Safety of Paclitaxel-Eluting Stents in Below-the-Knee Arteries for Critical Limb Ischemia Treatment: the Devil is in the Details

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Konijn et al. have reported the long-term 10-year safety outcomes with the use of paclitaxel-eluting stents (TAXUS) in below-the-knee arteries for critical limb ischemia treatment [1]. The report expands on previously published results from the multicenter randomized PADI trial that have shown promising results with improved patency and most importantly significantly reduced risk of amputation with bail-out use of the TAXUS paclitaxel-eluting stents in the infrapopliteal arteries. The work has been driven by our recently published meta-analyses documenting increased long-term risk of all-cause mortality with paclitaxel-coated balloons and stents in the femoropopliteal segment [2], and increased short-term risk of death or amputation in the infrapopliteal segment [3]. We certainly commend the authors on releasing their long-term results in view of the ongoing paclitaxel debate and we take the opportunity to highlight some key elements with regards to the design and the paclitaxel payload of the TAXUS stent compared to the ZILVER-PTX stent in the femoropopliteal artery and also to the rest of the paclitaxel-coated balloons approved for above or below knee applications (Table 1).

First, the TAXUS stent that was used in the PADI trial incorporates a triblock copolymer topcoat that allows for

sustained controlled elution of the anti-proliferative drug paclitaxel. On the contrary, the ZILVER-PTX stent is plainly coated with amorphous paclitaxel without any polymer or other agent or excipient to control drug transfer. On the other hand, paclitaxel-coated balloons universally incorporate a certain type of excipient to facilitate drug transfer to the vessel wall. Second, total paclitaxel payload is similar between the TAXUS and the ZILVER-PTX stent, but an order of a magnitude lower compared to paclitaxel-coated balloons. In addition, total dose delivered may vary significantly according to lesion length treated, e.g., from an average 0.3 mg in the PADI trial to as much as 4.9 mg in the IN.PACT BTK randomized trial. Of note, we have recently reported evidence of significantly worse long-term amputation-free survival in case of the IN.PACT BTK study [4].

Third, the pharmacokinetics of paclitaxel-coated balloons and stents follow complex nonlinear functions and are typically associated with long-lasting tissue residence with often unknown local and downstream effects. It has been elegantly shown that arterial bioavailability of paclitaxel is influenced by an interplay of paclitaxel crystallinity, coating and excipient dissolution kinetics, expression and saturation levels of local tissue binding sites and diffusion barriers imposed by atherosclerosis that may impede drug transfer. The latter observations are particularly important in the case of paclitaxel-coated balloons that suffer from high rates of systemic wash-off of paclitaxel particles producing variable but universal embolization of cytotoxic material into the distal ischemic tissues. On the contrary, should one assume that systemic release of cytotoxic paclitaxel is the primary cause of the observed mortality signals in PAD, then polymer-coated paclitaxel-eluting stents (like the TAXUS used in the PADI study)

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Table 1 Design of paclitaxel-eluting stents, paclitaxel-coated stents and paclitaxel-coated balloons tested in major randomized trials in the infringuinal arteries

	TAXUS coronary stent	ZILVER-PTX stent	Paclitaxel-coated balloons
Polymer coat	Yes	No	No
Excipient agent	No	No	Yes
Paclitaxel dose*	0.57 µg/mm ²	0.37–0.62 µg/mm ²	2.0–3.7 µg/mm ²
Embolization	Minimal	Some	High

*Adjusted paclitaxel density delivered (per mm² of vessel surface area)

may confer a more controlled and consequently safer delivery of the agent in question.

To conclude, not all paclitaxel-coated or -eluting devices are the same and each one stands on the risks and merits of each own design as reflected in relevant clinical trials.

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Compliance with Ethical Standards

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References

1. Konijn LCD, Wakkie T, Spreen MI, de Jong PA, van Dijk LC, Wever JJ, Veger HTC, Statius van Eps RG, Mali WPTM, van Overhagen H. 10-year paclitaxel dose-related outcomes of drug-eluting stents treated below the knee in patients with chronic limb-threatening ischemia (the PADI trial). *Cardiovasc Interv Radiol*. 2020. <https://doi.org/10.1007/s00270-020-02602-6>.
2. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(24):e011245. <https://doi.org/10.1161/JAHA.118.011245>.
3. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: a systematic review and meta-analysis of randomized controlled trials. *J Vasc Interv Radiol*. 2020;31(2):202–12. <https://doi.org/10.1016/j.jvir.2019.11.015>.
4. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Reply to: “Re: Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: a systematic review and meta-analysis of randomized controlled trials”. *J Vasc Interv Radiol*. 2020;31(6):1032–4. <https://doi.org/10.1016/j.jvir.2020.03.013>.
5. Tzafriri AR, Parikh SA, Edelman ER. Taking paclitaxel coated balloons to a higher level: predicting coating dissolution kinetics, tissue retention and dosing dynamics. *J Control Release*. 2019;28(310):94–102. <https://doi.org/10.1016/j.jconrel.2019.08.019>.

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