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EDITORIAL

Paclitaxel-coated balloons in peripheral artery disease: how much is enough?

Francesco Liistro[1] and Carlo Di Mario[2]*

[1]Ospedale San Donato, Arezzo, Italy; and [2]University Hospital Careggi, Florence, Italy

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This editorial refers to 'COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions'†, by S. Steiner *et al.*, on page 2541.

Over the past decade, drug-coated balloons (DCBs) have emerged as an effective treatment for atherosclerotic disease in femoropopliteal (fempop) arteries. This technology holds the promise of offering the well-proven antiproliferative effect of chemotherapic drugs without the risks of stents such as thrombosis or excessive intimal hyperplasia due to metal or polymer interaction and stent fractures. The latter complication is rare in coronary artery disease but becomes a major cause of stent failure in peripheral vascular disease.[1] Due to the lipophilicity and prolonged tissue retention rate, paclitaxel is the most widely used antiproliferative drug for this technology. There are a large number of DCB platforms currently available on the market but their comparative effectiveness in preventing restenosis and target lesion revascularization is not well studied. The trial by Steinert *et al.*[2] published in this issue of the *European Heart Journal* is the first direct comparison of a standard dose (3.5 μg/mm^2) vs. a low-dose (2 μg/mm^2) paclitaxel DCB in fempop lesions. The study population includes patients with claudication and critical limb ischaemia (CLI) with different lesion length and a high number (40%) of complete total occlusions (CTOs), a patient and lesion mix well representative of current routine clinical practice. Both standard and low-dose DCBs showed good efficacy in preventing 12-month restenosis, with a patency rate >80% in both groups and a bailout stenting rate of ∼20%. These findings are similar to those reported in a previous study with the same standard dose DCB platform and with the Zilver paclitaxel-eluting stent in a similar clinical and anatomical scenario.[3] The low rate of bailout stenting reported in the setting of TASC C-D lesions and in the DCB arm of recent studies comparing DCBs and drug-eluting stents (DESs) is probably due to a procedural strategy that includes long balloon inflation to seal flow-limiting dissections.[4] In previous studies, the rate of stenting in DCB angioplasty was significantly higher (up to 40%), probably because the operators preferred stents to long balloon inflations.[5] The DCB efficacy was lower in both arms in longer lesions when stent implantation was more often required for suboptimal results. Long lesions are more often calcified and show a large amount of plaque burden, factors that may limit the drug transfer from the balloon into the vessel wall. Lithotripsy has been advocated in these lesions, improving the immediate outcome of balloon dilatation and reducing the need for stent implantation, but also increasing the diffusion of the drug into the wall around the fragmented calcium particles.[6]

The efficacy of the inhibition of intimal hyperplasia depends on the amount of drug delivered to the vessel wall and the clearance kinetics that predict the duration of paclitaxel activity.[7] Drug load is far from the only determinant of this process which is also driven by the chemical status of paclitaxel (crystalline or amorphous), type of excipient or carrier (different for each DCB), characteristics of the balloon surface, and technologies used to assemble all these components. Solid particles of paclitaxel are inactive but, as soon as the drug becomes soluble and biologically active, it is immediately cleared. The carrier of the DCB controls the velocity of the solid to soluble transformation and plays a role at least as important as drug load in the paclitaxel delivery kinetics. Moreover, previous studies demonstrated a significant drug loss, up to 70%, into the systemic circulation during inflation. For the InPact technology (Medtronic, Minneapolis, MN, USA), the loss has been documented as distal embolization of small particles which may cause flow impairment and interfere with ischaemic wound healing.[8] However, none of these theoretical concerns was confirmed in randomized controlled trials (RCTs) of DCBs for fempop treatment. The Ranger technology has shown a smaller drug loss during balloon inflation, allowing a drug load of only 2.0 μg/mm^2, probably enough to provide a sufficient drug storage to obtain a comparable antirestenotic effect. No well conducted head to head studies were performed for the other low-dose DCBs available, but the results of the available registries suggest that their efficacy may differ (*Take home figure*). The Lutonix DCB (BARD, MS, USA) showed a 12-month patency rate of 65%,[9] while the Stellarex DCB (Spectranetics, CO, USA) reached 86%,[10] both in lesions shorter than 10 cm with a CTO rate of 20%, an easier scenario than the COMPARE study. The apparently lower efficacy of the

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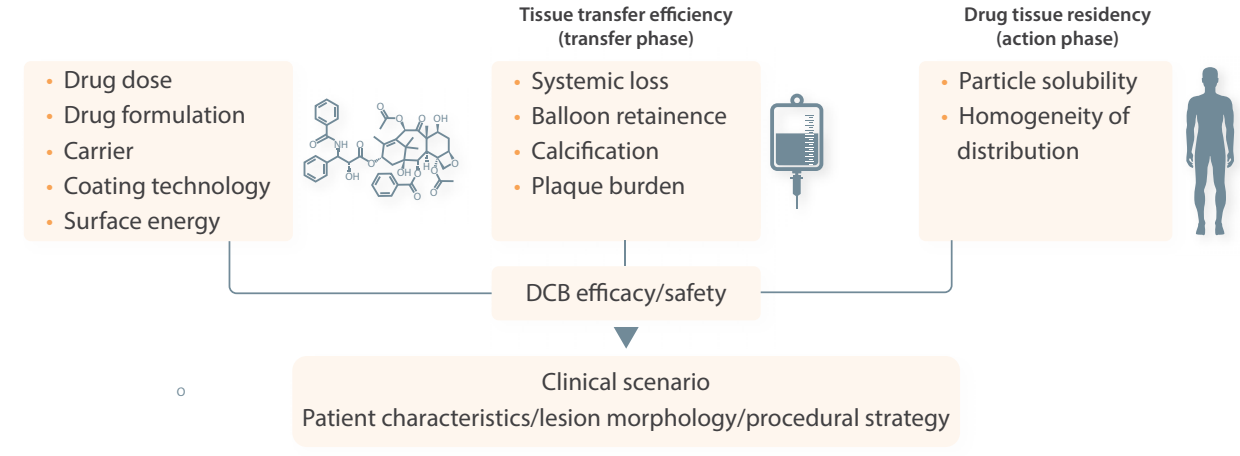
* Corresponding author. University Hospital Careggi, Largo G. Alessandro Brambilla 3, 50134 Florence, Italy. Email: carlo.dimario@unifi.it



