JOURNAL OF ENDOVASCULAR THERAPY
A SAGE Publication
An official publication of the International Society of Endovascular Specialists

Journal of Endovascular Therapy
2015, Vol. 22(1) 74–79

DOI: 10.1177/1526602814566907
www.jevt.org
SAGE

Paclitaxel-Coated Balloon Angioplasty for Symptomatic Central Vein Restenosis in Patients With Hemodialysis Fistulas

Alexander Massmann, MD[1], Peter Fries, MD[1], Kerstin Obst-Gleditsch, MD[1], Peter Minko, MD[1], Roushanak Shayesteh-Kheslat, MD[2], and Arno Buecker, MD[1]

Abstract

Purpose: To report a retrospective observational analysis of standard balloon angioplasty (BA) vs. paclitaxel-coated balloon angioplasty (PCBA) for symptomatic central vein restenoses in patients with impaired native hemodialysis fistulas. **Methods:** A retrospective review was conducted of 27 consecutive patients (15 men; mean age 66±13.8 years, range 39–90) with 32 central vein stenoses (CVS; 6 axillary, 11 subclavian, 12 brachiocephalic, and/or 3 superior caval veins) treated successfully using BA. Freedom from reintervention after BA of de novo lesions was 7.4±7.9 months (range 1–24). Twenty-five (92.6%) patients developed symptomatic restenoses and were treated one or more times by BA (n=32) or PCBA (n=20) using custom-made paclitaxel-coated balloons (diameter 6–14 mm). **Results:** Technical (<30% residual stenosis) and clinical (functional fistula) success rates for the initial and secondary angioplasty procedures were 100%. No minor/major procedure-associated complications occurred. Mean follow-up was 18.4±17.5 months. Kaplan-Meier analysis for freedom from target lesion revascularization (TLR) found PCBA superior to BA (p=0.029). Median freedom from TLR after BA was 5 months; after PCBA, >50% of patients were event-free during the observation period (mean freedom from TLR 10 months). Restenosis intervals were prolonged by PCBA (median 9 months) vs. BA (median 4 months; p=0.023). **Conclusion:** Paclitaxel-coated balloon angioplasty of central vein restenosis in patients with hemodialysis shunts yields a statistically significant longer freedom from TLR compared to standard balloon angioplasty.

Keywords

endovascular intervention, vein, central venous stenosis, drug-eluting balloon, restenosis, hemodialysis, arteriovenous fistula, target lesion revascularization

Introduction

Symptomatic central vein stenosis (CVS) is a clinically relevant complication in hemodialysis patients. Stenoses of central veins typically result in dysfunctional dialysis shunts, venous collaterals, edema, ipsilateral extremity tenderness, pain, and cellulitis.[1,2] Further complications include shunt vein thrombosis and excessive bleeding after puncture for dialysis. CVS is commonly associated with central vein catheterization with an incidence of 25% to 50%[3,4] or insertion of pacemaker wires in up to 27%.[5–7] The incidence of CVS without previous central vein catheterization is about 1% to 10%.[8,9] A typical mechanism for the development of CVS is intravasal trauma to the venous endothelium, which results in inflammation of the vessel wall. Microthrombus, intimal hyperplasia, and fibrotic alteration finally lead to CVS.[10,11] The pathophysiological mechanism of CVS in dialysis shunts without a history of central vein catheterization is unclear. A higher venous blood flow and increased pressure after creation of a dialysis fistula are considered the cause.[8,9]

Endovascular treatment with balloon angioplasty is generally accepted as the primary treatment for CVS.[3,12] However, restenosis is frequent. Restenotic lesions are characterized by a significant increase in fibroplastic proliferation within the venous neointima and media as compared to primary stenotic lesions.[13] Several experimental[14,15] and clinical[16–18] studies confirmed the hypothesis of vascular

[1]Department of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg/Saar, Germany
[2]Department of General, Abdominal, and Vascular Surgery, Saarland University Medical Center, Homburg/Saar, Germany

Corresponding Author:
Alexander Massmann, Department of Diagnostic and Interventional Radiology, Saarland University Medical Center, Kirrberger Straße Geb. 50.1, 66421 Homburg/Saar, Germany.
Email: alexander.massmann@uks.eu

remodeling owing to adventitial angiogenesis and scar development. This is the theoretical background for application of antiproliferative therapy at the time of balloon angioplasty within the venous system, as drug-coated balloon angioplasty has been shown to lead to a significant reduction in restenosis in peripheral artery disease.[19,20] Venous smooth muscle cells (SMCs) are more sensitive to the effects of antiproliferative agents as compared with arterial SMCs.[21] Paclitaxel in the perivascular area of hemodialysis grafts resulted in an effective inhibition of neointimal hyperplasia and prevention of restenosis in several animal models.[22,23] A recent randomized controlled clinical trial favored paclitaxel-coated balloon angioplasty (PCBA) for stenoses of hemodialysis access.[24]

Based on these in vitro and clinical results, the purpose of this study was to retrospectively evaluate standard balloon angioplasty (BA) vs. PCBA for the treatment of recurrent symptomatic CVS in patients with hemodialysis fistulas.

Methods

Study Design and Patient Cohort

Between 2008 and 2014, 27 consecutive patients (15 men; mean age 66±13.8 years, range 39–90), all with diabetic end-stage renal disease, presented with considerable edematous arm swelling and severely impaired native lower or upper arm hemodialysis fistulas inappropriate for dialysis. Catheter-directed venography depicted 32 de novo nonmalignant CVS (Figure 1) in the axillary (n=6), subclavian (n=11), brachiocephalic (n=12), and/or superior caval vein (n=3). Three patients had 2 venous stenoses and 1 patient had 3. Complete chronic occlusions were not detected. The interval between creation of the hemodialysis fistulas and development of the initial CVS was 39±49 months (range 1–216).

After institutional review board approval and patient informed consent, all 27 patients underwent initial balloon angioplasty. Overall, 52 reinterventions were necessary in 25 (92.6%) of the 27 patients due to clinically symptomatic restenosis and impaired hemodialysis fistula. Fifteen patients underwent 32 reinterventions using standard BA and 10 patients underwent 20 reinterventions using PCBA (Table 1). Selection of patients for BA or PCBA was at the operator's discretion.

Standard Balloon Angioplasty

Angiography was performed after needle (22-G) puncture of the brachial artery to exclude relevant stenoses in the hemodialysis fistula, arteriovenous anastomosis, and draining shunt veins. CVS was verified by direct phlebography via the shunt vein, into which a standard 0.035-inch hydrophilic guidewire and 7-F sheath (10- or 25-cm long) were inserted. Five thousand units of unfractionated heparin were given through the sheath. Intraluminal crossing of the CVS was always achieved with the 0.035-inch guidewire and 4-F catheter.

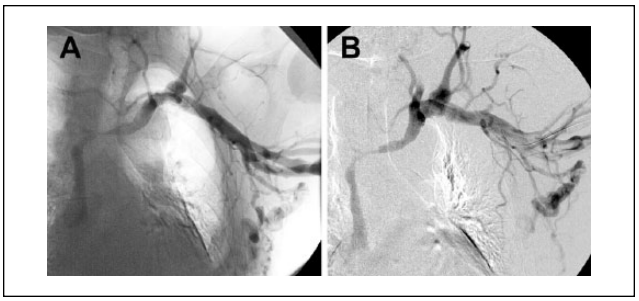

Figure 1. (A) Unsubtracted and (B) digital subtraction phlebography via an antecubital vein reveals typical extensive venous collaterals along the chest wall because of high-grade stenosis of the left brachiocephalic vein.

Balloon size was determined according to the diameter of the adjacent normal vein and the length of the stenosis. In most cases, the balloon catheters were typically 40-mm long with diameters ranging from 6 to 12 mm. Inflation pressure was 14 atmospheres for 60 seconds. Additional dilation with larger balloons was performed if recoil with relevant residual stenosis occurred; inflation pressure was also 14 atmospheres for 60 seconds. Pretreatment with 6-mm diameter cutting balloons (Boston Scientific, Natick, MA, USA) and posttreatment high-pressure balloon angioplasty (24 atm for 60 seconds) was also used as necessary for severe recalcitrant recoil. The diameter of the high-pressure balloon was identical to the largest size of the primary balloon. Technical success was defined as residual stenosis <30%. Heparin therapy was maintained for 48 hours. Clinical success was defined as the ability to successfully use the fistula for dialysis after angioplasty.

Paclitaxel-Coated Balloon Angioplasty Treatment

As drug-coated balloon catheters of appropriate size (diameter >7 to 14 mm) for central veins were not commercially available, all paclitaxel-coated balloons were custom-made using standard over-the-wire balloon catheters (Figure 2) coated with polymer-free microcrystalline paclitaxel at a concentration of 2 μg/mm^2 (Elutax-SV; Aachen Resonance, Aachen, Germany).

The PCBA followed the same BA protocol for vascular access, heparin use, sizing of the paclitaxel-coated balloons, and adjuvant procedures for pretreatment and recoil. Balloon catheter length was 40 mm for the 6- to 10-mm diameter balloons and 20 mm for the 10-, 12-, and 14-mm diameter balloons. Inflation pressure was 14 atmospheres for 60 seconds, similar to the BA group.

Table 1. Characteristics of Patients Treated for Central Vein Restenosis.[a]

	Standard Balloon Angioplasty	Paclitaxel-Coated Balloon Angioplasty
Patients	15	10
Age, y	66.8±15.0 (39–90)	64.5±11.2 (50–85)
Men	9 (56)	6 (60)
Diabetes mellitus	15	10
Native arteriovenous fistula	15	10
Dialysis access age, mo	26.9±22.9 (1–67)	50.9±62.8 (1–216)
Location left arm	10	7

[a]Continuous data are presented as the means ± standard deviations (range); categorical data are given as the counts (percentage).

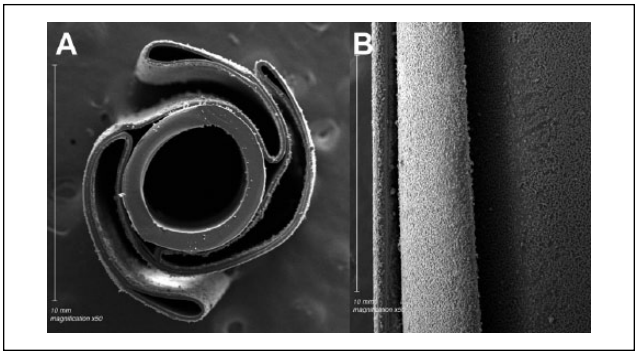

Figure 2. Scanning electron microscopy cross-sectional image illustrating (A) special balloon folding and (B) the paclitaxel-coated surface of Elutax SV completely covering the balloon. The drug itself is protected within the folds of the balloon.

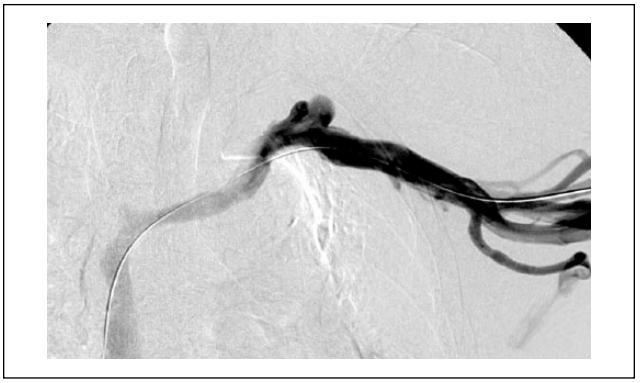

Figure 3. Postinterventional venography after dilation with a 10×40-mm paclitaxel-coated balloon depicts a successful reduction in the central venous stenosis. Consequently, there is an obvious improvement in venous inflow and a considerable reduction of venous collaterals.

Statistical Analysis

Continuous data are presented as the means ± standard deviations; categorical data are given as the counts. The differences between groups were evaluated using the unpaired *t* test; differences achieving $p<0.05$ were considered to be statistically significant. Freedom from target lesion revascularization (TLR) was estimated using the Kaplan-Meier method; differences between groups were examined with the log-rank test. Statistical analysis was performed using the Prism software for MacOSX (version 6.0.4, Graphpad, La Jolla, CA, USA).

Results

Primary technical success (residual stenosis <30%) in the BA and PCBA groups was 100% (Figure 3). Additional dilation with larger balloons was performed in 10 BA patients and 8 PCBA cases because of recoil with relevant residual stenosis. The mean diameters were 8±2 mm for the standard balloons and 10±2 mm (range 6–14) for the coated balloons. Pretreatment with cutting balloons and posttreatment high-pressure balloon angioplasty were necessary in 2 patients in each group. No minor or major procedure-associated complications were observed. There was no relevant bleeding, hematoma, superior vena cava thrombosis, or worsening of hemodialysis fistula function after BA or PCBA. Stent placement was avoided in all patients. Function of the hemodialysis shunts normalized after intervention, which allowed appropriate use for dialysis.

Four patients in the BA group experienced very early restenosis. One patient had 11 reinterventions within 2.7±1.3 months, another patient had 4 reinterventions over 7.8±2.2 months, and 2 patients had recurrences after 1 and 2 months. Although PCBA was under evaluation, the superior results in the PCBA group finally led to crossover of these 4 patients to PCBA for ethical reasons. After crossover to PCBA, the intervention-free time interval markedly increased up to 21 months. One patient died after 6 months without the need for reintervention.

Over a mean follow-up of 18.4±17.5 months, 9 (33%) patients died after 7.2±5.9 months (median survival 6 months, range 1–19); no death was related to the procedure. Failing hemodialysis fistula due to shunt occlusion after BA occurred in 4 patients after 4.0±3.1 months (range 1–9) and after PCBA in 1 patient after 3 months.

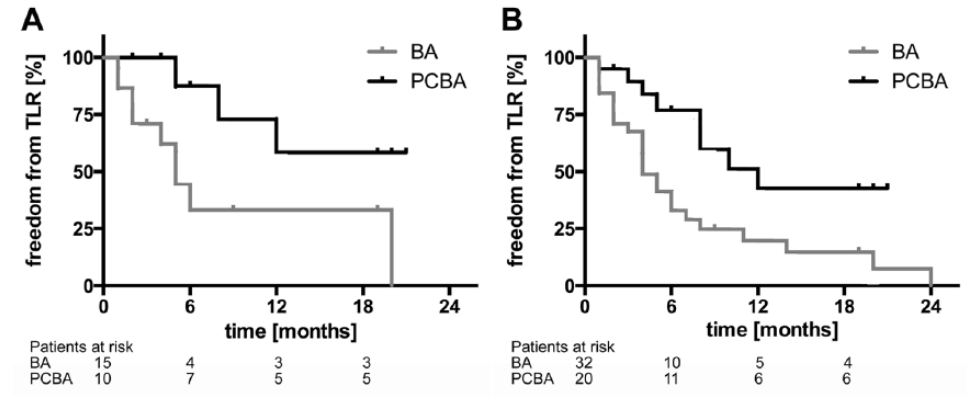

Figure 4. Kaplan-Meier plots demonstrate freedom from target lesion revascularization (TLR) after standard balloon angioplasty (BA) and paclitaxel-coated balloon angioplasty (PCBA) of central venous restenosis: (A) initial treatment and (B) pooled data in a crossover design of lesions treated.

