Journal club

Drug coated ballons for femoro-popliteal interventions

Interventional treatment of femoropopliteal arteries is challenging, as the superficial femoral artery is at high risk of restenosis. In previous publications, drug-coated balloons showed significant reduction of late-lumen loss, for example in the THUNDER-Study in 2008 [1].

The ILLUMENATE Study, a multi-centre, single-blind, randomized controlled study investigated 12-month outcomes of the Stellarex low-dose paclitaxel drug-coated balloon in comparison with conventional PTA (uncoated balloon angioplasty) between 2013 and 2015 [2]. In this study, 300 symptomatic patients with peripheral artery disease were randomized, either assigned to drug-coated balloon (DCB) treatment or PTA. The study population had presented with leg claudication, i.e. a Rutherford class 2–4, an angiographic evidence of 70–99 % stenosis or a chronic total occlusions between 30 and 180 mm length, within the superficial femoral or popliteal artery. Mean lesion length was 7.2 and 7.1 cm, with 19.2 and 19 % total occlusions. An angiography with pre-dilatation and a standard PTA balloon was performed, thereafter patients were randomized in a 3:1 ratio; 200 patients were treated with the DCB, 100 patients had a second PTA. The balloon inflation times per lesion were 3.9 ± 2.0 Minutes in the DCB group and 3.7 ± 2.3 Minutes in the PTA group.

The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically driven target lesion revascularization within the 12-month follow-up. The primary effectiveness endpoint was primary patency at 12 months.

Looking at safety outcomes, the DCB was non-inferior to PTA. Primary effectiveness endpoint was met as well. DCB was superior to PTA. DCB showed a significantly higher primary patency rate with 82.3 and 70.9 % in the PTA group (p = 0.002), estimated per Kaplan-Meier method through the full 12 months of follow-up. Freedom from CD-TLR per Kaplan-Meier estimates was significantly higher in the DCB group with 93.6 vs. 87.3 % in the PTA group (p = 0.025).

In the discussion, the ILLUMENATE study suggests superiority in safety and effectiveness of the Stellarex drug-eluting balloon in comparison with conventional PTA. The authors admit that the higher number, almost double amount, of restenosis lesions in the PTA group may have had an impact on the results (9.5 % in the DCB and 18.0 % in the PTA group).

Furthermore, the spread of the dilatation times as well as the exact modalities during pre-dilatation may have affected the measured endpoints. Concerning the necessity of pre-dilatation in revascularization with drug-eluting balloons, Schroeder et al. published a pilot study regarding this question [3]. The study had the objective to compare two-year outcomes of patients who underwent predilatation prior to DCB angioplasty with those who were treated directly with a DCB balloon. The summarized results showed lumen loss at six months to be lower in the predilatation group (0.03 ± 0.68 mm vs. 0.54 ± 0,97 mm) at similar rates of major adverse effects (15 % in predilatation vs. 19 % in the direct DCB group) and primary patency over two years (80.3 vs. 78.2 %). In the case in Schroeder's study, dilatation times were specified to a minimum of one minute, whereas the ILLUMINATE study did not specify a minimum dilatation time.

Another drug-coated balloon was already presented in the LEVANT 2 trial in 2015 [4], in which patients with comparable baseline characteristics where included and after predilatation were randomized to either treatment with the Lutonix drug-coated balloon or conventional PTA. In the results, the Lutonix group showed a primary patency rate, estimated with Kaplan-Meier survival analysis, of 73.5 and 56.8 % in the conventional PTA group at 12 months. Also, the composite safety endpoint, consisting of freedom from perioperative death and from limp-amputation, index-limb reintervention, and index-limb related death, showed a non-inferiority of the drug-coated balloon (83.9 % in the Lutonix vs. 79.0 % in the conventional PTA group). When comparing the results of the ILLUMINATE with the LEVANT 2 trial, a 12 months primary patency of 82.3 % in the Stellarex group and 83.9 % in the Lutonix group is observable. Although both studies showed superiority of drug-coated balloons in terms of technical endpoints, it is striking that one of the most important goals of interventions, for example improvement in quality of life, showed no difference in drug-coated balloons compared to conventional PTA in both the ILLUMENATE and the LEVANT study.

