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EDITORIAL COMMENT

Paclitaxel-Coated Balloons in the Femoropopliteal Artery

It Is All About the Pharmacokinetic Profile and Vessel Tissue Bioavailability*

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The femoropopliteal artery remains the 'lion's den' for peripheral endovascular procedures because of its unique biomechanical properties and high rates of restenosis (1). Since the report of the seminal THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) study (2), we have witnessed a paradigm shift in infrainguinal interventions with gradual adoption of paclitaxel-coated balloons (PCB) and paclitaxel-eluting stents as first-line treatment because of their proven antirestenotic properties (3). In the current issue, Giacoppo et al. (4) report the results of a rigorous meta-analysis of the treatment effect of PCB in the femoropopliteal segment. The investigators have synthesized 8 randomized controlled trials including 1,341 subjects and 1,843 patient-years of follow-up in total. Endpoints were set at target lesion revascularization (TLR) and all-cause patient death, and the meta-analysis included a thorough assessment of between-trial heterogeneity and potential risk modifiers.

Not surprisingly, PCB were found to produce a marked 67% reduction of TLR at 12 months (relative risk [RR]: 0.33) without any impact on all-cause patient death (RR: 0.96). Findings were very similar after incorporating the complete follow-up periods of different studies (Incidence Risk Ratio (IRR): 0.35; IRR: 1.13, respectively). The TLR findings are virtually identical to another recently published meta-analysis of 11 randomized controlled trials, including 1,609 patients in total (5), and also to a previous network meta-analysis of the different types of stents and balloons in the femoropopliteal artery (3). Overall, there seems to be quite solid evidence about the antirestenotic effect of paclitaxel loaded on balloon catheters that translates to a significant relative reduction of the need for revascularization by approximately two-thirds.

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Most important, in this issue of *JACC: Cardiovascular Interventions*, Giacoppo et al. (4) are to be commended for their in-depth assessment of between-trial heterogeneity and the analysis of baseline variables as potential confounders of the outcomes (meta-regression). Of interest, bail-out stenting was reported nearly twice as often in the control arms compared to the active PCB arms; the latter could be interpreted as the result of the inherent operator bias in the absence of double-blinded study designs. Still, the paclitaxel effect has been found to be stable across a wide range of stenting rates (4%-100%) for the outcomes of vascular restenosis and TLR (5), and in the present study paclitaxel effect was consistent across both de novo and restenotic lesion (in-stent as well).

Digging deeper into the potential sources of heterogeneity, the authors have discovered that the observed I^2 could be explained by the differential treatment effect reported in the LEVANT (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) trials that investigated the Lutonix DCB catheter in particular. In fact, exclusion of the 2 latter studies would correct for the underlying publication bias and diminish the observed

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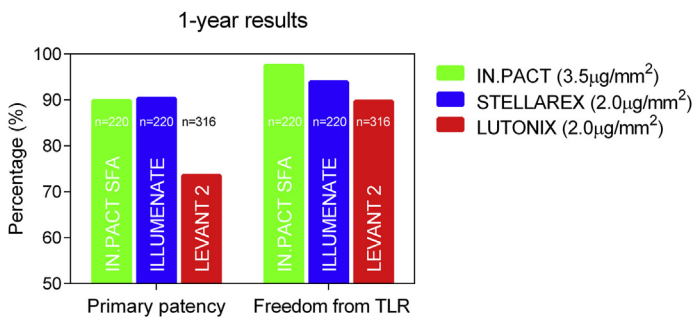
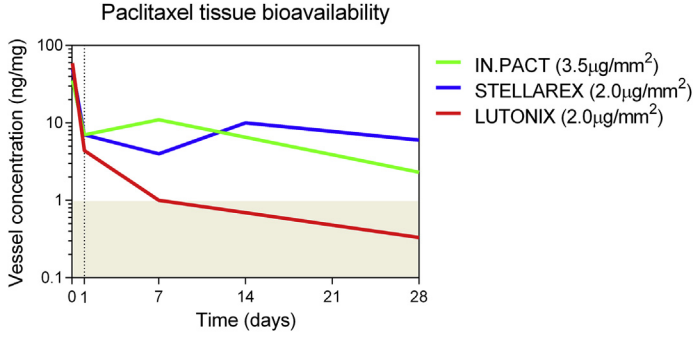
FIGURE 1 Primary Patency