Comparative Analysis

Kaplan-Meier analysis of freedom from TLR after first reinterventions revealed PCBA significantly superior to BA (p=0.025; Fig. 4A). The median freedom from TLR after BA was 5 months. For PCBA, 66.7% of patients were event-free during the observation period, resulting in a mean freedom from TLR of 10 months.

A crossover-design analysis in which each patient serves as his or her own control was completed to integrate additional data from recurrent restenosis. Additional statistical analysis of pooled data respecting all consecutive treatments showed a median freedom from TLR after PCBA of 12 months vs. 4 months after BA (p=0.006; Fig. 4B). Time to recurrent restenosis was also significantly prolonged by PCBA (mean 9.5±1.9 months in 4 patients) vs. BA (mean 5±4.9 months in 5 patients, 1 early death). The median time interval to restenosis after PCBA was 9 months vs. 4 months after BA (p=0.021).

Discussion

Preservation of hemodialysis fistula function in patients with central vein occlusive disease is a relatively common problem. Unfortunately, all available interventional treatment options result in poor midterm patency. As a consequence, several reinterventions are often mandatory. Standard BA is so far the common first-line treatment of choice in CVS. Compared with standard balloons, paclitaxel-coated balloons in endovascular treatment of peripheral artery disease have demonstrated lower restenosis rates and superior clinical outcomes with prolonged time to reintervention. However, due to a limited number of patients and variable designs of existing studies, definitive recommendations for optimal treatment of CVS are lacking. Furthermore, the pathophysiology of atherosclerotic disease is different from the development of CVS. Nonetheless, looking at the histopathology, CVS has similarities to arterial stenosis. In both, hyperproliferation of fibroblasts have been identified as part of the problem.[10,12,13,21,22,24] Neointimal hyperplasia is a local inflammatory process. Local wall delivery of the antiproliferative agent paclitaxel reduces neointimal hyperplasia by inhibition of SMC proliferation and migration. Paclitaxel stabilizes the arrangement of microtubules by binding β-tubulin dimers, inhibiting their depolymerization. The long-lasting disruption of normal microtubule function interferes with a number of cell properties, including division, motility, and shape. Low doses of paclitaxel cause cell-cycle arrest in the G1 phase without causing cellular apoptosis. The resulting cytostatic response with inhibition of SMC proliferation and migration represent the key processes for reduction of neointimal hyperplasia.[25–27] Other studies demonstrated a varying technical success rate for standard balloon dilation of CVS between 70% and 90%. Unsatisfactory initial results and short-term restenosis are often observed.[28] Primary patency rates range from 23% to 55% and 12% to 50% at 6 and 12 months, respectively. A high technical failure rate of 10% to 30% necessitates close surveillance with the need for multiple reinterventions.[29–32]

Bare metal or covered stents have been evaluated with differing results. While bare stents have high primary technical success rates of 82% to 100%, midterm results are as disappointing as they are with BA. Primary patency of self-expanding bare stents range from 42% to 89% at 6 months and 14% to 73% at 12 months.[32–34] Intimal hyperplasia, stent fracture, and migration due to (respiratory) motion and compression lead to early restenosis. Furthermore, bare stents may complicate further endovascular or surgical treatment.[32–34]

The use of covered stents should combine the advantages of mechanical stability and lower in-stent restenosis caused by intima hyperplasia. The primary technical success rate was 100%, but primary patency was only 32% to 67% at 12 months, which makes stenting questionable in vessel segments exposed to high biomechanical stress.[35–37]

Recently, drug-coated balloon angioplasty was used for venous anastomotic stenosis of dialysis fistulas and synthetic grafts. The use of the IN.PACT Amphirion paclitaxel-coated balloon showed a statistically significant improvement in primary patency (70%) compared to BA (25%) after 6 months ($p<0.001$).[24] In failing dialysis fistulas caused by de novo or recurrent juxta-anastomotic stenoses, PCBA achieved a primary patency rate of 92% after 9 months.[38]

In our study, patients with symptomatic CVS initially underwent the well-accepted treatment of choice with BA. As mentioned above, the restenosis rate was high and the intervention-free time interval was relatively short. Even though BA of CVS is a fast and low-risk procedure, patients have to be hospitalized recurrently, and balloon angioplasty itself is uncomfortable and painful. To avoid the disadvantages and complications related to stent implantation, we evaluated the use of PCBA in patients with symptomatic CVS. A technical prerequisite for successful treatment of CVS using PCBA is an appropriate sizing of the drug-coated balloon catheters. Central veins are usually larger in diameter than coronary or peripheral arteries, for which several balloons of different sizes (diameter ≤7 mm) are commercially available. In most of our cases, the diameter of the central veins was too large for commercially available balloon catheters. Consequently, all the PCBA catheters needed to be especially produced, but there was no balloon rupture or disintegration of coating before application. Notably, the treatment with a "double dose" of paclitaxel in 8 patients did not result in any vascular damage, for example, but the patients are too few for subgroup analysis.

Short-term results of a randomized controlled trial of PCBA in the peripheral venous system showed PCBA superior to BA for the treatment of hemodialysis access stenoses.[24] Similar to these results and those of drug-coated balloons in coronary and peripheral artery disease, our patients experienced significantly fewer restenoses of the central veins after PCBA. Furthermore, vessel patency was improved, which resulted in a prolonged freedom from TLR.

Limitations

The study was limited by its small cohort and single-center observational retrospective design. Furthermore, the fact that all patients were diabetics may mean that our results are not reproducible in non-diabetic patients. However, the improved outcome supports the use of PCBA in the management on CVS, at least after inadequate primary BA of de novo lesions.

Conclusion

Paclitaxel-coated balloon angioplasty of central vein restenosis yields a statistically significant longer freedom from TLR in patients with hemodialysis shunts. A randomized controlled trial for the use of PCBA as first-line strategy is justified.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Prof Dr med Arno Buecker was a co-founder of Aachen Resonance.

Funding

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

References

1. Baker GL, Barnes HJ. Superior vena cava syndrome: etiology, diagnosis, and treatment. *Am J Crit Care*. 1992;1:54–64.
2. Khanna S, Sniderman K, Simons M, et al. Superior vena cava stenosis associated with hemodialysis catheters. *Am J Kidney Dis*. 1993;21:278–281.
3. Lumsden AB, MacDonald MJ, Isiklar H, et al. Central venous stenosis in the hemodialysis patient: incidence and efficacy of endovascular treatment. *Cardiovasc Surg*. 1997;5:504–509.
4. Glanz S, Gordon DH, Lipkowitz GS, et al. Axillary and subclavian vein stenosis: percutaneous angioplasty. *Radiology*. 1988;168:371–373.
5. Asif A, Salman L, Carrillo RG, et al. Patency rates for angioplasty in the treatment of pacemaker-induced central venous stenosis in hemodialysis patients: results of a multi-center study. *Semin Dial*. 2009;22:671–676.
6. Shingarev R, Barker-Finkel J, Allon M. Association of hemodialysis central venous catheter use with ipsilateral arteriovenous vascular access survival. *Am J Kidney Dis*. 2012;60:983–989.
7. Vanherweghem JL, Yassine T, Goldman M, et al. Subclavian vein thrombosis: a frequent complication of subclavian vein cannulation for hemodialysis. *Clin Nephrol*. 1986;26:235–238.
8. Kotoda A, Akimoto T, Kato M, et al. Central venous stenosis among hemodialysis patients is often not associated with previous central venous catheters. *ASAIO J*. 2011;57:439–443.
9. Oguzkurt L, Tercan F, Yildirim S, et al. Central venous stenosis in haemodialysis patients without a previous history of catheter placement. *Eur J Radiol*. 2005;55:237–242.
10. Kelly BS, Heffelfinger SC, Whiting JF, et al. Aggressive venous neointimal hyperplasia in a pig model of arteriovenous graft stenosis. *Kidney Int*. 2002;62:2272–2280.
11. Lee T, Roy-Chaudhury P. Advances and new frontiers in the pathophysiology of venous neointimal hyperplasia and dialysis access stenosis. *Adv Chronic Kidney Dis*. 2009;16:329–338.

12. Shi Y, Ye M, Liang W, et al. Endovascular treatment of central venous stenosis and obstruction in hemodialysis patients. *Chin Med J (Engl)*. 2013;126:426–430.
13. Chang C-J, Ko P-J, Hsu L-A, et al. Highly increased cell proliferation activity in the restenotic hemodialysis vascular access after percutaneous transluminal angioplasty: implication in prevention of restenosis. *Am J Kidney Dis*. 2004;43:74–84.
14. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation*. 2001;104:1188–1193.
15. Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. *Circulation*. 2001;103: 2289–2295.
16. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.
17. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350:221–231.
18. Sousa JE, Costa MA, Abizaid A, et al. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation*. 2005;111: 2326–2329.
19. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358:689–699.
20. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118:1358–1365.
21. Kim S-J, Masaki T, Leypoldt JK, et al. Arterial and venous smooth-muscle cells differ in their responses to antiproliferative drugs. *J Lab Clin Med*. 2004;144:156–162.
22. Masaki T, Rathi R, Zentner G, et al. Inhibition of neointimal hyperplasia in vascular grafts by sustained perivascular delivery of paclitaxel. *Kidney Int*. 2004;66:2061–2069.
23. Kelly B, Melhem M, Zhang J, et al. Perivascular paclitaxel wraps block arteriovenous graft stenosis in a pig model. *Nephrol Dial Transplant*. 2006;21:2425–2431.
24. Katsanos K, Karnabatidis D, Kitrou P, et al. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial. *J Endovasc Ther*. 2012;19:263–272.
25. Axel DI, Kunert W, Göggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation*. 1997;96:636–645.
26. Wiskirchen J, Schöber W, Schart N, et al. The effects of paclitaxel on the three phases of restenosis: smooth muscle cell proliferation, migration, and matrix formation: an in vitro study. *Invest Radiol*. 2004;39:565–571.
27. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med*. 1995;332:1004–1014.
28. Kovalik EC, Newman GE, Suhocki P, et al. Correction of central venous stenoses: use of angioplasty and vascular Wallstents. *Kidney Int*. 1994;45:1177–1181.
29. Quinn SF, Schuman ES, Demlow TA, et al. Percutaneous transluminal angioplasty versus endovascular stent placement in the treatment of venous stenoses in patients undergoing hemodialysis: intermediate results. *J Vasc Interv Radiol*. 1995;6:851–855.
30. Dammers R, de Haan MW, Planken NR, et al. Central vein obstruction in hemodialysis patients: results of radiological and surgical intervention. *Eur J Vasc Endovasc Surg*. 2003;26:317–321.
31. Surowiec SM, Fegley AJ, Tanski WJ, et al. Endovascular management of central venous stenoses in the hemodialysis patient: results of percutaneous therapy. *Vasc Endovascular Surg*. 2004;38:349–354.
32. Bakken AM, Protack CD, Saad WE, et al. Long-term outcomes of primary angioplasty and primary stenting of central venous stenosis in hemodialysis patients. *J Vasc Surg*. 2007;45:776–783.
33. Aytekin C, Boyvat F, Yağmurdur MC, et al. Endovascular stent placement in the treatment of upper extremity central venous obstruction in hemodialysis patients. *Eur J Radiol*. 2004;49:81–85.
34. Haage P, Vorwerk D, Piroth W, et al. Treatment of hemodialysis-related central venous stenosis or occlusion: results of primary Wallstent placement and follow-up in 50 patients. *Radiology*. 1999;212:175–180.
35. Kundu S, Modabber M, You JM, et al. Use of PTFE stent grafts for hemodialysis-related central venous occlusions: intermediate-term results. *Cardiovasc Intervent Radiol*. 2011;34:949–957.
36. Jones RG, Willis AP, Jones C, et al. Long-term results of stent-graft placement to treat central venous stenosis and occlusion in hemodialysis patients with arteriovenous fistulas. *J Vasc Interv Radiol*. 2011;22:1240–1245.
37. Anaya-Ayala JE, Smolock CJ, Colvard BD, et al. Efficacy of covered stent placement for central venous occlusive disease in hemodialysis patients. *J Vasc Surg*. 2011;54:754–759.
38. Patanè D, Giuffrida S, Morale W, et al. Drug-eluting balloon for the treatment of failing hemodialytic radiocephalic arteriovenous fistulas: our experience in the treatment of juxtaanastomotic stenoses. *J Vasc Access*. 2014;15:338-343.

Cardiovasc Intervent Radiol (2019) 42:835–840
https://doi.org/10.1007/s00270-019-02213-w

Drug-Eluting Balloon Angioplasty for Juxta-Anastomotic Stenoses in Distal Radiocephalic Hemodialysis Fistulas: Long-Term Patency Results

Aytac Gulcu[1] · Orkun Sarioglu[1] · Ahmet Peker[1] · Ozkan Alatas[1]

Received: 21 November 2018 / Accepted: 26 March 2019 / Published online: 29 March 2019

Abstract

Purpose To evaluate long-term primary and secondary patency results of drug-eluting balloon angioplasty for the treatment of juxta-anastomotic stenoses in distal radiocephalic arteriovenous fistulas.

Materials and Methods Thirty-eight patients with juxta-anastomotic stenotic distal radiocephalic arteriovenous fistulas who underwent endovascular treatment with drug-eluting balloons between January 2014 and August 2016 in our interventional radiology department were included in this retrospective study. Color Doppler examination for follow-up was performed 15 days, 6 months, 12 months, 18 months, 24 months, 36 months, and 48 months after the procedure. Kaplan–Meier analysis was used to estimate primary and secondary patency rates.

Results Totally, 42 angioplasty with drug-eluting balloons was performed in 38 patients (20 men and 18 women; mean age 66.42 ± 12.01). Technical and clinical success rate was 100% (42/42). The mean follow-up period was 27.71 months ± 12.98 (range, 1–54 months). The estimated primary patency rates at 6 months were 94.7% (95% CI, 80.9%–99.0%), at 12 months were 81.2% (95% CI, 64.6%–91.4%), at 24 months were 60.7% (95% CI, 43.6%–75.7%), and at 48 months were 53.1% (95% CI, 36.5%–69.1%). The estimated secondary patency rates at 6 months were 97.3% (95% CI, 84.5%–99.8%), at 12 months were 86.5% (95% CI, 70.7%–94.8%), at 24 months were 69.0% (95% CI, 51.8%–82.4%), and at 48 months were 61.7% (95% CI, 44.6%–76.5%).

Conclusion Drug-eluting balloon angioplasty is a useful, effective technique in dysfunctional radiocephalic fistulas due to juxta-anastomotic stenoses. We demonstrated remarkably high primary patency rates at 6, 12, 24, and 48 months.

Keywords Drug-eluting balloon · Percutaneous transluminal angioplasty · Juxta-anastomotic stenosis

Introduction

End-stage renal disease (ESRD) is the final stage of chronic kidney disease. It is predicted that the prevalence of ESRD and the need for hemodialysis will grow in the future as the average lifespan increases [1]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines advise autologous arteriovenous fistula (AVF) for vascular access [2]. Distal radiocephalic AVFs are the first option due to its technical simplicity, lower complication, and higher patency rates [3]. However, in spite of being superior to other accesses, fistulas also have a limited time for appropriate usage. Stenosis, which usually occurs in 3 cm before and after the anastomosis, is the main reason for

✉ Orkun Sarioglu
orkunsarioglu@gmail.com

Aytac Gulcu
aytac.gulcu@deu.edu.tr

Ahmet Peker
doktorpeker@gmail.com

Ozkan Alatas
ozkanalatas@hotmail.com

[1] Department of Radiology, Faculty of Medicine, Dokuz Eylul University, Mithatpasa Cad., Inciralti, 35340 Izmir, Turkey

dysfunctional AVFs [4–6]. These types of stenoses are regarded as juxta-anastomotic stenoses (JASs) [7].

