance with the standards of care at the participating centers. Postoperatively, patients received 75 mg per day of clopidogrel for the first month after surgery, 0.6 mL per day of low-molecular-weight heparin for the first 3 weeks (following the institution's standard postoperative protocol), and 100 mg per day of aspirin indefinitely.

All patients were followed according the standard hospital schedule (1 month, 6 months, and every year after index intervention). Furthermore, patients were encouraged for intermediate control visits on suspicion of complaint recurrence. At each examination, the following assessments were performed: a clinical examination, a color-flow duplex ultrasonographic study to detect stenosis in the bypass graft or native artery, and measurement of distal pulses.

The primary endpoints in this evaluation were survival and primary graft patency, defined as blood flow through a graft for which there had been no reinter-

TABLE II.—Risk factor distribution and patient demographics.

Characteristic	Value*
Mean age (y) (range) [N.=138 patients]	73 (45-92)
Sex	
Male	97 (70.29)
Female	41 (29.71)
Risk factors	
Previous peripheral vascular disease treatment	101 (73.19)
Coronary artery disease	42 (30.43)
Cerebrovascular disease	18 (13.04)
Renal insufficiency	12 (8.70)
Obesity	17 (12.32)
Diabetes	37 (26.81)
Hypertension	88 (63.77)
Hypercholesterolemia	59 (42.75)
Nicotine use	66 (47.83)
Preoperative Rutherford class [N.=153 limbs]	
3	85 (55.56)
4	29 (18.95)
5	39 (25.49)
Preoperative run off [N.=153 limbs]†	
No patent artery	7 (4.58)
One patent artery	76 (49.67)
Two patent arteries	43 (28.10)
Three patent arteries	27 (17.65)

*Values are number (percentage) unless otherwise indicated.

†Number of arteries with outflow from the area of the proposed vascular bypass.

vention to restore flow. Secondary endpoint was cumulative secondary patency, defined as blood flow through a graft that required reintervention to restore flow. In the patients with CLI, limb salvage was additionally monitored and was defined as prevention of any major amputation (ie, above-heel amputation). All data were statistically assessed by using Kaplan Meier or log-rank analyses. Differences resulting in $P < 0.05$ were considered significant.

Results

In total, 153 infrainguinal bypass procedures were performed with the GORE-TEX[®] Propaten Vascular Graft. Intermittent claudication was seen in 85 (55.6%) patients (Rutherford 2 and 3), whereas 68 (45.4%) patients presented with CLI (Rutherford 4, 5 and 6). Concerning infragenicular vessel patency, 76 (49.7%) patients had only one distal runoff vessel. Only 7 (4.6%) patients presented without any patent artery below the knee. A more detailed overview of the risk factor distribution and patient demographics is shown in Table II.

Peri-procedurally, there were no major suture bleed-

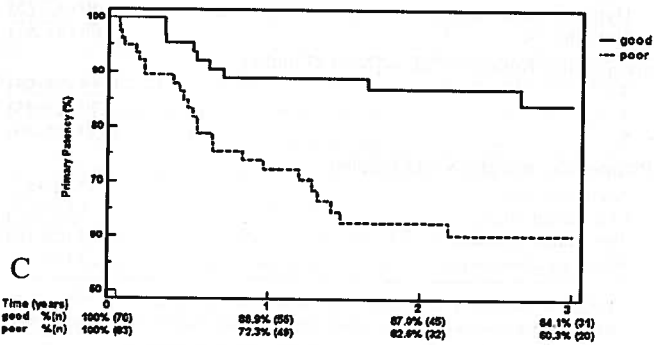
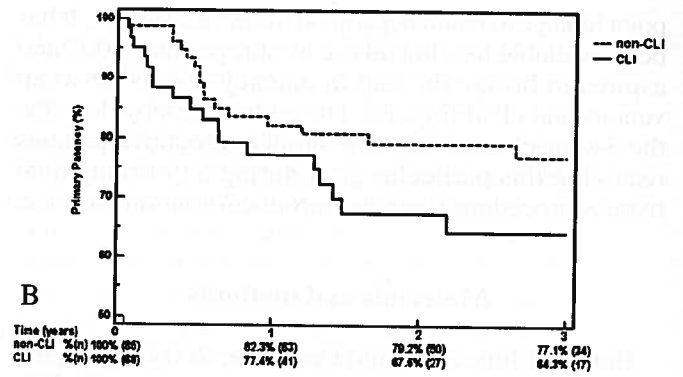
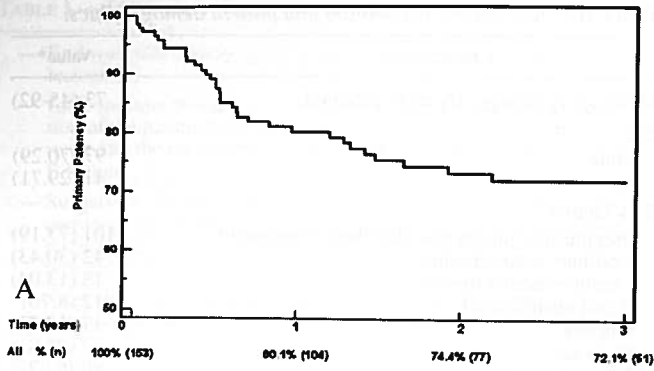


