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.

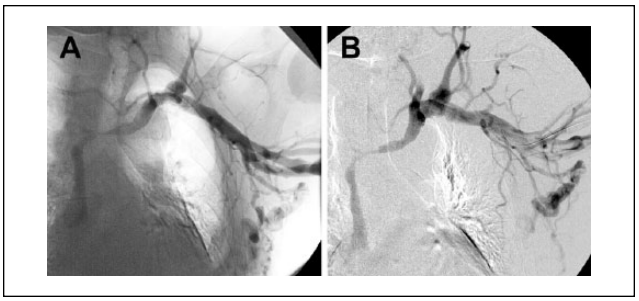

Figure 1. (A) Unsubtracted and (B) digital subtraction phlebography via an antecubital vein reveals typical extensive venous collaterals along the chest wall because of high-grade stenosis of the left brachiocephalic vein.

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).

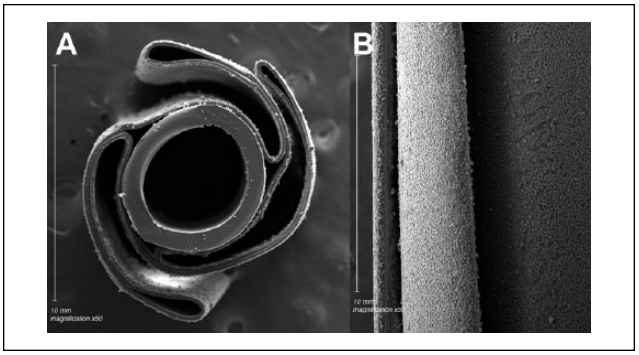

Figure 2. Scanning electron microscopy cross-sectional image illustrating (A) special balloon folding and (B) the paclitaxel-coated surface of Elutax SV completely covering the balloon. The drug itself is protected within the folds of the balloon.

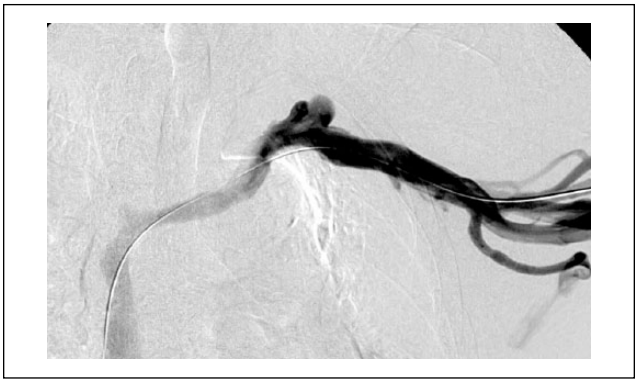

Figure 3. Postinterventional venography after dilation with a 10×40-mm paclitaxel-coated balloon depicts a successful reduction in the central venous stenosis. Consequently, there is an obvious improvement in venous inflow and a considerable reduction of venous collaterals.

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.

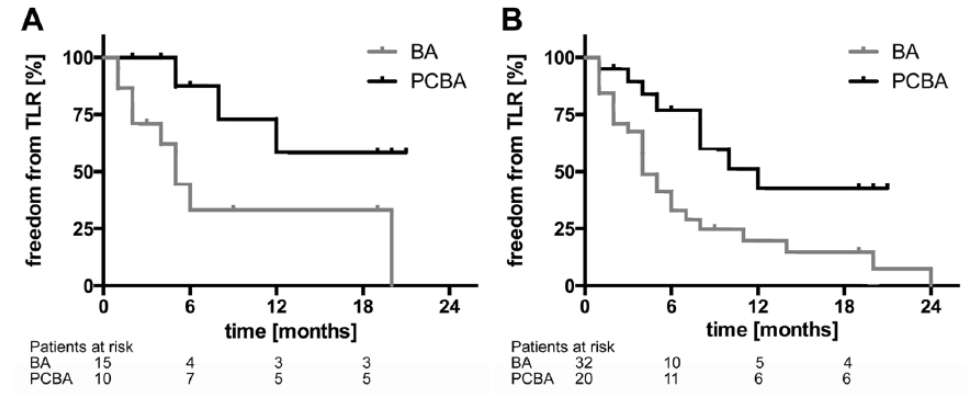

Figure 4. Kaplan-Meier plots demonstrate freedom from target lesion revascularization (TLR) after standard balloon angioplasty (BA) and paclitaxel-coated balloon angioplasty (PCBA) of central venous restenosis: (A) initial treatment and (B) pooled data in a crossover design of lesions treated.

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.

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.

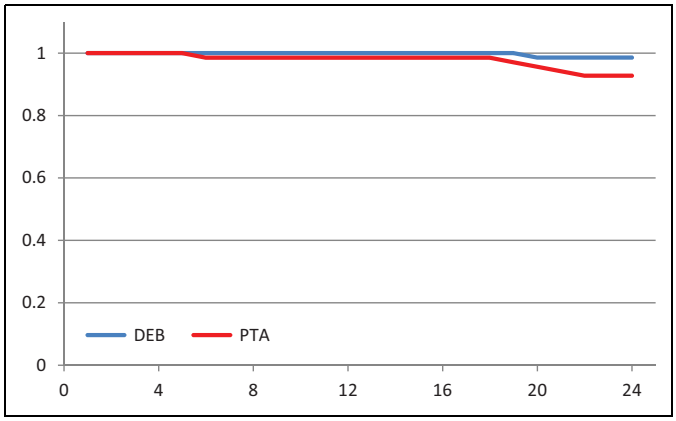

Figure 1. Cumulative Survival Rate.

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

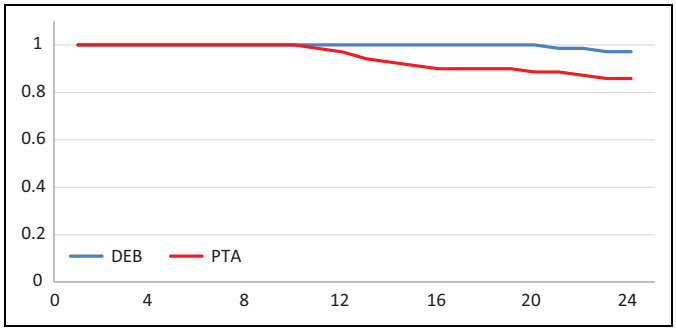

Figure 2. Amputation Rate.

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.