Endovascular treatment in AVFs is recommended in K/DOQI guidelines. Several reports have revealed the efficacy of endovascular treatment in AVFs [6, 8–10], but most of the studies have included all types of fistulas such as radiocephalic, radioulnar, or brachial-basilic. Moreover, long-term patency results after percutaneous transluminal angioplasty (PTA) in the most preferred fistula type, radiocephalic fistulas [3], are lacking. Over the past few years, drug-eluting balloons (DEBs) have evolved and taken part in stenotic AVF treatment by inhibiting neointimal hyperplasia [11]. However, it is still needed to be demonstrated how effective is the DEB angioplasty, which has been proven as the primary treatment method [12], in distal radiocephalic fistulas.

The aim of our study was to assess long-term patency results of DEB angioplasty for the treatment of JASs in distal radiocephalic AVFs.

Materials and Methods

Patients

Local ethics committee approval was obtained for this retrospective study. Patients who underwent fistulography and endovascular treatment in our department between January 2014 and August 2016 were reviewed. Since we wanted to elucidate long-term outcomes, patients with a minimum follow-up of 2 years were selected for the present study. The interventions performed before the year 2014 were not scanned for the lack of acceptable demographic and clinical data. The inclusion criteria were as follows: autologous distal radiocephalic fistulas with JASs. Arteriovenous grafts, patients without follow-up information, and fistulas that had treated formerly in different hospitals were the exclusion criteria. JASs were described as stenoses occurred in 3 cm before and after the anastomosis. After all, a total of 38 patients (20 men and 18 women; mean age 66.42 ± 12.01) with sufficient demographic, clinical, and radiologic follow-up data were incorporated in the study.

Pretreatment Evaluation

Patients in the study were directed to our department with AVF problems from dialysis units. The decrease of the blood flow greater than 20% per month, observing total access blood flow less than 300 mL/min were the conditions that displayed AVF dysfunction. One operator with 15 years of experience performed all the color Doppler examinations and operated all the endovascular treatments (A.G.). Color Doppler examination was used to localize the abnormality, estimate the degree of stenosis, evaluate the outflow vein, figure out the treatment method, and determine the access site. Along with clinical problems, narrowing greater than 50%, peak systolic velocity (PSV) ratio greater than 2:1 compared to the 2-cm proximal from the lesion, and PSV of $\geq$ 500 cm/sec were considered abnormal [13]. Further evaluation with fistulography was performed in these patients.

Endovascular Treatment

A digital subtraction angiography device (Allura Xper FD10, Philips Healthcare, the Netherlands) was used for fistulography and endovascular procedures. Retrograde outflow vein puncture was performed by ultrasound guidance to minimize hematoma in all procedures. Inflow, fistula, and outflow segments were assessed carefully before the procedure. Blood pressure cuff was used to observe arterial anastomosis better. Initially, we performed a fistulography via 18G cannula. Fistulography images were evaluated, and treatment decision was made by the same experienced interventional radiologist who had performed patients' initial color Doppler examination.

A standard technique was used for the treatment of JASs [14]. If we decided to do angioplasty after fistulography, we placed the sheath using 0.035-inch guidewire through the 18G cannula under local anesthesia. Heparin (5000 IU) was administered intravenously after vascular sheath placement in all cases. Juxta-anastomotic target lesion was passed by manipulation of a 0.035-inch hydrophilic guidewire and a 4F multipurpose vertebral catheter. After advancing the catheter to the arterial side, hand injection was performed for the final decision of balloon size. Then, 0.035- or 0.018-inch guidewire was advanced, and the catheter was removed. After predilatation with plain balloons, DEBs were advanced via guidewire to the lesion. Types of DEBs we used were Elutax SV OTW, ab medica, Dusseldorf, Germany (in 12 procedures), and IN.PACT Admiral Drug-coated balloon, Medtronic, California, USA (in 30 procedures). After the termination of the stenosis, the balloon was held on inflated for 2 min to prevent the elastic recoiling. For refractory lesions, cutting balloons were used. When successful appearance was gained, the procedure was terminated with control of central veins. After sheath removal, hemostasis was gained by manual compression.

Clinical Outcome and Follow-Up

Technical success, clinical success, primary patency, secondary patency, and minor and major complication rates were considered during clinical outcome analysis.

Technical success was described as the increase in the "thrill" and residual stenosis lower than 30% in both angiographic images and color Doppler examination. The operator performed color Doppler examination and thrill assessment before and after the procedure. During the procedure, the operator evaluated the angiographic images. However, all angiographic images were reviewed retrospectively by 6-year (O.S.) and 5-year (A.P.) experienced radiologists. The radiologists were unaware of the patients' diagnosis and operation findings. The two radiologists assessed the pre- and post-dilatation images and recorded the residual stenoses of $\geq$ 30% if any. Clinical success was defined as the access of the fistula without any problem during dialysis. Total access blood flow of $>$ 300 mL/min was a supportive criterion of the clinical success. Clinical success was evaluated by dialysis unit nephrologists. In the first dialysis session after the procedure, feedback was received via phone call.

Primary patency and secondary patency rates were evaluated based on the instructions of Society of Interventional Radiology Technology Assessment Committee [15]. Primary patency was defined as the time between the first intervention until access thrombosis and repeated endovascular treatment. The interval after the first intervention until the fistula is surgically revised or abandoned was regarded as secondary patency.

Color Doppler examination for follow-up was performed 15 days, 6 months, 12 months, 18 months, 24 months, 36 months, and 48 months after the procedure by an 8-year experienced radiologist (O.A). If a problem was detected by nephrologist, or dialysis unit nurse, patients were directly referred without waiting for the follow-up date. Color Doppler examinations, repeated angiography images, and records of dialysis units were inspected for follow-up data. Follow-up ended in August 2018. Complications were graded according to the CIRSE classification [16].

Statistical Analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier survival analysis was used to estimate primary and secondary patency rates after intervention. Stated patency rate intervals in this study were 95% confidence intervals (CIs). Renal transplantation, exitus because of an independent cause from renal disease with functional AVF, and loss to follow-up were regarded as censored data.

Results

Characteristics of AVFs and patients' demographic data are demonstrated in Table 1. Forty-two PTA with DEBs was performed in 38 patients. The mean size of the balloons was 5.55 mm $\pm$ 0.67. Cutting balloon was used in one procedure due to refractory stenosis after DEB.

Our technical and clinical success rate was 100% (42/42). Grade 1 complications were experienced in 4 cases. Hematomas at the puncture site that did not affect blood flow were reported after two interventions (2/42, %4.76). Contrast extravasation was observed in two procedures and was managed with balloon inflation (2/42, %4.76).

The mean follow-up period in this study was 27.71 months $\pm$ 12.98 (range, 1–54 months). Eight patients died of an unrelated cause from renal disease with functional fistula during the follow-up period.

At the sixth month, one patient underwent surgical creation of a new fistula; one patient needed reintervention due to stenosis of the same location; one patient died with functional fistula. Thirty-five patients had successfully working AVF at the end of 6 months.

Between the 6th and 12th months, 4 fistulas were thrombosed and abandoned. Repeated endovascular treatment to the same region was performed in one patient.

After 18 months, 4 patients died with functional fistula. 3 fistulas were surgically revised. One patient had recurrent JAS and reintervention was done.

At 24-month follow-up, 3 patients could not continue dialysis with their fistulas and underwent surgical revision.

Table 1 Demographic features of the patients and characteristics of the AVFs

Number of patients	38
Age (years)	66.42 $\pm$ 12.01
Female to male ratio	18/20
Hypertension	21/38 (55.3%)
Hyperlipidemia	17/38 (44.7%)
Diabetes mellitus	
Type 1	1/38 (2.6%)
Type 2	20/38 (52.6%)
Type of AVF	
Radiocephalic	38/38 (100%)
Side of AVF	
Right	13/38 (34.2%)
Left	25/38 (65.8%)
Age of AVF at the first intervention (months)	15.2 $\pm$ 18.3
Stenosis location	
Juxta-anastomotic	38/38 (100%)

AVF arteriovenous fistula

One patient died with functional fistula. At the end of 2 years, there were 18 patients remaining with no necessity for additional intervention.

Between the 24th and 36th months, 2 patients died of heart problems with functional fistula. No endovascular intervention or surgery was performed during this period.

At 48th month, two fistulas were occluded, and surgery was performed to revise. By the end of 48 months, 14 patients did not need any intervention and underwent dialysis successfully. At the end of the follow-up interval, 17 patients (%44.7) had functional AVFs.

At the follow-up, three patients were needed reintervention. At 5 months, one patient had stenosis and the patient was treated by angioplasty with DEB. Two months later, restenosis was detected and the same procedure was performed; 11 months later, restenosis was detected again at the same region and treated with DEB again. No further intervention was needed, and fistula is still patent. The second patient had stenosis at the same site after the intervention, and the patient was treated by angioplasty with DEB. No further stenosis was detected during the follow-up period. The other patient also had recurrent stenosis at 14 months of follow-up; he was treated by angioplasty with DEB. No more stenosis occurred during the follow-up period.

The estimated primary patency rates at 6 months were 94.7% (95% CI, 80.9%–99.0%), at 12 months were 81.2% (95% CI, 64.6%–91.4%), at 18 months were 70.3%, (95% CI, 53.1%–83.4%), at 24 months were 60.7% (95% CI, 43.6%–75.7%), at 36 months were 60.7% (95% CI, 43.6%–75.7%), and at 48 months were 53.1% (95% CI, 36.5%–69.1%).

The estimated secondary patency rates at 6 months were 97.3% (95% CI, 84.5%–99.8%), at 12 months were 86.5% (95% CI, 70.7%–94.8%), at 18 months were 78.4%, (95% CI, 61.6%–89.4%), at 24 months were 69.0% (95% CI, 51.8%–82.4%), at 36 months were 69.0% (95% CI, 51.8%–82.4%), and at 48 months were 61.7% (95% CI, 44.6%–76.5%). Figure 1 summarizes the patency results.

Discussion

Our study demonstrated that endovascular treatment of JASs in radiocephalic hemodialysis fistulas with DEBs is an effective method. We recorded pretty high primary patency rates even at 48 months with DEBs in this study. Secondary patency rates were greater than primary patency rates as expected.

PTA is an established procedure and is the first option for the management of JASs with its minimally invasive nature [7, 17, 18]. Although surgical creation of a new fistula has lower rates of recurrence [19], secondary patency rates are comparable with surgery and PTA [20]. Despite high recurrence rates, endovascular treatment allows immediate usage of AVF after the procedure and prevents waiting for maturation after the new surgery.

Many studies compared the DEBs and plain balloons in the treatment of stenotic AVFs [12, 21, 22]. All these studies demonstrated that DEBs provide significantly higher primary patency rates and lower recurrence rates. Animal trials displayed the efficacy of paclitaxel on preventing neointimal hyperplasia and reported that local therapy is more useful [23, 24].

Although miscellaneous reports assessed the efficacy of DEBs in AVFs, the sample in these studies included radiocephalic and brachiocephalic fistulas or grafts, juxta-anastomotic, or outflow venous stenoses [6, 8, 9, 25, 26]. As far as we know, minimal number of studies assessed the long-term patency rates after DEB angioplasty in a uniform sample such as autologous radiocephalic AVFs with JASs [7].

We demonstrated better primary patency rates at 6 (94.7%) and 12 (81.2%) months compared to other studies [6, 9, 27, 28]. These results illustrate the efficacy of DEB angioplasty in JAS. Patanè D et al. [7] achieved similar results. The treatment of JASs with DEBs reduces the rate of restenosis and therefore makes the primary patency rates higher. With less repeated interventions, patient comfort and cost-effectiveness get better [22]. After the intervention, two restenoses occurred, and reintervention was performed within 1 year in our study. This number was much better than most of the other studies, except one study had the same number [7].

Patanè D et al. [7] showed a significant decrease in the primary patency rates from the 12th month to the 24th month. Similarly, there was a decline in our study from the 18th (70.3%) month to the 24th (60.7%) month. This decrease may be the consequence of repetitious punctures and vascular damage. However, the results remained the same at the 36th (60.7%) month. These rates are significantly higher than all studies that assessed the management of JASs in radiocephalic fistulas [7, 17, 27, 28].

Manninen et al. [17] assessed the effectiveness of the brachial arterial approach to the failing radiocephalic fistulas. Their primary patency rate was 32.0% at 36 months. This significant lower result compared to our study may be due to the heterogeneous target lesion (JASs or other segments) selection. Moreover, not only DEB angioplasty but also other treatment options such as thromboaspiration or stent deployment were performed in their study. Mortamais et al. [28] evaluated long-term results after endovascular treatment in JASs. They included only radiocephalic AVFs with JASs in their research and reported primary patency rates of 25.5% at 36 and 48 months. We demonstrated significantly greater rates at

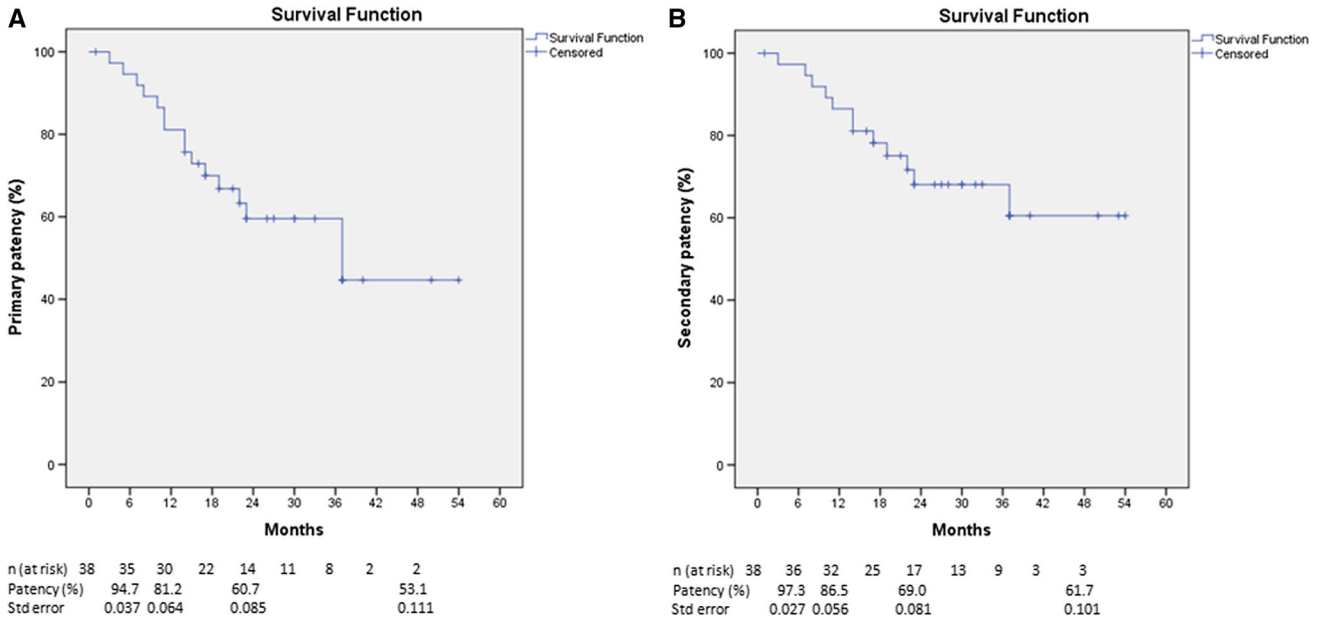

Fig. 1 Kaplan–Meier survival curves of estimated primary (**A**) and secondary (**B**) patency

48 months (53.1%). These encouraging rates at 6, 12, 18, 24, 36, and 48 months may be the result of DEB selection for the particular lesions in radiocephalic AVFs.