One study that showed inferior results, when compared to the previously described drug-coated balloons, was the BIOLUX P-II trial [8], a prospective, multicentre, randomized first-in-man study with a total of 72 patients, who were randomized 1:1, assigned to either a Passeo-18 LUX drug-coated balloon or conventional PTA. The primary performance endpoint was six-month target lesion primary patency. At 12 months, a patency loss occurred in 50.8 % in the drug-coated balloon group; 41.1 % of the patients

experienced a major adverse event with a major amputation rate of 3.3%, which is high compared with the safety endpoints of the mentioned studies. In total, the authors concluded that there was no superiority in either safety- or performance-endpoints of the drug-coated balloon compared to conventional PTA. The authors justify the results with the smallest vessel diameter compared to similar studies (2.3 mm vs. 2.5 to 2.9 mm), which evokes the question, whether the use of drug-coated balloons has limitations in safety and efficacy when performed on small vessels, for example in below-the-knee lesions.

In the recently issued guidelines of the European Society of Cardiology (ESC-Guidelines [5]), drug-coated balloons are mentioned for the first time as a recommendation for revascularization of femoropopliteal occlusive lesions with a class of recommendation of IIB and an A level of evidence in short (<25 mm) lesions, and with a B level of evidence in the treatment of in-stent restenosis, as they proved to meet the requirements for long-term patency improvements in the very mobile femoropopliteal region. Regarding the improvement of the long-term patency, the recommendations are also supported by the results of the IN.PACT SFA study [6], a prospective, multicentre, multinational, randomized trial with the goal of investigating the longer term outcomes of drug-coated balloons compared to conventional PTA. Like the previously mentioned studies, superiority in primary patency rates was shown for the drug-coated balloon group (78.9 vs. 50.1% in the conventional PTA group), but no change was found with regard to quality of life. Nonetheless, it should be acknowledged that, when comparing the two-year results of the IN.PACT study with the 12-month patency rates of the ILLUMENATE and LEVANT 2 trial, although there was one year of difference between the final follow-ups, the patency rates do not seem to decrease significantly. The data are also supported by the results of the two-year results of a real-world registry, published in 2016 [9]. In the study, 288 limbs treated either with the IN.PACT Pacific or Admiral DCB were retrospectively analysed with up to two years of follow-up. Kaplan-Meier estimates of primary patency were 79.2 ± 2.6% at one year and 53.7 ± 3.4% at two years for the entire cohort. It should be acknowledged that the mean lesion length was 24.0 ± 10.2 cm and 65.3% were total occlusions. Furthermore, two-thirds of the treated lesions were classified as TASC D (Trans-Atlantic Intersociety Consensus), which surely had an impact on the primary patency rate for the two-year follow-up. So the results suggest that drug-coated balloons are effective in delaying rather than preventing restenosis in long, complex lesions and restenosis of the femoropopliteal vessels.

Although the described trials suggest good patency rates for up to two years, there are still questions that need to be answered in regard to drug-eluting balloons. Besides one of the most important questions, whether an improvement in quality of life and walking impairment can truly be achieved, long-term patency rates above the two-year mark must still be attended. Another important question is, whether the use of drug-coated balloons can improve the outcome of below-the-knee revascularization, which imposes another difficult task in endovascular treatment of PAD, especially in patients with diabetes and/or chronic kidney disease as well as with a high level of lesion calcification. Regarding the last question, the actual guidelines of the German Society of Angiology [7] recommend primarily an endovascular approach in general for critical limb ischaemia in the infrapopliteal region, without primary stent implantation. On top of that, the advantage of drug-coated balloons has yet to be evaluated in its entirety.

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