Figure 1.—Primary patency. A) Total population; B) intermittent claudication vs critical limb ischemia; C) good (2-3 vessels) vs poor (0-1 vessel) outflow.

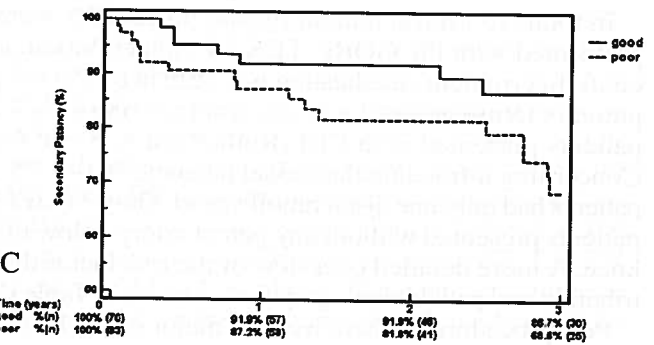
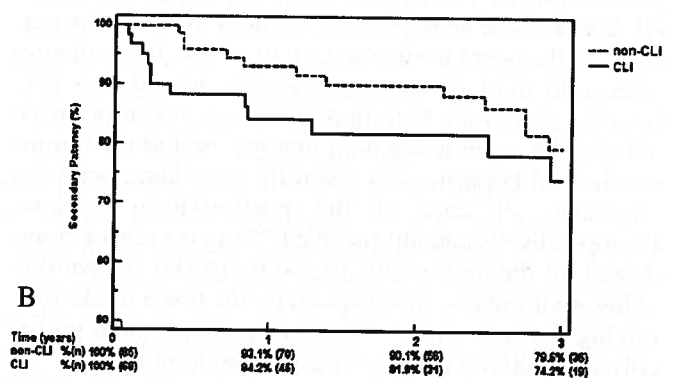
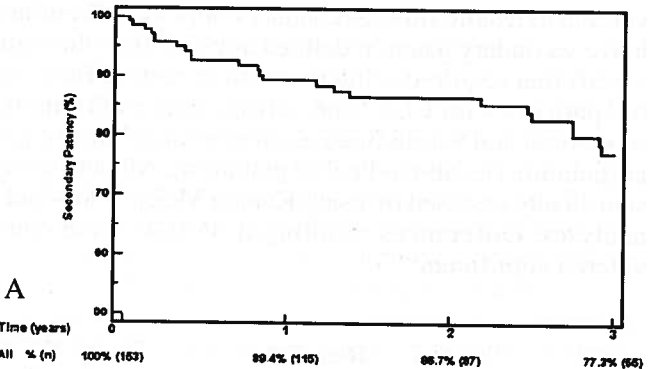


Figure 2.—Secondary patency. A) Total population; B) intermittent claudication vs critical limb ischemia; C) good (2-3 vessels) vs poor (0-1 vessel) outflow.

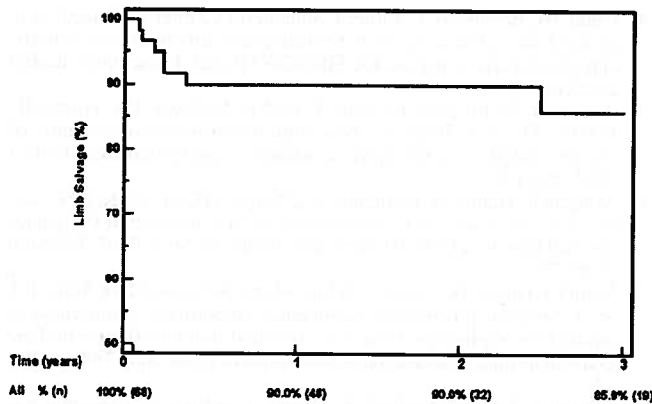


Figure 3.—Limb salvage in patients with critical limb ischemia.

ings. Distributed according to distal anastomosis, 75 above-knee (AK) femoro-popliteal bypasses, 41 below-knee (BK) femoro-popliteal grafts and 37 femoro-crural (FC) implants were placed. No procedural deaths occurred and only 1 case of infection was reported.