During our follow-up period, recurrent stenosis in the juxta-anastomotic region occurred in only three patients. This promising result may be due to the relatively small sample group. Mortamais et al. [28] reported that residual stenosis after the intervention, stenosis length, and time before the first restenosis significantly increase repeated interventions. On the other hand, Rajan et al. [8] demonstrated that no clinical or anatomic variable affects patency outcome.

The study had some limitations. The retrospective study design was the major limitation of the present study. Second significant limitation was the lack of a control group who were treated by plain balloons. Another limitation was the relatively small sample size of the patient group.

In conclusion, DEB angioplasty is a safe, effective treatment method with high primary patency rates even at long terms. The results we gained in this study demonstrate that JASs in distal radiocephalic AVFs can be effectively treated with DEBs and AVFs can be used safely for years after DEB angioplasty.

Acknowledgements This study was carried out in Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study, formal consent is not required. Ethics committee approval was received for this study from the local ethics committee.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

References

1. Perico N, Remuzzi G. Chronic kidney disease: a research and public health priority. Nephrol Dial Transpl. 2012;27(Suppl 3):19–26.
2. NKF-K/DOQI. DOQI clinical practice guidelines for vascular access: update 2000. Am J Kidney Dis. 2001;37(Suppl 1):S137–81.
3. Santoro D, Benedetto F, Mondello P, Pipitò N, Barillà D, Spinelli F, et al. Vascular access for hemodialysis: current perspectives. Int J Nephrol Renovasc Dis. 2014;8(7):281–94.
4. Asif A, Gadalean FN, Merrill D, Cherla G, Cipleu CD, Epstein DL, et al. Inflow stenosis in arteriovenous fistulas and grafts: a multicenter, prospective study. Kidney Int. 2005;67(5):1986–92.
5. Clark TW, Hirsch DA, Jindal KJ, Veugelers PJ, LeBlanc J. Outcome and prognostic factors of restenosis after percutaneous treatment of native hemodialysis fistulas. J Vasc Interv Radiol. 2002;13(1):51–9.
6. Asif A, Lenz O, Merrill D, Cherla G, Cipleu CD, Ellis R, et al. Percutaneous management of perianastomotic stenosis in arteriovenous fistulae: results of a prospective study. Kidney Int. 2006;69(10):1904–9.
7. Patanè D, Giuffrida S, Morale W, L'Anfusa G, Puliatti D, Bisceglie P, et al. Drug-eluting balloon for the treatment of failing hemodialytic radiocephalic arteriovenous fistulas: our experience in the treatment of juxta-anastomotic stenoses. J Vasc Access. 2014;15(5):338–43.

8. Rajan DK, Bunston S, Misra S, Pinto R, Lok CE. Dysfunctional autogenous hemodialysis fistulas: outcomes after angioplasty—are there clinical predictors of patency? Radiology. 2004;232(2):508–15.
9. Tapping CR, Mallinson PI, Scott PM, Robinson GJ, Lakshminarayan R, Ettles DF. Clinical outcomes following endovascular treatment of the malfunctioning autologous dialysis fistula. J Med Imaging Radiat Oncol. 2010;54(6):534–40.
10. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G, et al. Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. Nephrol Dial Transpl. 2000;15(12):2029–36.
11. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med. 2008;358(7):689–99.
12. Lučev J, Breznik S, Dinevski D, Ekart R, Rupreht M. Endovascular treatment of haemodialysis arteriovenous fistula with drug-coated balloon angioplasty: a single-centre study. Cardiovasc Interv Radiol. 2018;41(6):882–9.
13. Wo K, Morrison BJ, Harada RN. Developing duplex ultrasound criteria for diagnosis of arteriovenous fistula stenosis. Ann Vasc Surg. 2017;38:99–104.
14. Beathard GA, Arnold P, Jackson J, Litchfield T. Aggressive treatment of early fistula ailure. Kidney Int. 2003;64(4):1487–94.
15. Gray RJ, Sacks D, Martin LG, Trerotola SO. Reporting standards for percutaneous interventions in dialysis access. J Vasc Interv Radiol. 2003;14(9 Pt 2):S433–42.
16. Filippiadis DK, Binkert C, Pellerin O, Hoffmann RT, Krajina A, Pereira PL. Cirse quality assurance document and standards for classification of complications: the cirse classification system. Cardiovasc Interv Radiol. 2017;40(8):1141–6.
17. Manninen HI, Kaukanen ET, Ikäheimo R, Karhapää P, Lahtinen T, Matsi P, et al. Brachial arterial access: endovascular treatment of failing Brescia-Cimino hemodialysis fistulas–initial success and long-term results. Radiology. 2001;218(3):711–8.
18. Patanè D, Failla G, Coniglio G, Russo G, Morale W, Seminara G, et al. Treatment of juxta-anastomotic stenoses for failing distal radiocephalic arteriovenous fistulas: drug-coated balloons versus angioplasty. J Vasc Access. 2018;30:1129729818793102.
19. Jiménez-Almonacid P, Gruss-Vergara E, Jiménez-Toscano M, Lasala M, Rueda JA, Portolés J, et al. Surgical treatment of juxta-anastomotic stenosis in radiocephalic fistula. A new proximal radiocephalic anastomosis. Nefrologia. 2012;32(4):517–22.
20. Kwon H, Choi JY, Ko HK, Kim MJ, Kim H, Park H, et al. Comparison of surgical and endovascular salvage procedures for juxta-anastomotic stenosis in autogenous wrist radiocephalic arteriovenous fistula. Ann Vasc Surg. 2014;28(8):1840–6.
21. Katsanos K, Karnabatidis D, Kitrou P, Spiliopoulos S, Christeas N, Siablis D. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial. J Endovasc Ther. 2012;19(2):263–72.
22. Kitrou PM, Katsanos K, Spiliopoulos S, Karnabatidis D, Siablis D. Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access: final results and cost-effectiveness analysis from a prospective randomized controlled trial (NCT01174472). Eur J Radiol. 2015;84(3):418–23.
23. Kohler TR, Toleikis PM, Gravett DM, Avelar RL. Inhibition of neointimal hyperplasia in a sheep model of dialysis access failure with the bioabsorbable Vascular Wrap paclitaxel-eluting mesh. J Vasc Surg. 2007;45(5):1029–37.
24. Kelly B, Melhem M, Zhang J, Kasting G, Li J, Krishnamoorthy M, et al. Perivascular paclitaxel wraps block arteriovenous graft stenosis in a pig model. Nephrol Dial Transpl. 2006;21(9):2425–31.
25. Kim WS, Pyun WB, Kang BC. The primary patency of percutaneous transluminal angioplasty in hemodialysis patients with vascular access failure. Korean Circ J. 2011;41(9):512–7.
26. Mantha M, Killen JP, Baer R, Moffat J. Percutaneous maintenance and salvage of dysfunctional arteriovenous fistulae and grafts by nephrologists in Australia. Nephrology. 2011;16(1):46–52.
27. Long B, Brichart N, Lermusiaux P, Turmel-Rodrigues L, Artru B, Boutin JM, et al. Management of perianastomotic stenosis of direct wrist autogenous radial-cephalic arteriovenous accesses for dialysis. J Vasc Surg. 2011;53(1):108–14.
28. Mortamais J, Papillard M, Girouin N, Boutier R, Cougnaud L, Martin X, et al. Endovascular treatment of juxta-anastomotic venous stenoses of forearm radiocephalic fistulas: long-term results and prognostic factors. J Vasc Interv Radiol. 2013;24(4):558–64.

Vascular and Endovascular Surgery
1-5

DOI: 10.1177/1538574416647500
ves.sagepub.com
SAGE

The Mid-Term Clinical Follow-Up Using Drug-Eluting Balloons on Tibial Artery "De Novo" Lesions in Patients With Critical Limb Ischemia: A Cohort Study

Valerio Tolva, MD, PhD, FEBVS[2], Renato Casana, MD[2], Anne Huibers, MD[3,4], Gianfranco Parati, MD, FESC[5,6], Paolo Bianchi, MD[1], Lea Cireni, MD[1], Emanuele Ferrero, MD[7], and Allison Halliday, MS, FRCS[3]

Abstract

Rationale: Restenosis due to intimal hyperplasia (IH) is a major clinical issue that affects the success of lower limb endovascular surgery. After 1 year, restenosis occurs in 40% to 60% of the treated vessels. The possibility to reduce IH using local antiproliferative drugs, such as taxols, has been the rationale for the clinical applications of drug-eluting stents and drug-eluting balloons (DEBs). The purpose of this study was to evaluate the clinical and instrumental efficacy of DEBs versus simple percutaneous transluminal angioplasty (PTA) in patients affected by chronic limb ischemia (CLI) with tibial artery "de novo" lesions. **Methods:** A retrospective analysis was performed and included all consecutive patients who underwent endovascular treatment for CLI in our centers between January 2011 and March 2013. Inclusion criteria were (1) "de novo" tibial artery stenosis and (2) Rutherford class >4. Lesions were further divided by TransAtlantic Inter-Societal Consensus (TASC) classification into groups A, B, C, and D. **Results:** Between January 2010 and March 2013, a total of 138 patients underwent simple PTA or DEB for CLI, and the groups were clinically and demographically homogenous. We decided to use DEBs in 70 cases. An improvement in the Rutherford Scale in cumulative and single TASC lesions classification was better in the DEB group (74% vs 51%; $P = .024$) at 24 months than in the PTA group. In the DEB group, the increase in ankle–brachial index was significantly higher than in the PTA group ($P = .039$). **Conclusions:** Our experience in addition to the existing literature supports the use of DEB in patients with CLI Rutherford class >3.

Keywords

intimal hyperplasia, drug-eluting balloon, restenosis

Introduction

Restenosis due to intimal hyperplasia (IH) is a major clinical issue that affects the success of lower limb endovascular surgery. After 1 year, restenosis occurs in 40% to 60% of the treated vessels. The possibility to reduce IH using local antiproliferative drugs, such as taxols, has been the rationale for the clinical applications of drug-eluting stents and drug-eluting balloons (DEBs). TransAtlantic Inter-Societal Consensus (TASC) II classification has been recently updated.[1] The intent of this new revision is to provide a complete anatomic lower limb TASC lesion classification, including the infrapopliteal segment, and an updated literature review of new endovascular techniques and practice patterns employed by vascular specialists today.[4] The new infrapopliteal lesion classification incorporates several features that attempt to address the multivessel nature of possible infrapopliteal anatomies.[6,7,12] Occlusive disease in a single tibial artery rarely leads to clinical signs or symptoms. Thus, a clinically significant reduction in distal arterial perfusion requires multivessel disease that can occur from multiple anatomic patterns of arterial occlusions. According to the new TASC II classification,[1] the purpose of this study

[1]Department of Vascular Surgery, Policlinico Di Monza Hospital, Monza, Italy
[2]Department of Surgery, IRCCS Istituto Auxologico Italiano, Milan, Italy
[3]Nuffield Department of Surgical Sciences, John Radcliff Hospital, University of Oxford, Oxford, United Kingdom
[4]Department of Vascular Surgery, University Medical Center, Utrecht, the Netherlands
[5]Department of Cardiovascular, Neural and Metabolic Sciences, S.Luca Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy
[6]Department of Health Sciences, University of Milano-Bicocca, Milan, Italy
[7]Vascular and Endovascular Surgery Unit, Mauriziano Umberto Hospital, Turin, Italy

Corresponding Author:
Valerio Tolva, Department of Vascular Surgery, Policlinico Di Monza Hospital, Via Francesco Petrarca, 51, Verano Brianza MB, Monza, Italy.
Email: valerio.tolva@policlinicodimonza.it

Table 1. Demographic and Clinical Data.

Variables Data	DEB	PTA	*P* Value
Patients (138)	70	68	
Age, years	65.4 ± 9.0	66.1 ± 9.6	.125
Male	37 (75.5%)	35 (71.4%)	.234
CAD	18 (36.7%)	20 (40.8%)	.389
Smoking	36 (73.4%)	38 (77.5%)	.202
Diabetes	12 (24.4%)	11 (22.4%)	.371
Hyperlipidemia	18 (36.7.7%)	16 (32.6%)	.442
Obesity	4 (8.1%)	6 (12.2%)	.312
Reactive C-protein, mg/dL, >9.8 mg/dL	8 (16.3%)	7 (14.2%)	.256
Plasmatic homocysteine >15 μmol/L	11 (22.4%)	12 (24.4%)	.371
Ankle–brachial index (ABI)	0.35 ± 0.18	0.36 ± 0.21	.231
Rutherford classification			Cumulative
4	45	43	.291
5	17	14	
6	8	11	
TASC classification			Cumulative
A	2	2	.451
B	13	14	
C	26	22	
D	8	11	

Abbreviations: CAD, coronary artery disease; DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Societal Consensus.

was to evaluate the clinical and instrumental efficacy of DEBs versus simple percutaneous transluminal angioplasty (PTA) in patients affected by chronic limb ischemia (CLI) with tibial artery "de novo" lesions.

Methods

Patients

A retrospective analysis was performed, including all consecutive patients who underwent an endovascular treatment for CLI in our centers between January 2011 and March 2013. Inclusion criteria were (1) "de novo" tibial arteries stenosis and (2) Rutherford class >4. Exclusion criteria were as follows: (1) recurrent stenosis; (2) inability to undergo aortography before the procedure; and (3) inability to give informed consent. Lesions were further divided by TASC II classification[1,2] into groups A, B, C, and D. A comparison was made between patients who were treated with paclitaxel DEB and simple balloon angioplasty (PTA). Patient selection was reviewed retrospectively to select patients with similar clinical and demographic data, but with different types of treatment (DEB or PTA), to reduce the bias of a nonrandomized cohort study (Table 1). All patients underwent aortography before the procedure to exclude iliac and femoral "in-flow" lesions and to study all of the tibial and plantar vessels. A written consent was obtained before the intervention for all patients. All bailout stenting and technical failures were considered a bias and were excluded from the analysis.[3] Study medication regimens and schedules were according to local clinical practice with aspirin (100-325 mg/d indefinitely) and clopidogrel or prasugrel loading dose (75 or 300 mg) with maintenance for 1 month. Clinical follow-up and instrumental follow-up were performed 24 months after the procedure.

Table 2. Type of Device.

Device	DEB	PTA
Elutax Aachen resonance	32	
Lutonix Bard	25	
Armada Abbott		38
FoxPlus Abbott		28
ClearPac Clearstream		36

Abbreviations: DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty.