DCB with proved Level I - Evidence of efficacy

Paclitaxel Eluting Balloon (BRAND)	Dose mcg/mm²	Carrier	Drug formulation and activation	Patency 12-month in RCT	Lesion Length/ CTO	Safety	Head to head comparison
In.Pact (Medtronic)	3.5	Urea	FreePacTM hydrophilic coating (excipient: urea)	86.6%	15cm/60%	Alleged mortality increase not confirmed Distal particle embolism	Vs Ranger DCB equal Vs Zylver ptx DCB equal
Orchid (ACOTEC)	3.0	Mg-stearate	Crystalline	76%	14.7cm/57%	Alleged mortality increase not confirmed	none
Stellarex (Spectranetics)	2.0	Polyethylene glycole	EnduraCoatTM coating	86%	7.5cm/19%	Alleged mortality increase not confirmed	none
Lutonix (Bardi)	2.0	Polysorbate & sorbitol	Proprietary hydrophilic nonpolymeric carrier	65.2%	6.3cm/20%	Alleged mortality increase not confirmed	none
Ranger (Boston scientiphic)	2.0	Citrate ester	TransPax coating	86%	6cm/34%	Alleged mortality increase not confirmed	Vs In.Pact equal

Take home figure Characteristics and clinical evidence of the current DCB technologies with level 1 evidence of efficacy are reported in the table. The determinants of DCB safety and efficacy are summarized in the flow-chart.

Lutonix DCB may be due to its amorphous drug formulation. This may facilitate the drug transfer but also causes a faster clearance of the drug with a short persistance of solid-phase deposits and a shorter antiproliferative effect. On the contrary, the endurance coating of the Stellarex DCB seems to provide a more prolonged intimal inhibition. The Transpax coating of the Ranger DCB reduces drug loss during transfer when compared with other coating technologies and seems to provide sufficient drug storage to ensure a prolonged antiproliferative effect. There is no evidence that a low drug dose offers a better safety profile, at least at 12 months follow-up, when compared with higher drug doses such as those used in the In.Pact technology. Major amputation in the COMPARE study was 0 in both arms, and no difference in mortality was observed.

A recent summary-level meta-analysis of 38 RCTs on DCBs for fempop treatment shook the interventional community, showing higher global mortality at 5 years with paclitaxel-coated balloons compared with POBA (plain old balloon angioplasty) and a dose–effect interaction, with the highest mortality in patients receiving the highest drug dose.[11] The Katzanos meta-analysis has major methodological limitations. It is a summary-level and not patient-level data analysis, there is crossover between treatments, a relatively high percentage of patients are missed at follow-up, and the power calculations were designed to study restenosis and not mortality. The main limitation, however, is conceptual rather than methodological. There was no clear cluster of mortality so that a cause–effect relationship between use and dose of paclitaxel and mortality is not a plausible hypothesis. Patients suffering from symptomatic peripheral arterial disease are often diabetic, suffer from coronary and cerebral artery disease, have low ejection fraction, heart failure, and renal insufficiency, and may have a high risk of 5-year mortality. High competing risk of death complicates the assessment of a single causation and its estimate is potentially unreliable. Moreover, a recent retrospective analysis on patient-level data showed no mortality difference in the long term and no dose–effect interaction, with a similar risk for patients receiving different drug doses.[12,13] This well-designed and impeccably conducted German study is the first RCT that proved no difference in terms of efficacy and safety at 12-month follow-up between the standard dose DCB InPact and the low-dose Ranger. If a longer follow-up to check late patency confirms the absence of safety signals, this study will represent a major challenge to the conclusions of the Katzanos meta-analysis. Unfortunately, these results are not transferrable to other low-dose DCBs because many other subtle technology differences may affect the performance of these devices.

In conclusion, the strict methodology of the COMPARE study offers a model of the new standard required to introduce new DCBs, including the promising sirolimus-based coatings, reviving the

stringent head to head comparisons of coronary stent technologies that led to the discovery of the safety and efficacy advantage of second-generation limus-based DESs.

Conflict of interest: F.L. was the Principal Investigator of the ACOART BTK, an investigator-driven trial partially sponsored by ACOTEC, and the IN.PACT BTK study, sponsored by Medtronic. C.D.M. was the Principal Investigator of the DISRUPT I & II trials, both sponsored by Shockwave medical. Neither of them receive consultancy or speakers' fees or hold stocks of any of the companies involved in peripheral vascular disease treatment.

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