Results for the total study cohort

In total, 51 patients were seen for control after 3 years. A survival rate of 74.0% was reported. The primary patency rate at this time was 72.1% (Figure 1A). In the same patient cohort, the 3-year primary patency for patients with intermittent claudication was 77.1%, compared to 64.3 in patients with CLI (Figure 1B). Patients with good outflow (2 or 3 arteries patent below the knee) scored better than those with poor outflow (no or 1 artery patent below the knee) with primary patency rates of 84.1% versus 60.3%, respectively (Figure 1C).

Data on secondary patency at 3 years was obtained for 55 patients and was 77.3% (Figure 2A). Claudicants had a 3-year secondary patency of 79.6% versus 74.2% in the CLI-patient cohort (Figure 2C). Stratification of good and poor outflow before the procedure, resulted in secondary patencies of 86.7% and 68.6% after 3 years (Figure 2D).

A 3-year limb salvage rate for the CLI population of 85.9% was obtained (Figure 3). No statistical differences were found during stratification for bypass type or runoff state within the CLI subgroup.

Results for below-knee (BK) bypasses

Of the total 153 infrainguinal bypasses that were implanted, 75 were AK femoro-popliteal bypasses, 41 were BK femoro-popliteal grafts and 37 were FC implants. The 3-year primary patency rates for BK bypasses were based 18 BK femoropopliteal grafts and 11 bypasses in BK infrapopliteal position, and were reported to be 74.7% and 60.4%, respectively (Figure 4A). Secondary patency after 3 years was also based on 18 BK femoropopliteal implants and 11 BK infrapopliteal implants, and was 80.2 and 61.6% (Figure 4B).

Discussion

Heparin coating has been used in medical devices since years with the aim of controlling formation of the initial fibrin and platelet layers.¹⁵ Application of a heparin coating using the CBAS technology with covalent end-point linkage to retain heparin on the Gore Propaten Vascular Graft yields satisfying results in

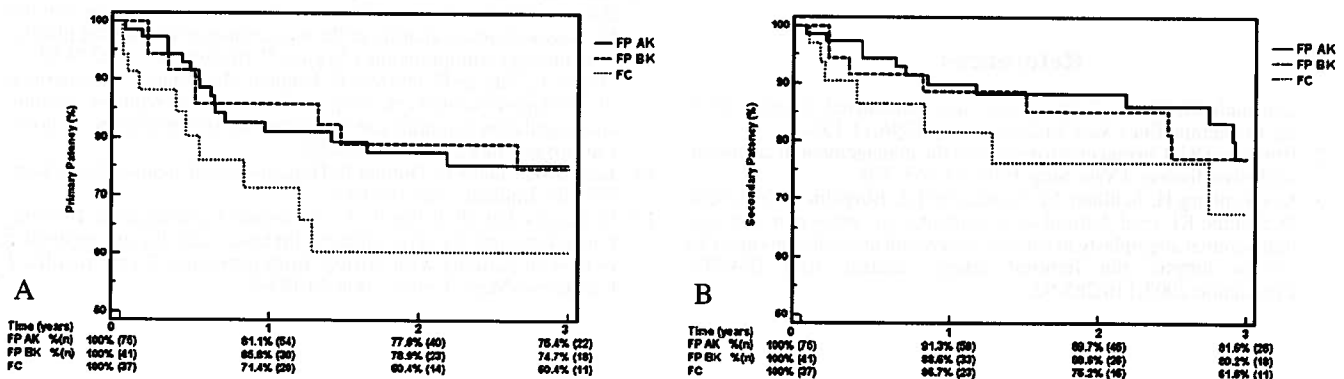


Figure 4.—Primary and secondary patency in BK bypasses. A) Primary patency; B) secondary patency.

this clinical series of infrainguinal bypasses, with good safety and decent 3-year primary and secondary patency rates. This sustained heparin activity, up to 12 weeks,⁶ may explain its apparently better clinical performance. Our own findings are supported by other publications have also indicated the value of this new type of heparin bonding.

In a recent publication by Dorrucchi *et al.*¹⁹ discussed their results on 27 femoropopliteal below-knee and femorodistal Gore-Tex Propaten Vascular Grafts in 26 patients (18 male). Mean age of the study population was 76 years and Rutherford classes 4 to 6 were included. Mean patient follow-up was 24 months. After 2 years, primary patency was 85%, secondary patency was 93% and limb salvage rate was 96%.