Techniques and Devices

An antegrade approach was used in the majority of the interventions. Procedures were performed with a portable imaging fluoroscopic C-arm (OEC 9900 elite; GE Medical Siemens, Milwaukee, Wisconsin) or in a hybrid operating room using an Artis Zeego system (Artis Zeego; Siemens AG, Forchheim, Germany). Iodinated or gadolinium contrast was used, respectively, in patients with normal creatinine or with creatinine level >1.5 mg/dL. Intraoperative anticoagulation was achieved using 100 U/kg heparin, and the activating clotting time was maintained above 250 seconds. A 4F (for Elutax Aachen, FoxPlus Abbott, ClearPAc Clearstream) or 6F (for Lutonix Bard, Armada Abbott) introducer sheath was used with a 0.14-inch guidewire. Catheters for PTA or DEB were selected from a dedicated vascular shelf (Table 2). Predilatation was performed in 100% of the DEB cases. A 1-mm oversizing, after PTA, was considered for DEB diameter. Hence, all patients were primarily treated with PTA after, according to the operator's choice, they did or did not undergo DEB. The interventionist's decision was based on clinical and angiogram findings, his or her experience, cost-effectiveness of the procedure, and final results after POBA.

End Points

All patients were clinically and instrumentally evaluated 24 months after the procedure in a dedicated outpatient study. The primary end point of our study was a significant improvement in Rutherford Scale (IRS). Secondary end points were ankle–brachial index (ABI), the rate of restenosis (RR) measured by color-duplex scanning, mortality, and amputation rate. Finally, we considered the single endovascular tool in terms of clinical and instrumental efficacy. The RR was defined as a peak systolic velocity >2.4 m/s and a circumferential IH with a lumen loss more than 70% detected on ultrasound.[8]

Table 3. Type of Lesions and IRS.

IRS	DEB	PTA	*P* Value
Cumulative	74%	51%	.024
TASC II A lesions	76%	69%	.047
TASC II B lesions	86%	59%	.012
TASC II C lesions	65%	41%	.042
TASC II D lesions	55%	31%	.044

Abbreviations: DEB, drug-eluting balloon; IRS, Rutherford Scale; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Societal Consensus.

Statistical Analysis

Data were collected in a dedicated Office Xcel (Microsoft, Redmond, Washington) file and analyzed using SPSS 21.0 software (IBM, Armonk, New York). Continuous variables with a normal distribution are expressed as the mean ± standard deviation, and categorical variables as frequency and percentage. The study required at least 110 patients to provide ≥80% power to detect an improvement in the Rutherford classification, expressed as the change in the class number between baseline and the 24-month control (calculated for individual patients). Significance between the treatment groups was tested by Cochran-Mantel-Haenszel statistics. Categorical variables (given as number and percentage) were compared by the use of Fisher exact test. Survival and amputation are presented as Kaplan-Meier analysis with Mantel-Cox log-rank test. Differences were considered statistically significant at $P < .05$.

Results

Between January 2010 and March 2013, we treated 138 patients with CLI using simple PTA or DEB; the groups were clinically and demographically homogenous. We decided to perform DEB in 70 cases. Preoperative Rutherford classification showed an equal distribution for both the groups, and the same results were obtained when considering the anatomy of the lesions with TASC II classification[1] (lesion types A, B, C, and D). An antegrade and retrograde approach was used in 83.3% (110 cases) and 16.7% (28 cases), respectively.

Primary End Point

Rutherford Scale in cumulative and single TASC lesion classification was superior in the DEB group (74% vs 51%; $P = .024$) at 24 months than in the PTA group. The TASC II B lesions showed further superior results with a significant improvement in IRS with respect to the PTA group (Table 3). When matching the IRS in both groups, a longer lesion was associated with worst long-term results, even if the DEB group had a superior significant improvement in IRS. Irrespective of the type of treatment, TASC II type C and D lesions showed the worst results when compared to types A and B.

Table 4. ABI and RR in the Two Groups.

	DEB	PTA	*P* Value
ABI cumulative	0.64 ± 0.35	0.52 ± 0.22	.039
ABI TASC II A	0.65 ± 0.19	0.58 ± 0.15	.078
ABI TASC II B	0.71 ± 0.23	0.48 ± 0.12	.025
ABI TASC II C	0.49 ± 0.15	0.43 ± 0.21	.041
ABI TASC II D	0.40 ± 0.15	0.39 ± 0.21	.044
RR cumulative (psv >2.4 m/s + stenosis >70%)	19%	32%	.028
RR TASC II A	16%	19%	.068
RR TASC II B	15%	24%	.043
RR TASC II C	21%	38%	.034
RR TASC II D	38%	62%	.012

Abbreviations: ABI, ankle–brachial index; DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; RR, rate of restenosis; TASC, TransAtlantic Inter-Societal Consensus; psv, peak of systolic velocity.

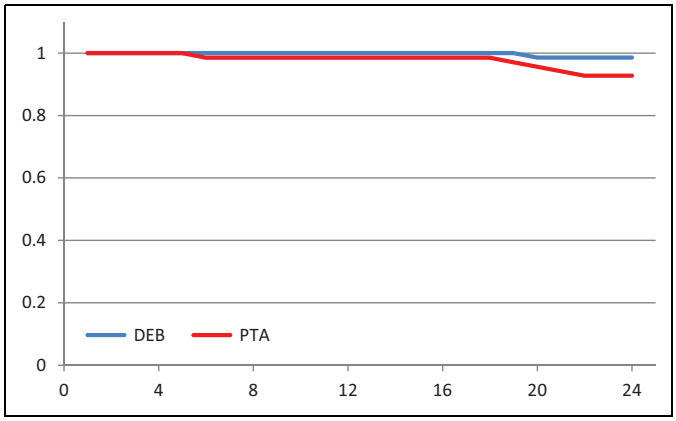

Figure 1. Cumulative Survival Rate.

Secondary End Point

In the DEB group, the increase in ABI was significantly higher than in the PTA group ($P = .039$; Table 4). For patients with TASC B lesions, DEB was most beneficial, resulting in a significant ABI increase and a lower RR (TASC B with DEB: from 0.35 ± 018 to 0.71 ± 0.23; TASC B with PTA: from 0.36 ± 0.21 to 0.48 ± 0.12; $P = .025$). In patients with TASC C and D lesions, the ABI improved less and the RRs were higher compared to the patients with TASC A and B lesions. Both the cumulative survival rate and the amputation rate showed significantly superior results for the DEB group (Figures 1 and 2). Major amputations were only performed in patients who were IRS 5 and 6. All analyzed variables were similar between the PTA and the DEB groups.

Discussion

In practical terms, although the level of evidence is low, the initial revascularization strategy for femoropopliteal disease is commonly an endovascular approach.[5,12,15] This is supported by a recent meta-analysis of the published literature regarding

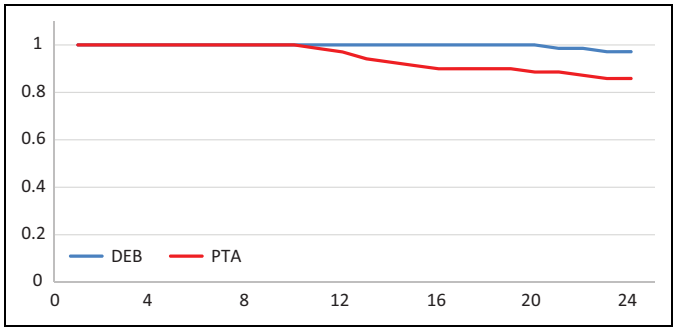

Figure 2. Amputation Rate.

endovascular versus surgical revascularization for femoropopliteal disease.[9] We investigated the long-term clinical results in patients with critical limb ischemia treated with PTA or DEB. Demographic data (Table 1) showed a homogenous distribution of the patients in the 2 groups, which reduced the bias resulting from a lack of randomization. Chronic limb ischemia remains a remarkable risk factor for cardiovascular events and amputation 1 year after the onset of symptoms. This aggressive pathology has been deeply investigated,[2,10] and there is a common agreement that CLI requires urgent and complete treatment. As reported by the TASC II and American Heart Association guidelines, endovascular therapy is the preferred treatment for type A and B lesions, whereas surgery is the preferred treatment for low-risk patients with type C and D lesions.[2,10] The patient's comorbidities, fully informed patient preference, and the local operator's long-term success rate must be considered when making treatment recommendations for type C and D lesions. According to this recommendation, we treated 98 patients with "de novo" lesions for CLI. Type C and D lesions were considered for endovascular therapy according to our endovascular experience, and all patients in the type C and D group were successfully treated with angioplasty. There has been an evolution of newer technologies, specifically patency-enhancing drug coating for balloons and stents. There is growing evidence from randomized trials that supports the use of DEB.[11,13,16,17] These trials underline the long-term benefit of lowering restenosis both for quality of life[18,19] and for life expentancy.[20] In our experience, we focused on clinical improvement using the IRS. Restoring an effective blood flow in the pedal and tibial vessels permits lesions to heal, relieves pain, and reduces the release of inflammatory cytokines.[21-23] The efficacy of endovascular therapy is correlated with vessel outflow, meaning there is a strict correlation between the number of patent vessels and the final outcome.[24] In our experience, we have used Lutonix Bard and Elutax Aachen as DEB. Lutonix has been supported by clinical trials,[10] and a second trial of Levant 2 is still ongoing to validate this DEB. No randomized trial has been considered for Elutax, and the literature lacks data[25] concerning the use of this DEB for tibial vessels. Nonetheless, we decided to use this device based on the good results in other experiences.[1,25] The 6-month results of Elutax SV showed this DEB to be comparable to and as effective as other DEBs that have undergone clinical trials. Our preliminary experiences reported that the ABI improved from 0.49 to 0.89, and the Rutherford stage decreased from 3 to 1. Another "pro" for the use of this DEB is the low-profile catheter, which always permits the use of a 4F introducer sheath with all of the diameters in peripheral vessels. Patients with reduced tibial outflow (3-vessel runoff) showed a significantly reduced patency relative to patients with 3-vessel runoff.[17,24] In our experience, we noted that reduced tibial outflow, such as in C type lesions, might be a causative factor in the reduced primary patency of percutaneous interventions; it is also possible that it is simply a marker for increased disease severity. Those with more severe or extensive disease might be more likely to represent with recurrent symptoms, thus leading to more frequent documentation of failure in this group relative to those with type A and B lesions. Drug-eluting balloons were shown to be more effective in controlling the worsening of IRS with significant cumulative results. Restenosis was significantly controlled in the DEB group, and an increased ABI was noted. The ABI provides key information on long-term prognosis, with an ABI $\leq$0.90 associated with a 3- to 6-fold increased risk of cardiovascular mortality. The benefits of a long-term improvement in ABI are evidenced by the better results in the free-from-amputation and survival rates as shown by Kaplan-Meier analysis (Figures 1 and 2).[7,14,15] The rationale of DEB has been already described,[11,13,18] but it is important to underline that the coated balloon releases most of the drug immediately during the first inflation when there is short contact with the vessel wall for 60 seconds. The duration of inhibition of cell proliferation exceeds the time that cells are actually exposed to the drug. In some studies,[11,18] only approximately 6.4% $\pm$ 2.9% of the original paclitaxel dose was found to be extractable from the surface of the balloons used in our trial. Although animal studies indicate that as much as 70% to 80% of the drug dose might be lost in the bloodstream,[25] the remaining dose and duration of drug exposure seem to be sufficient to prevent neointimal proliferation.

Conclusion

Although this study has a limitation due to the lack of randomization, we observed superior results with DEB. The cumulative free-from-amputation rate shows the benefit of using DEB. All patients who required an amputation belonged to Rutherford class 5 and 6. We showed that the DEB group obtained a better IRS, leading to a lower risk of amputation for these patients. Further research is needed before we can consider the DEB as the gold standard therapy for CLI. However, our experience, in addition to the existing literature, supports the use of DEB in patients with CLI Rutherford class >4. With the reduced need for a stent and considering the statement "leaving nothing behind", DEB can be considered a safe treatment of choice in CLI.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

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

References

1. TASC Steering Committee, Jaff MR, White CJ, Hiatt WR, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II). *J Endovasc Ther*. 2015; 22(5):663-677. doi: 10.1177/1526602815592206.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45(suppl s):s5-s67.
3. Karnabatidis D, Spiliopoulos S, Diamantopou-los A, et al. Primary everolimus-eluting stenting versus balloon angioplasty with bailout bare metal stenting of long infrapopliteal lesions for treatment of critical limb ischemia. *J Endovasc Ther*. 2011;18(1):1-12.
4. Ansel GM, Lumsden AB. Evolving modalities for femoropopliteal interventions. *J Endovasc Ther*. 2009;16(2 suppl 2):82-97.
5. Geraghty PJ, Mewissen MW, Jaff MR, Ansel GM; VIBRANT Investigators. Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease. *J Vasc Surg*. 2013;58(2):386-395.
6. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119(23):2986-2994.
7. TASC. Management of peripheral arterial disease (PAD). Trans-Atlantic Inter-Society Consensus (TASC). *Eur J Vasc Endovasc Surg*. 2000;19(suppl a):si-xxviii, s1-s250.
8. Troutman DA, Madden NJ, Dougherty MJ, Calligaro KD. Duplex ultrasound diagnosis of failing stent grafts place for occlusive disease. *J Vasc Surg*. 2014;60(6):1580-4.
9. Antoniou GA, Chalmers N, Georgiadis GS, et al. Review A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. *J Vasc Surg*. 2013;57(1):242-253.
10. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation*. 2006;113(1):1474-1547.
11. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization. *JACC Cardiovasc Interv*. 2014;7(1):10-19.
12. Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. *Lancet*. 1999;354(9176):407-413.
13. Tepe G, Laird J, Schneider P, et al; IN.PACT SFA Trial Investigators. Trial Investigators. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131(5):495-502.
14. Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? *Circulation*. 2004;109(21 suppl 1):ii18-ii26.
15. Tolva VS, Casana R, Lonati L, et al. Percutaneous transluminal angioplasty improves glucose control and quality of life in patient with critical limb ischemia. *Eur Rev Med Pharmacol Sci*. 2012; 16(15):2082-2087. PMID:23280023.
16. Liistro F, Grotti S, Porto I, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). *JACC Cardiovasc Interv*. 2013;6(12):1295-1302.
17. Zeller T, Rastan A, Macharzina R, et al. Drug-coated balloons vs. drug-eluting stents for treatment of long femoropopliteal lesions. *J.Endovasc Ther*. 2014.21(3):359-368.
18. Fanelli F, Cannavale A, Boatta E, et al Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther*. 2012,19(5): 571-558.
19. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. *JAMA*. 2007;297(6):611-619.
20. Herten M, Torsello GB, Schönefeld E, Imm B, Osada N, Stahlhoff S. Drug-eluting balloons for femoropopliteal lesions show better performance in de novo stenosis or occlusion than in restenosis. *J Vasc Surg*. 2015;61(2):394-399.
21. Molloy KJ, Nasim A, London NJ, et al. Percutaneous transluminal angioplasty in the treatment of critical limb ischemia. *J Endovasc Ther*. 2003;10(2):298-303.
22. Huang ZS, Schneider DB. Endovascular intervention for tibial artery occlusive disease in patients with critical limb ischemia. *Semin Vasc Surg*. 2014;27(1):38-58.
23. Bleda S, de Haro J, Varela C, Acin F. C-reactive protein and endovascular treatment of lower limb peripheral artery disease: an independent prognostic factor. *J Endovasc Ther*. 2015;22(2): 233-239.
24. Derubertis BG, Pierce M, Ryer EJ, Trocciola S, Kent KC, Faries PL. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb threatening ischemia. *J Vasc Surg*. 2008;47(1): 101-108.
25. Tolva V, Mazzola S, Zerbi P, et al. A successful experimental model for intimal hyperplasia prevention using a Resveratrol eluting balloon. *J Vasc Surg*. 2016;63(3):788-794.