Primary patency (freedom from vascular restenosis on the basis of peak systolic velocity ratio of >2.5) and freedom from target lesion revascularization at 1 year for the 3 largest drug-coated balloon (DCB) cohorts available to date (n > 100). Kaplan-Meier estimates are presented.

between-trial heterogeneity. The same finding was reported previously in another meta-analysis with the same scope (5). We have calculated that the dose of paclitaxel related to the treatment effect size; standard dose PCB (3.0 to 3.5 μg) were more than twice as effective compared with low-dose PCB (2.0 μg) in reducing both vascular restenosis (RR: 2.1) and TLR (RR: 2.5) (5). This author would also agree with the investigators that the differences in effect size may be explained by either a lower efficacy of the Lutonix device and/or conceptual differences in the design and level of bias of different randomized trials. Collectively, however, there is clear evidence that there is no class effect and that the treatment effects of different DCB devices most likely originate from different distributions expressing the different design characteristics of the individual PCB devices.

FIGURE 2 Pharmacokinetic Profile



Pharmacokinetic profile of the respective drug-coated balloon devices up to 28 days. In vivo animal data on the log scale are presented.

Consequently, every DCB device needs to be put to the test to prove its clinical efficacy.

Figure 1 shows the 1-year clinical outcomes (Kaplan-Meier estimates) of the 3 largest DCB cohorts (n > 100) to date, including the IN.PACT SFA study (Randomized Trial of IN.PACT Admiral Drug Eluting Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease) (n = 220) (6), the ILLUMENATE (ProspectIve, Randomized, SingLe-Blind, U.S. MuLti-Center Study to EvalUate Treat-Ment of Obstructive SupErficial Femoral Artery or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon) study (n = 220; interim results) (7), and the LEVANT 2 study (n = 316) (8). Arguably, it is not the nominal paclitaxel dose that determines the treatment effect size of PCB devices, but the actual pharmacokinetic properties and eventual bioavailability of paclitaxel in the vessel tissues (9). Uptake and retention of paclitaxel depend on paclitaxel dose and formulation (amorphous versus crystalline) and on the chemical properties of the spacer or excipient used to deliver paclitaxel onto the vessel wall (10). **Figure 2** illustrates the pharmacokinetic profile (log scale) of the 3 respective PCB devices up to 28 days including the 3.5-μg/mm² IN.PACT by Medtronic, the 2.0-μg/mm² Lutonix by BARD, and the 2.0-μg/mm² STELLAREX by SPECTRANETICS (9–12, and Landini M, Spectranetics internal data on file, personal communication 2016). Of note, in vitro studies have shown that successful growth inhibition of human arterial smooth muscle and endothelial cells is achieved at around 1 ng/mg drug tissue concentration after a short-lasting exposure to paclitaxel (13). In vivo therapeutic levels for effective inhibition of restenosis remain unknown, especially in the presence of atherosclerotic disease and vessel wall calcifications. Hence, it could be argued that differences in the pharmacokinetic profile and paclitaxel tissue bioavailability may explain directly the noted differential treatment outcomes when comparing different DCB devices regardless of the nominal paclitaxel dose. However, head-to-head randomized comparisons of different DCB catheters are missing to confirm or refute the above hypothesis.

The evidence presented by Giacoppo et al. (4) refers to a predominantly claudicant population with intermediate length lesions. Even though PCB have been also shown to be cost effective in the femoropopliteal segment (14), the amassed evidence to date would arguably not apply to complex lesions and to the treatment of critical limb ischemia that has different endpoints and is routinely characterized by a more comorbid patient background.

In conclusion, PCB should be considered the new standard of care for the treatment of noncomplex lesions in a claudicant population. However, current DCB devices have no class effect and more randomized studies are needed to expand our knowledge into the role of paclitaxel pharmacokinetics, application in more complex lesions, combination with stenting and treatment of critical limb ischemia for limb salvage.

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