These series of patients treated with the heparin-bonded Propaten Vascular Graft scored better than what could be expected from regular PTFE grafts. Still, the results obtained by venous conduits for infrainguinal arterial reconstruction are superior. Nevertheless, given this favourable outcome with the Propaten Vascular Graft in above-knee and below-knee configurations, it can be concluded that heparin-bonded PTFE bypasses have a place for peripheral arterial reconstruction below the knee. Especially for infrapopliteal lesions, it is our opinion that the Propaten Vascular Graft may succeed in bridging the gap between venous conduits and regular PTFE grafts.

Although these results are encouraging, they are not powered to draw firm conclusions. Longer patient follow-up and a larger clinical experience are required before definitive statements in this regard can be made. Only a randomized study can determine whether the CBAS-ePTFE prosthesis will consistently yield better outcomes.

References

- Lepantalo M, Matzke S. Outcome of unreconstructed chronic critical leg ischaemia. *Eur J Vasc Endovasc Surg* 1996;11:153-7.
- Brewster DC: Current controversies in the management of aortoiliac occlusive disease. *J Vasc Surg* 1997, 25:365-379.
- Krankenbergh H, Schlüter M, Steinkamp HJ, Bürgelin K, Scheinert D, Schulte KL *et al.* Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). *Circulation* 2007;116:285-92.
- Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Tielbeek A *et al.* Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease: the SIROCCO II trial. *J Vasc Interv Radiol* 2005;16:331-8.
- Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG *et al.* Bypass versus angioplasty in severe ischemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 2005;366:1925-34.
- Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASCII). *Eur J Vasc Endovasc Surg*. 2007;33(Suppl 1):S1-75.
- Veith FJ, Gupta SK, Ascer E, White-Flores S, Samson RH, Scher LA *et al.* Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. *J Vasc Surg* 1986;3:104-14.
- Grimm J, Muller-Hulsbeck S, Jahnke T, Hilbert C, Brossmann J, Heller M. Randomized study to compare PTA alone versus Palmaz stent placement for femoropopliteal lesions. *J Vasc Interv Radiol* 2001;12:935-42.
- Zdanowski Z, Albrechtsson U, Lundin A, Jonung T, Ribbe E *et al.* Percutaneous transluminal angioplasty with or without stenting for femoropopliteal occlusions? A randomized controlled study. *Int Angiol* 1999;18:251-5.
- Becquemini JP, Favre JP, Marzelle J, Nemoz C, Corsin C, Leizorovicz A. Systematic versus selective stent placement after superficial femoral artery balloon angioplasty: a multicenter prospective randomized study. *J Vasc Surg* 2003;37:487-94.
- Klinert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoropopliteal bypass. A review of the literature. *Eur J Vasc Endovasc Surg* 2004;27:357-62.
- Begovac PC, Thomson RC, Fisher JL, Hughson A, Gällhagen A. Improvements in GORE-TEX® Vascular Graft performance by Carmeda® BioActive Surface heparin immobilization. *Eur J Vasc Endovasc Surg* 2003;25:432-7.
- Lin PH, Bush RL, Yao Q, Lumsden AB, Chen C. Evaluation of platelet deposition and neointimal hyperplasia of heparin-coated small-caliber ePTFE grafts in a canine femoral artery bypass model. *J Surg Res* 2004;118:45-52.
- Lin PH, Chen C, Bush RL, Yao Q, Lumsden AB, Hanson SR. Small-caliber heparin-coated ePTFE grafts reduce platelet deposition and neointimal hyperplasia in a baboon model. *J Vasc Surg* 2004;39:1322-8.
- Laredo J, Xue L, Husak VA, Ellinger J, Singh G, Zamora PA *et al.* Silyl-heparin bonding improves the patency and in vivo thromboresistance of carbon-coated polytetrafluoroethylene vascular grafts. *J Vasc Surg* 2004;39:1059-65.
- Palanzo DA, Zarro DL, Manley NJ, Montesano RM, Quinn M, Elmore BA *et al.* Effect of Carmeda BioActive Surface coating versus Trillium Biopassive Surface coating of the oxygenator on circulating platelet drop during cardiopulmonary bypass. *Perfusion* 2001;16:279-83.
- Ovrum E, Tangen G, Oystese R, Ringdal MA, Istad R. Comparison of two heparin-coated extracorporeal circuits with reduced systemic anticoagulation in routine coronary artery bypass operations. *J Thorac Cardiovasc Surg* 2001;121:324-30.
- Kocsis JF, Llanos G, Holmer E. Heparin-coated stents. *J Long Term Eff Med Implants* 2000;10:19-45.
- Dorrucchi v, Griselli F, Petralia G, Spinamano L, Adornetto R. Heparin-bonded expanded polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb ischemia: 2-year results. *J Cardiovasc Surg (Torino)* 2008;49:145-9.