Cardiovasc Intervent Radiol
https://doi.org/10.1007/s00270-019-02279-6

Drug-Coated Balloon Angioplasty of Infrapopliteal Lesions in Patients with Critical Limb Ischaemia: 1-Year Results of the APOLLO Trial

Ulf Teichgräber[1] · Thomas Lehmann[2] · Marcus Thieme[3] · Kersten-Uwe Wahl[4] · Christian Stelzner[5] · Albrecht Bormann[6] · Linda Götz[7] · Tobias Kroeßner[8] · Harald Boden[9] · Lars Maiwald[10] · René Aschenbach[1]

Received: 2 May 2019 / Accepted: 26 June 2019

Abstract

Purpose This study intended to assess effectiveness and safety of the drug-coated balloon (DCB) angioplasty of infrapopliteal atherosclerotic lesions in patients with critical limb ischaemia (CLI) in a real-world setting.

Methods Consecutive patients with critical limb ischaemia who underwent infrapopliteal drug-coated balloon angioplasty with the ELUTAX SV DCB were enrolled into the prospective, multicentre, single-arm observational registry. Primary outcome was clinical improvement at 6 and 12 months. Secondary outcomes were change in quality of life, primary patency, freedom from repeat revascularisation, and amputation-free survival at 6 and 12 months.

Results A total of 164 patients (74.7 ± 9.2 years) with CLI were included at nine German sites between November 2015 and September 2017. The majority (79.9%) of patients had diabetes mellitus, 57.3% had renal insufficiency, and 35.3% had coronary artery disease. Mean lesion length was 71.2 ± 76.5 mm. The Rutherford category improved by 3.0 ± 2.0 ($p < 0.0001$) within 12 months, resulting in a clinical improvement by at least one Rutherford category in 80.2% of the patients. Walking impairment questionnaire score, European Quality of Life index, and patient-reported pain improved significantly from baseline to 6 and 12 months. Primary patency was 68.5%, freedom from target lesion revascularisation 90.6%, and amputation-free survival 83.5% at 12 months.

Conclusion Infrapopliteal drug-coated balloon angioplasty with the ELUTAX SV DCB in patients with critical limb ischaemia was efficacious and safe over the medium term. The study is registered with Clinical.Trials.gov (Identifier: NCT02539940).

Keywords Below the knee · Critical limb ischaemia · Drug-coated balloon angioplasty · Drug-eluting balloon · Infrapopliteal · Paclitaxel · Peripheral artery disease

✉ Ulf Teichgräber
ulf.teichgraeber@med.uni-jena.de

[1] Department of Radiology, Jena University Hospital, Am Klinikum 1, 07747 Jena, Germany

[2] Center for Clinical Studies, Jena University Hospital, Jena, Germany

[3] REGIOMED Klinikum Sonneberg, Sonneberg, Germany

[4] Oberlausitz Kliniken, Bautzen, Germany

[5] Städtisches Krankenhaus Dresden-Friedrichstadt, Dresden, Germany

[6] Klinikum Altenburger Land, Altenburg, Germany

[7] Saale-Unstrut Klinikum Naumburg, Naumburg, Germany

[8] SRH-Waldklinikum Gera, Gera, Germany

[9] Ilm-Kreis-Kliniken Arnstadt-Ilmenau, Ilmenau, Germany

[10] Kreiskrankenhaus Torgau, Torgau, Germany

Introduction

Patients with critical limb ischaemia (CLI) have a risk of about 50% of major amputation or death within the first year from presentation [1, 2]. Even after major amputation, almost half of those aged 70 and older probably will die in the following year [3].

Published online: 08 July 2019

CLI is usually a multilevel artery disease, mostly involving the infrapopliteal arteries. The majority of CLI patients concomitantly suffer from diabetes and other cardiovascular diseases, unfavourably reinforcing each other. Guidelines require infrapopliteal revascularisation for limb salvage whenever possible, and endovascular therapy should be considered in patients with stenosis, short occlusions, or at high risk for open surgery [4]. However, infrapopliteal artery disease is characterised by small vessels, particularly prone to elastic recoil [5], low flow, and a diffuse pattern of lesions, frequently accompanied by medial calcification. The incidence of restenosis of about 40–60% at 1 year after standard balloon angioplasty (POBA) is disappointing [6, 7]. Even bare-metal stent implantation does not make a substantial improvement [8]. In short lesions, drug-eluting stents were found to be superior to POBA or bare-metal stents, but did not decrease mortality.

In medium-length lesions, drug-coated balloons (DCBs) tended to prevent restenosis and target lesion revascularisation but did not improve the amputation-free survival [9]. However, advanced technology of DCBs could have improved efficacy and safety. This study aimed to assess the effectiveness of the ELUTAX SV paclitaxel-coated balloon in a real-world setting over a period of 12 months.

Methods

Study Design and Setting

The APOLLO study is a prospective, multicentre, observational, investigator-initiated trial. Recruitment took place over a period of 23 months at nine German sites. Clinical evaluation, duplex ultrasonography (DUS), assessment of quality of life (QoL) measures including Walking Impairment Questionnaire (WIQ) score [10], European Quality of Life-5 Dimensions (EQ-5D) index [11, 12], and patient-reported pain, as well as determination of the ankle–brachial index (ABI) were conducted at baseline and at 6 and 12 months after revascularisation. All target limb-related adverse events, device-related adverse events, adverse cardiovascular events, and all severe adverse events had to be reported by the investigators. The study is registered with ClinicalTrials.gov (Identifier: NCT02539940).

Patients

Patients who were at least 18 years of age and were scheduled for DCB angioplasty with the ELUTAX SV DCB for the treatment of below-the-knee artery stenosis of $\geq$ 70% or occlusion and suffered from critical limb ischaemia (Rutherford category 4–6 or CLI confirmed by photoplethysmography) were eligible. Inclusion was independent of a successful guide wire passage and lesion preparation. All patients provided written informed consent. The inflow artery had to be patent; however, its treatment prior to the index procedure was permitted. Per definition, a target vessel reconstitutes at or above the ankle. Key exclusion criteria were planned major target limb amputation, acute limb ischaemia, or application of DCB other than ELUTAX SV in a target limb artery.

Study Device and Procedure

The semi-compliant ELUTAX SV drug-coated balloon (Aachen Resonance, Aachen, Germany) is coated with a matrix, consisting of two layers of paclitaxel and a seal layer of dextran. Paclitaxel is supposed to inhibit neointimal proliferation and thus to prevent restenosis. The inner paclitaxel layer has an amorphous and the outer layer a crystalline structure. Paclitaxel dose density is 2.2 µg/mm^2. Dextran protects the paclitaxel layers from abrasion during introduction of the catheter, minimises the paclitaxel wash off by providing a continuous drug transfer to the vessel wall, and supports platelet inhibition. The DCB had to be used according to the manufacturer's instruction and the standard clinical practice of the participating centres. Inflation time recommended by manufacturer is 30 s. Pre-dilation was not mandatory. However, pre-dilation as well as prolonged inflation, bailout stenting, or post-dilation in case of significant residual stenosis or flow-limiting dissection were left to investigator's discretion.

Concomitant study medication had to comply with current guidelines. To prevent systematic vascular events and limb events, long-term treatment with aspirin and, in case of bailout stenting, dual antiplatelet therapy with aspirin and clopidogrel for at least one month was recommended.

Study Outcome Measurements

Primary effectiveness outcome was clinical improvement based on the change in Rutherford category from baseline to 6 and 12 months. Secondary effectiveness outcome was change in QoL, incidence of primary patency, freedom from target lesion revascularisation (TLR), and freedom from target vessel revascularisation (TVR) at 6 and 12 months. QoL was determined by means of WIQ score, EQ-5D index, and patient-reported pain on a scale from zero to ten. Primary patency was given if DUS examination showed sufficient flow upon investigator's assessment without the need of prior TLR. Safety endpoints were freedom from minor amputation, freedom from major amputation, amputation-free survival, and all-cause mortality at 6 and 12 months. Minor amputation was defined as

transmetatarsal or distal amputation and major amputation as above transmetatarsal amputation.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) and categorical variables as counts and percentages. Differences between variables were assessed with the two-sided sign test or the Wilcoxon sign-rank test. Kaplan–Meier analysis was performed to estimate freedom from TLR, TVR, amputation, or death, as well as primary patency. Results are presented as parameter estimates and their corresponding 95% confidence intervals (CIs). Logistic regression was used to assess predictors of clinical improvement without the need of TLR at 6 months and the composite of death and any amputation at 12 months. Established candidate variables were pre-screened based on univariable analysis with a *P* value cut-off of 0.25 based on Wald test from logistic regression. Subsequently, variable selection for multivariable modelling was continued by stepwise backward regression with an entry and removal threshold P value of 0.1. A two-sided value of $p < 0.05$ indicated statistical significance. Statistical analysis was performed using SPSS Statistics (version 25.0. IBM, Armonk, NY, USA).

Results

Study Population and Treatment

From November 2015 to September 2017, 164 consecutive CLI patients with 248 infrapopliteal artery lesions were enrolled at nine German centres. All but one underwent DCB angioplasty with the ELUTAX SV DCB. About 80% of the patients had diabetes mellitus and 44% were obese. Fifty-seven per cent of patients had renal insufficiency (Table 1). Mean lesion length was 71.2 ± 76.5 mm. Chronic occlusion and severe calcification were present in 43% and 27% of patients, respectively (Table 2). Inflow intervention was conducted in 31% and pre-dilation in 68% of patients (Table 3). Completion of DUS follow-up was 55.5% (91 of 164 patients) at 6 months and 47.0% (77 of 164 patients) at 12 months.

Table 1 Patient demographics and clinical characteristics (n = 164[a])

Age, years	74.7 ± 9.2
Sex	
Female	55 (33.5)
Male	109 (66.5)
Diabetes mellitus	131 (79.9)
Insulin dependent	82/130 (63.1)
Hyperlipidemia	88/159 (55.3)
Body mass index	29.2 ± 5.4
> 30	71/162 (43.8)
Hypertension	148 (90.2)
Smoking	66/146 (45.2)
Current	17/146 (11.6)
Coronary artery disease	55/156 (35.3)
Heart failure	41/160 (25.6)
Renal insufficiency	94 (57.3)
Cerebrovascular disease	29/154 (18.8)
Stroke	24/154 (15.6)
ABI (n = 83)	0.91 ± 0.46
< 0.5	13/83 (15.7)
≥ 1.3	22/83 (26.5)
Rutherford category	
3—severe claudication	7[b] (4.3)
4—ischaemic rest pain	29 (17.7)
5—minor tissue loss	109 (66.5)
6—major tissue loss	19 (11.6)
Previous amputation	42 (25.6)
Major amputation[c]	7/164 (4.3)
Medication	
Statin	100/162 (61.7)
Platelet inhibitor	64/163 (39.3)

Categorical values are presented as counts (percentages); continuous values are presented as mean ± standard deviation

[a]One patient did not receive the study device. No information about the kind of treatment is available

[b]Photoplethysmography indicated critical limb ischaemia

[c]Above transmetatarsal

Primary Effectiveness Outcome

Rutherford category improved by 2.5 ± 2.0 at 6 months ($p < 0.0001$) and 3.0 ± 2.0 at 12 months ($p < 0.0001$) (Fig. 1A). Clinical improvement by at least one Rutherford category was observed in 74.0% (94 of 127 patients) at 6 months (Fig. 1B) and in 80.2% (85 of 106 patients) at 12 months (Fig. 1C). Excluding patients who did not receive the study device or had peripheral artery diseases (PAD) of Rutherford category 3 at baseline, the 12-month incidence of clinical improvement was 79.0%.

Secondary Effectiveness Outcomes

The WIQ score improved by 7.1 ± 27.9% (p = 0.0119) of the maximum score within 6 months and by 10.7 ± 32.4% (p = 0.0035) from baseline to 12 months (Fig. 2A). The EQ-5D index improved by 0.08 ± 0.30 (p = 0.0013) within 6 months and by 0.07 ± 0.33 (p = 0.0003) over a period of 12 months (Fig. 2B). Patient-reported pain

Table 2 Lesion characteristics[a] (n = 248)

Lesion length, mm	71.2 ± 76.5
Total lesion length, mm	107.2 ± 92.6
Diameter stenosis, %	89.4 ± 10.5
Chronic total occlusion	
Artery based	105/273 (38.5)
Patient based	70/164 (42.7)
Severe calcification[b]	22/83 (26.5)
TASC classification[c]	
TASC A	48/162 (29.6)
TASC B	68/162 (42.0)
TASC C	39/162 (24.1)
TASC D	7/162 (4.3)
Affected arteries	273
Popliteal artery	29 (10.6)
Tibioperoneal trunk	42 (15.4)
Anterior tibial artery	100 (36.6)
Peroneal artery	55 (20.1)
Posterior tibial artery	47 (17.2)
Number of crural arteries with runoff to the foot	
0	27/155 (17.4)
1	73/155 (47.1)
2	43/155 (27.7)
3	12/155 (7.7)

Categorical values are presented as counts (percentages); continuous data are presented as mean ± standard deviation

[a]Adjacent lesions without angiographic evidence of healthy segments 20 mm or greater were considered as single lesion

[b]Assessed by visual estimate or medial calcification indicated by ABI ≥ 1.3

[c]Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) classification of infrapopliteal lesions

Table 3 Procedure characteristics

Inflow intervention	51/164 (31.1)
SFA	25/51 (49.0)
P1	10/51 (19.6)
P2	11/51 (21.6)
P3	5/51 (9.8)
Pre-dilation (patient-based)	110/163 (67.5)
Pre-dilation (DCB-based)	159/286 (55.6)
Balloon length, mm	88.5 ± 46.6
Nominal diameter, mm	2.7 ± 3.3
Maximum pressure, atm	10.6 ± 3.3
Pre-dilation time, sec	48.5 ± 41.8
Drug-coated balloon[a]	286
DCB/lesion	1.15
Balloon length, mm	86.4 ± 43.8
Nominal diameter, mm	2.9 ± 2.2
Maximum pressure, atm	8.5 ± 2.0
Inflation time, sec	114.4 ± 34.7
Post-dilation	18/163 (11.0)
Scoring balloon	2 (1.2)
Balloon length, mm	63.1 ± 47.1
Nominal diameter, mm	5.0 ± 8.8
Maximum pressure, atm	10.0 ± 3.3
Inflation time, sec	82.8 ± 59.7
Bailout stenting[b]	5/163 (3.1)
Medication at 6 months	
Statin	98/137 (71.5)
Platelet inhibitor	50/136 (36.8)
Medication at 12 months	
Statin	89/119 (74.8)
Platelet inhibitor	33/116 (28.4)

Categorical values are presented as counts (percentages); continuous values are presented as mean ± standard deviation

DCB drug-coated balloon; *SFA* superficial femoral artery; *P1* proximal popliteal artery segment; *P2* mid-popliteal artery segment; *P3* distal popliteal artery segment

[a]One of 164 patients did not receive a drug-coated balloon

[b]Four lesions were stented due to dissection and one lesion due to residual stenosis > 30%

decreased by 1.2 ± 2.1 pain scale units ($p < 0.0001$) within 6 months and by 1.0 ± 2.8 units ($p = 0.003$) within 12 months (Fig. 2C). ABI increased significantly from baseline to 6 months (1.1 ± 0.4, $p = 0.0009$) and from baseline to 12 months (1.2 ± 0.4, $p = 0.0047$).

