EDITORIAL COMMENT

Favorable Angiographic Outcome After Treatment of Infrapopliteal Lesions With Drug-Coated Balloons Without Clinical Benefit

What We Learn From a Meta-Analysis*

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Despite significant improvements in clinical outcomes of patients suffering from femoropopliteal peripheral artery disease treated with drug-eluting technologies, dedicated bare-metal stent designs, and atherectomy endovascular technologies (1-8), durability of endovascular treatment of longer infrapopliteal lesions remains one of the last significant challenges (9-11). In this issue of JACC: Cardiovascular Interventions, Cassese et al. (12) include 5 randomized—only 2 of them independently controlled—trials in a meta-analysis comparing the performance of drug-coated balloons (DCB) and either uncoated percutaneous transluminal angioplasty (PTA) (4 trials) or drug-eluting stent (DES) (1 trial) placement. Of note is that 4 of those 5 trials used the same DCB—the IN.PACT Amphirion balloon (Medtronic, Brescia, Italy)—which was withdrawn from the market after releasing the negative outcomes of the largest interventional RCT in infrapopliteal arterial disease to date, the IN.PACT DEEP study (9,13-15). This leaves only 72 of 641 patients in the analysis treated with a still commercially available study device in certain countries, the Passeo 18 Lux (Biotronik AG, Buelach, Switzerland)(10). The 1 study where DES served as the control cohort was small in size, including only 25 patients into each study arm with limited follow-up to 6 months only (13).

The authors conclude that DCBs result in superior angiographic outcomes expressed as a lower late lumen loss (LLL) at a median follow-up of 1 year without clinical outcome differences. Their explanation for the missing link between angiographic superiority and clinical benefit is the heterogeneity of the study populations in terms of disease severity and differences in clinical patient follow-up protocols in particular regarding wound care (12). Is this conclusion justified?

First of all, are the angiographic findings correct? Are DCB really superior in terms of LLL over uncoated PTA and DES? Interestingly, only the 3 uncontrolled studies using the IN.PACT Amphirion DCB resulted in superior LLL outcomes (13-15) whereas both independently core laboratory adjudicated and fully industry funded studies found identical LLL outcomes for the DCB and PTA cohorts suggesting a lack of biological efficacy of both DCB brands examined in those 2 studies (9,10). Are controlled and uncontrolled trial outcomes comparable in particular if uncontrolled single-center trials are typically borne “within highly expert endeavors, highly committed to the cause, dedicated and enthusiastic”? Positive technical outcomes of those mostly self-reported, self-adjudicated trials may be affected by systematic (positive), unmeasured errors or confounders and simply mirror the center’s practice resulting in limited generalizability. The most relevant bias results from unblinded quantitative angiographic measurements and data analysis as it has already shown for renal denervation studies (16).

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The potentially incorrect interpretation of a favorable angiographic outcome without a clinical benefit in this meta-analysis might result in problematic conclusions such as the one suggesting that patency does not matter in infrapopliteal interventions in general. The Zilver-BTK (ZUKON-Drug Eluting Stent Below The Knee-Randomised Double-Blind) study (17) comparing DES with BMS resulted not only in a significantly reduced restenosis rate favoring the DES at 2 years of follow-up but as a result of the improved patency also resulted in a reduced target vessel revascularization and amputation rate, underlining the relevance of a patent vessel in the long run.

The conclusion from this meta-analysis that DCBs result in favorable angiographic outcome as compared to DES is misinterpreting the outcome of the original IDEAS (Infrapopliteal Drug Eluting Angioplasty versus Stenting) study (13). In this study, DES significantly outperformed the DCB cohort with regard to the primary study endpoint of binary restenosis rate at 6 months (28% vs. 57.9%; p = 0.0457). The nonsignificantly reduced LLI in the DCB cohort (1.15 ± 0.3 mm vs. 1.35 ± 0.2 mm; p = 0.62) in this study was simply the result of an acutely higher lumen gain in the DES cohort (9.6 ± 2.2% vs. 24.8 ± 3.5%; p < 0.0001). LLI is not the appropriate study endpoint comparing a stent-based therapy with a balloon-based therapy.

In summary, despite the superior angiographic outcome defined as LLI in this meta-analysis the performance of DCB in infrapopliteal lesions remains controversial. In particular the independently controlled studies did not result in any proof of efficacy of short-term balloon-based paclitaxel release to the wall of infrapopliteal arteries. The only remaining commercially available DCBs with infrapopliteal indication analyzed in this meta-analysis, the Passio 18 Lux DCB, did not show any technical or clinical benefit over. Thus, the conclusion drawn Cassese et al. that DCBs result in favorable angiographic outcome compared to PTA or DES must be interpreted with caution. The results of this meta-analysis cannot be generalized to other commercially available DCBs without published clinical study data or to those DCBs still under clinical evaluation. As a result of the limited proof of efficacy for DCBs with infrapopliteal indication this technology is not reimbursed even in countries where dedicated reimbursement is established for DCB treatment of femoropopliteal lesions, such as Germany.

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