Freedom from TLR was achieved in 97.1% (standard error [SE] 1.4%) and 90.6% (SE 2.6%) of patients at 6 and 12 months, respectively (Fig. 3A). Freedom from TVR (including TLR) was achieved in 94.9% (SE 1.9%) and 88.4% (SE 2.8%) at 6 and 12 months, respectively (Fig. 3B). Patency at discharge was achieved in 97.8% (176 of 180 lesions). Cumulative incidence of patient-based primary patency was 91.6% (SE 3.0%) and 68.5% (SE 5.2%) at 6 and 12 months, respectively (Fig. 3C). Post hoc multivariable analysis revealed male sex as independent risk factor for worse clinical response at 6 months (odds ratio [OR] 0.17, $p = 0.010$). Inversely, statin medication at 6 months tended to be associated with clinical improvement (OR 3.08, $p = 0.053$) (Fig. 4).

Safety Outcomes

Freedom from minor amputation was 82.5% (95% CI: 75.1–87.9) at 6 months and 77.8% (95% CI: 69.4–84.1) at 12 months. Limb salvage was 97.1% (SE 1.4%) and 95.4% (SE 1.9%) at 6 and 12 months, respectively (Fig. 5A). Survival was 94.5% (SE 1.8%) and 87.8% (SE 2.7%) at 6

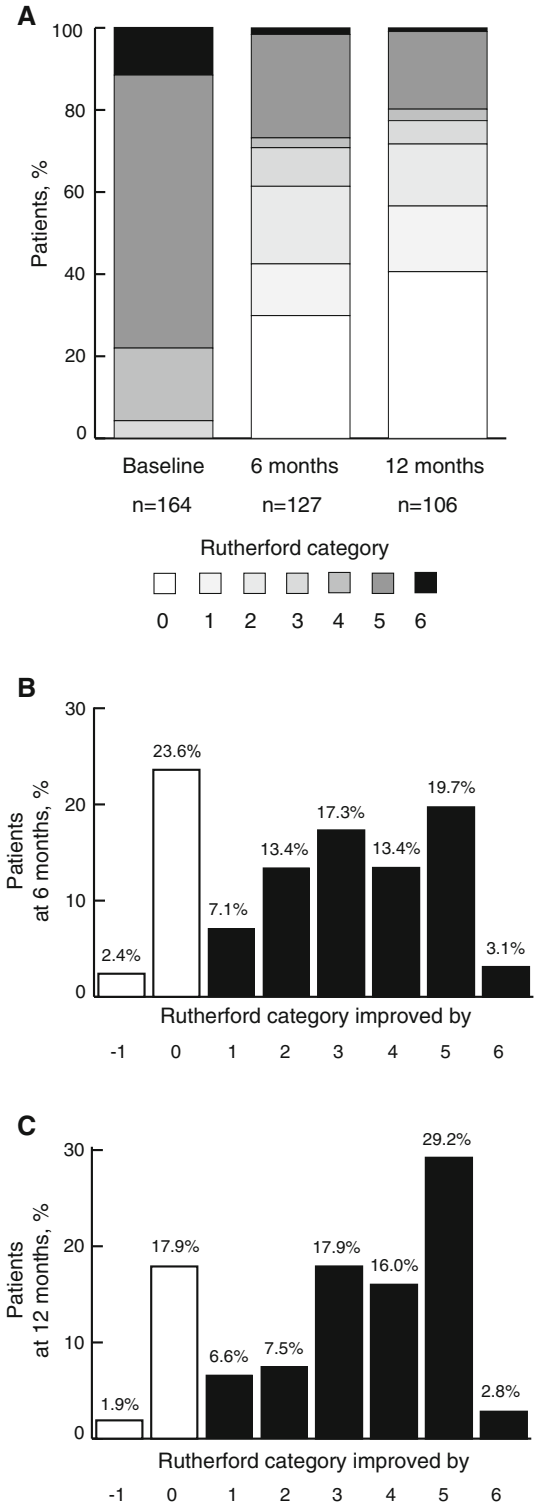

Fig. 1 Distribution of Rutherford categories at baseline and follow-ups (**A**), and clinical improvement from baseline to 6 months (**B**) and to 12 months (**C**)

and 12 months, respectively (Fig. 5B), and major amputation-free survival was 90.7% (SE 2.3%) and 83.8% (SE 3.0%) at 6 and 12 months, respectively (Fig. 5C).

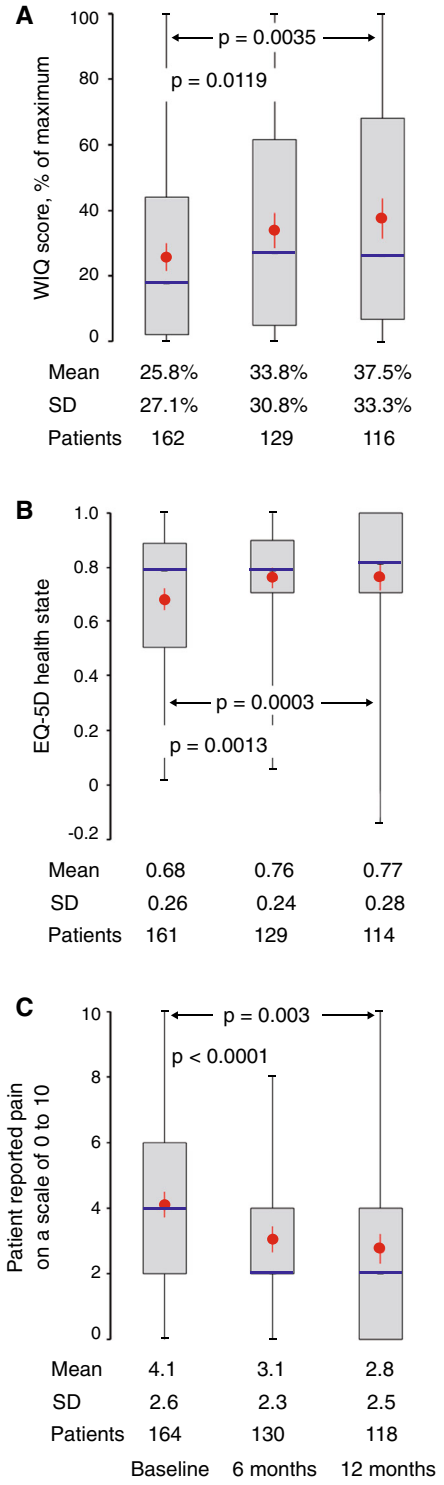

Fig. 2 Quality of life at baseline and at 6- and 12-month follow-ups expressed in Walking Impairment Questionnaire score (**A**), European Quality of Life-5 Dimensions score (**B**), and patient-reported pain (**C**). Box plots indicate median and interquartile range. Whiskers end with the lowest and highest data point. Red dots represent means with their corresponding 95% confidence interval. *SD* standard deviation, *WIQ* Walking Impairment Questionnaire, *EQ-5D* European Quality of Life-5 Dimensions score

A total of twenty patients (15.9%) died within one year of the intervention. Five patients died from heart failure, four from sepsis, two each from stroke, renal failure, pneumonia, or haemorrhage, and one each from myocardial infarction or arrhythmia. One death remained unexplained (Table 4). Without consideration of patients who did not receive the study device or had PAD of Rutherford category 3 at baseline, 12-month incidence of restenosis was 25.7%, of repeat revascularisation 11.3%, of minor or major amputations 26.5% and 5.3%, respectively, and of mortality 15.8%.

Post hoc logistic regression revealed a higher BMI and inflow vessel intervention as independent predictors for a reduced risk of death or amputation at 12 months (OR 0.88 [$p = 0.007$] and OR 0.37 [$p = 0.040$], respectively). Renal insufficiency tended to increase the risk of death or amputation (OR 2.2, $p = 0.078$) (Fig. 6).

Discussion

After angioplasty with the ELUTAX SV DCB, the majority of patients improved clinically. A significant share reported on an improved quality of life that maintained throughout the following year. Repeat revascularisation was needed in about one of eight patients, and minor amputation in one of four. Eighty-four per cent of the patients survived the first year after revascularisation without major amputation.

Clinical Improvement

Clinical improvement and quality of life (QoL) are rarely reported in trials on CLI because limb salvage is paramount. Although QoL is highly subjective, it is a useful complement of clinical effectiveness outcomes. This study found a sustained improvement of QoL in a population with advanced disease and multiple comorbidities. Increased walking ability and activity might have contributed to patency and collateralisation. The favourable impact of statin on clinical improvement is supported by previous results from the CRITISCH registry [13] and a large-scale Swedish registry [14]. Therefore, preventive pharmacological treatment pursuant to guidelines [4] should be strongly recommended. The former registry additionally confirms the worse treatment response in men.

Patency and Repeat Revascularisation

Meta-analysis on three randomised trials that compared infrapopliteal DCB angioplasty with POBA in CLI patients (DEBATE-BTK [15], IN.PACT DEEP [16], BIOLUX P-II [17]) reported on a non-significant trend in favour of DCB angioplasty regarding restenosis [7, 9]. However, heterogeneity was significant. One-year incidence of restenosis after POBA varied between 47 and 74% [6, 9, 15]. In contrast, incidence of restenosis after DCB is reported with 30% and thus is in line with the findings from this study. This advantage is probably due to inhibition of neointimal proliferation by paclitaxel.

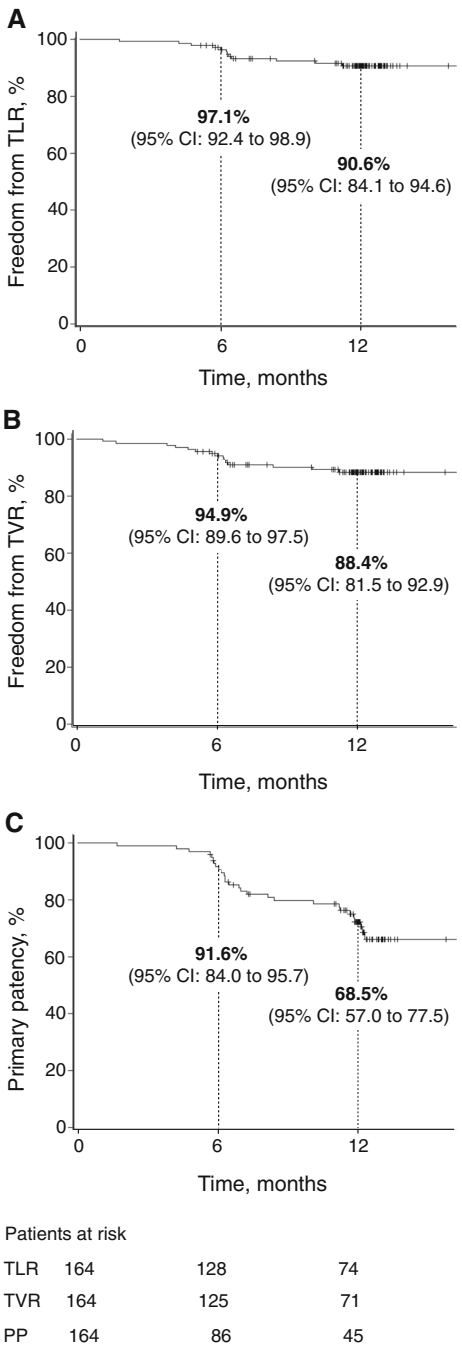

Fig. 3 Kaplan–Meier survival estimates for freedom from target lesion revascularisation (**A**), freedom from target vessel revascularisation (**B**), and primary patency (**C**). *CI* confidence interval, *PP* primary patency, *TLR* target lesion revascularisation, *TVR* target vessel revascularisation

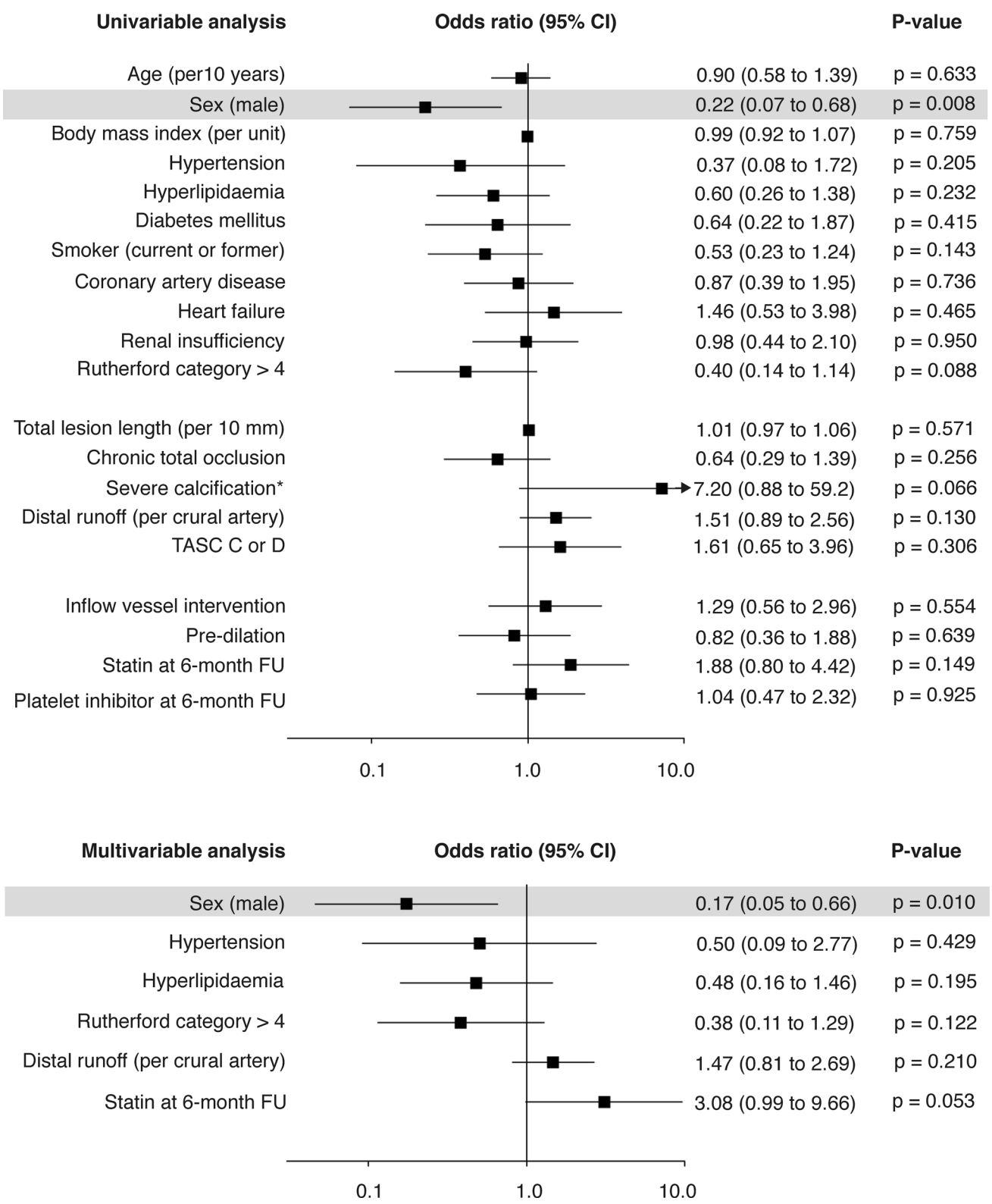

Fig. 4 Probability of improvement by at least one Rutherford category at 6 months without the need of target lesion revascularisation. *Not included into multivariable regression due to numerous missing data. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

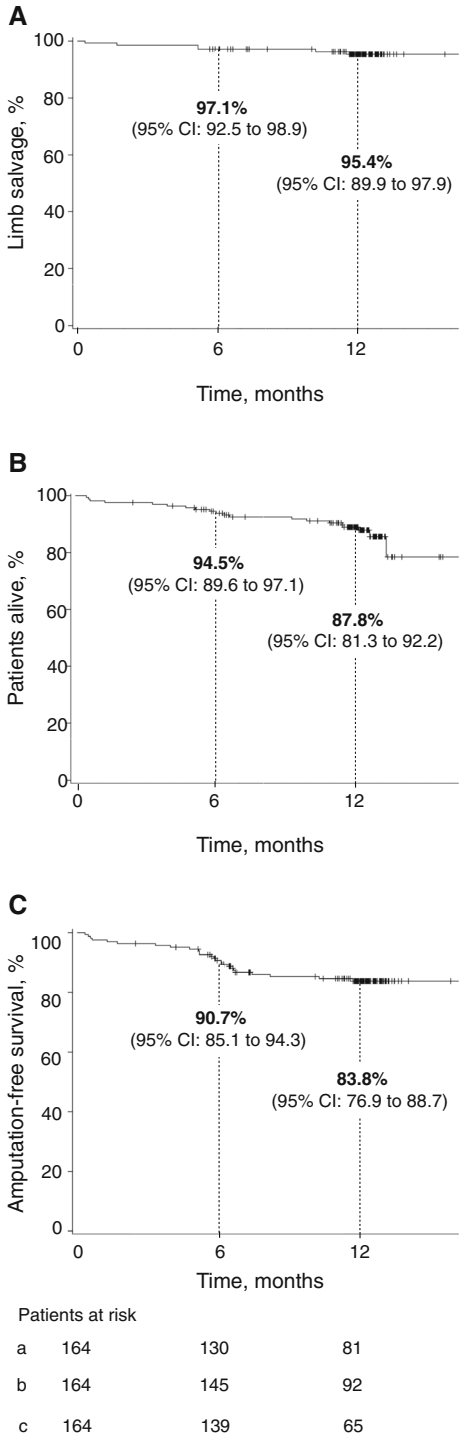

Fig. 5 Kaplan–Meier estimates for limb salvage (**A**), survival (**B**), and major amputation-free survival (**C**). *CI* confidence interval

In this study, TLR was less frequently conducted than in previous DCB studies. It might be assumed that in shorter, less complex lesions, restenosis more rarely needs to be revascularised. The above-mentioned meta-analysis revealed a difference to POBA that was just below statistical significance [9]. From this, one could conclude that

Table 4 Incidence of safety outcomes

	At 6 months	At 12 months
All-cause mortality[a]	10/141 (7.1)	20/126 (15.9)
Major target limb amputation[b]	4/137 (2.9)	6/119 (5.0)
Minor target limb amputation[c]	26/137 (19.0)	30/119 (25.2)
Repeat revascularisation[d]	9/137 (6.6)	13/119 (10.9)
Restenosis[e]	10/91 (11.0)	18/77 (23.4)
Thrombectomy	1/163 (0.6)	1/163 (0.6)
Atherectomy	0/162 (0.0)	0/162 (0.0)

Values are given as counts (percentages)

[a]Five patients died from heart failure, four patients from sepsis, two patients each from stroke, renal failure, pneumonia, or haemorrhage, and one patient each from myocardial infarction, or arrhythmia. On death remained unexplained

[b]Above transmetatarsal

[c]Transmetatarsal or distal

[d]Target vessel revascularisation including target lesion revascularisation

[e]No sufficient flow through the target lesion by duplex ultrasonography

with new-generation DCB, there might be a significant advantage over POBA. However, a meta-analysis of 27 trials on infrapopliteal POBA revealed a somewhat lower incidence of TLR with significant heterogeneity [6]. Thus, superiority of DCB angioplasty over POBA remains to be proven by future randomised trials.

Amputation and All-Cause Mortality

Limb salvage is the primary objective of revascularisation in CLI patients. In this study, considerable fewer patients underwent major amputation than during previous studies on infrapopliteal POBA [6] and DCB angioplasty [9].

Incidence of all-cause mortality in this study was slightly higher compared to previous meta-analysis on DCB [9, 18], similar to POBA [6], and lower compared to any kind of CLI revascularisation [19]. Except for renal insufficiency, every single comorbidity statistically was not associated with death or amputation. However, CLI patients frequently suffer from multiple comorbidities which may adversely affect one another and may enhance disease progression. Advanced age, physical constitution, and cardiovascular medication probably carry weight. Finally, mortality and causes of death of patients who withdrew or were lost to follow-up remain unknown.

Shammas et al. [20] reported on a threefold increased risk of major amputation and a 14-fold increased risk of death in diabetic compared to non-diabetic CLI patients. In addition, the above-mentioned Swedish registry supports the finding on an increased risk of death or amputation in

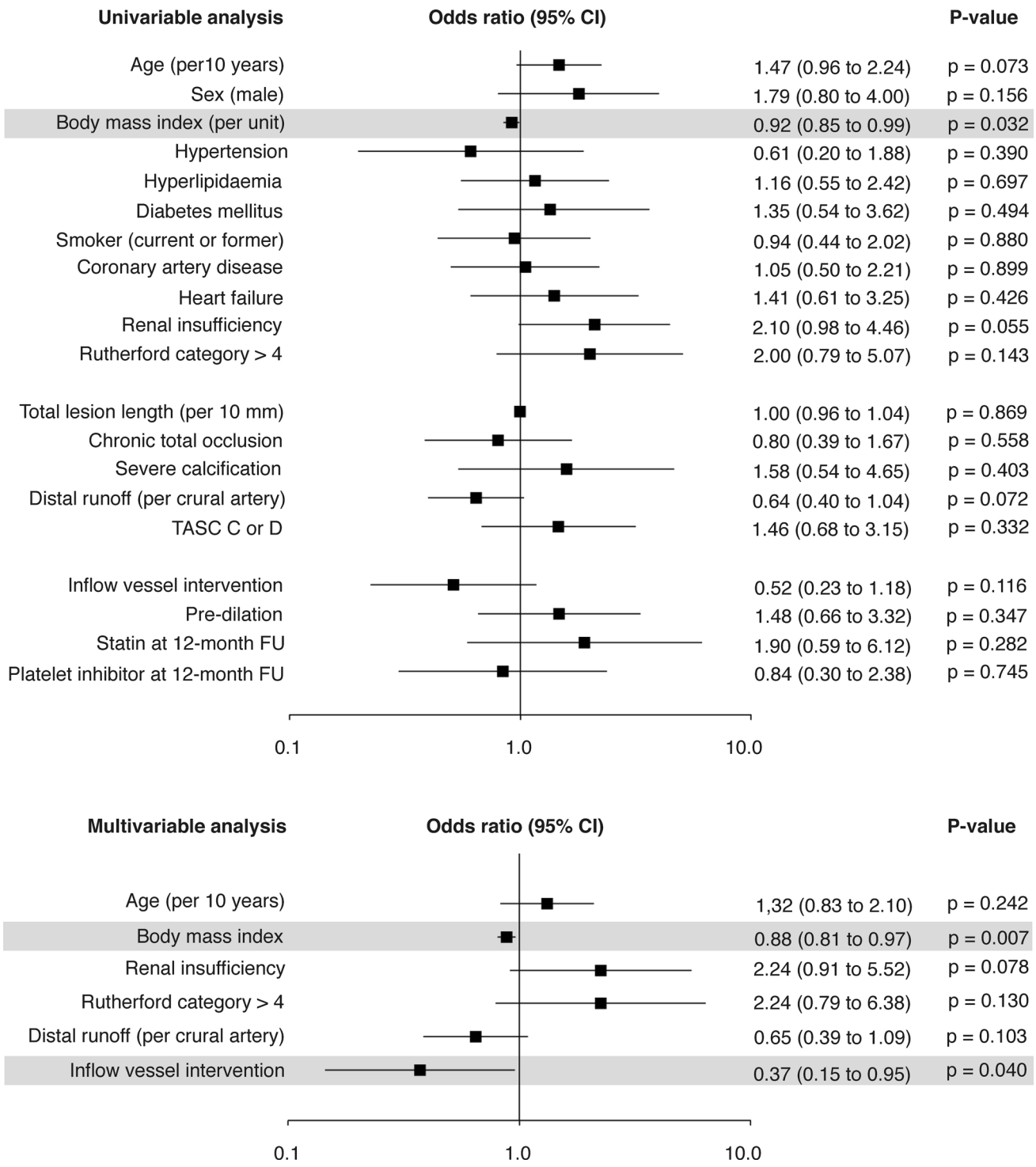

Fig. 6 Probability of death or any amputation at 12 months. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

patients with renal insufficiency [14]. In the light of this, mortality in this study was consistent.

A higher BMI was associated with less mortality or amputation. Accordingly, Moussa et al. [21] found a worse in-hospital mortality of underweight compared to normal-BMI patients with severe peripheral artery disease. This might suggest that in CLI patients, downward deviations from the normal BMI may be indicative for poor health. Inflow intervention did not considerably increase clinical improvement but significantly reduced the risk of death or

amputation. This might be attributed to patients who underwent minor amputation and subsequently improved clinically. A previously suggested interaction between diameter stenosis and major adverse events [18] could not be confirmed by this study. Total occlusions at baseline were not associated with death or amputation. Finally, with regard to recent concerns about adverse long-term effects of paclitaxel-coated devices, data from trials that prioritise safety endpoints are needed [22].

Strength and Limitations

The strength of this study is that it provides detailed results on clinical improvement and change in quality of life. Moreover, post hoc analysis identified predictive variables for clinical improvement and risk factors for death and amputation. The study has some limitations. First, return of patients for DUS follow-up was low. Standard errors of primary patency at 6 and 12 months, however, were reasonable. Second, patency was given if flow was clearly demonstrated by DUS. To simplify study-related follow-up evaluations, quantitative measurement was not mandatory. Third, ABI data were obtained by only about half of the patients. In addition, due to medial calcification, a high proportion of ABIs were not suitable to determine the hemodynamic condition. Fourth, severity of calcification was not rated based on an established calcium scoring system but only by investigator's estimate or ABI $\geq$ 1.3. Fifth, classification of wounds and quality of wound care management were not inquired. Sixth, seven patients with PAD of Rutherford category 3 were included. Exclusion of these patients from the analysis led to slightly worse results.

Conclusions

In conclusion, infrapopliteal angioplasty with the ELUTAX SV DCB improved the clinical status and quality of life of CLI patients over a period of 12 months. Restenosis, TLR, and all-cause death were comparable to previous data from infrapopliteal DCB angioplasty in CLI patients and less frequent than known from POBA. Considerably fewer major amputations were necessary than previously reported from any other strategy of revascularisation.

Funding This study was funded by Aachen Resonance.

Compliance with Ethical Standards

Conflict of interest All other authors declare that they have no conflict of interest, except of Prof. Teichgräber who received a funding for the APOLLO study by Aachen Resonance.

Ethical Approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Jaff MR, White CJ, Hiatt WR, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II): the TASC steering comittee(.). Ann Vasc Dis. 2015;8(4):343–57.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45(Suppl S):S5–67.
3. Klaphake S, de Leur K, Mulder PG, et al. Mortality after major amputation in elderly patients with critical limb ischemia. Clin Interv Aging. 2017;12:1985–92.
4. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763–816.
5. Baumann F, Fust J, Engelberger RP, et al. Early recoil after balloon angioplasty of tibial artery obstructions in patients with critical limb ischemia. J Endovasc Ther. 2014;21(1):44–51.
6. Mustapha JA, Finton SM, Diaz-Sandoval LJ, Saab FA, Miller LE. Percutaneous transluminal angioplasty in patients with infrapopliteal arterial disease: systematic review and meta-analysis. Circ Cardiovasc Interv. 2016;9(5):e003468.
7. Wu R, Tang S, Wang M, Li Z, Yao C, Wang S. Drug-eluting balloon versus standard percutaneous transluminal angioplasty in infrapopliteal arterial disease: a meta-analysis of randomized trials. Int J Surg. 2016;35:88–94.
8. Katsanos K, Kitrou P, Spiliopoulos S, Diamantopoulos A, Karnabatidis D. Comparative effectiveness of plain balloon angioplasty, bare metal stents, drug-coated balloons, and drug-eluting stents for the treatment of infrapopliteal artery disease: systematic review and Bayesian network meta-analysis of randomized controlled trials. J Endovasc Ther. 2016;23(6):851–63.
9. Zhang J, Xu X, Kong J, et al. Systematic review and meta-analysis of drug-eluting balloon and stent for infrapopliteal artery revascularization. Vasc Endovasc Surg. 2017;51(2):72–83.
10. Regensteiner JG, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral artery disease. J Vasc Med Biol. 1990;2:142–52.
11. EuroQol. A new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199–208.
12. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53–72.
13. Stavroulakis K, Borowski M, Torsello G, Bisdas T. Association between statin therapy and amputation-free survival in patients with critical limb ischemia in the CRITISCH registry. J Vasc Surg. 2017;66(5):1534–42.

14. Baubeta Fridh E, Andersson M, Thuresson M, et al. Editor's choice—impact of comorbidity, medication, and gender on amputation rate following revascularisation for chronic limb threatening ischaemia. Eur J Vasc Endovasc Surg. 2018;56(5):681–8.
15. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. Circulation. 2013;128(6):615–21.
16. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the INPACT DEEP randomized trial. J Am Coll Cardiol. 2014;64(15):1568–76.
17. Zeller T, Beschorner U, Pilger E, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). JACC Cardiovasc Interv. 2015;8(12):1614–22.
18. Cassese S, Ndrepepa G, Liistro F, et al. Drug-coated balloons for revascularization of infrapopliteal arteries: a meta-analysis of randomized trials. JACC Cardiovasc Interv. 2016;9(10):1072–80.
19. Baubeta Fridh E, Andersson M, Thuresson M, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. Eur J Vasc Endovasc Surg. 2017;54(4):480–6.
20. Shammas AN, Jeon-Slaughter H, Tsai S, et al. Major limb outcomes following lower extremity endovascular revascularization in patients with and without diabetes mellitus. J Endovasc Ther. 2017;24(3):376–82.
21. Moussa Pacha H, Al-Khadra Y, Darmoch F, et al. Association between underweight body mass index and in-hospital outcome in patients undergoing endovascular interventions for peripheral artery disease: a propensity score matching analysis. J Endovasc Ther. 2019. https://doi.org/10.1177/1526602819839046.
22. Shishehbor MH, Secemsky EA, Varcoe RL. Is there a real association between paclitaxel devices and mortality? Time to pause and re-evaluate what we know about this statistical finding. J Am Heart Assoc. 2019;8(10):e012524.