## LETTERS TO THE EDITOR

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### Re: "Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-analysis of Randomised Controlled Trials"

In a recent systematic review and meta-analysis of randomised controlled trials,[1] Katsanos *et al.* investigated the long term risk of major amputation associated with the use of paclitaxel drug coated balloons (DCBs) in the lower limbs. A significantly higher long term risk of major limb loss using DCBs was found. The authors must be congratulated for this very valuable work and the concerns raised must be confirmed or refuted by specific trials.

It should be emphasised that the comparator arm used in one of the trials included in the analysis was not standard plain balloon angioplasty. In the PACUS trial,[2] whose results were significantly against DCBs (hazard ratio 7.96; 1.38–46.00, the worst of all the included studies), uncoated balloon angioplasty was followed by local intravascular ultrasound energy treatment. A balloon was then inflated distal to the lesion to create flow cessation, and a paclitaxel iodinated contrast mixture was injected into the stagnant blood column and allowed to absorb into the vessel wall for 60 seconds. The readers of the journal should be aware that the control arm of this study also received paclitaxel using a different method.

#### CONFLICT OF INTEREST

Raphaël COSCAS had received speaking honoraria from Becton Dickinson, Medtronic, Boston Scientific.

#### REFERENCES

1 Katsanos K, Spiliopoulos S, Teichgräber U, Kitrou P, Del Giudice C, Björkman P, et al. Risk of major amputation following application of paclitaxel coated balloons in the lower limb arteries: a systematic review and meta-analysis of randomised controlled trials. *Eur J Vasc Endovasc Surg* 2022;**63**:60–71.
2 Gandini R, Del Giudice C. Local ultrasound to enhance paclitaxel delivery after femoral-popliteal treatment in critical limb ischemia: the PACUS trial. *JACC Cardiovasc Interv* 2016;**9**:2147–53.

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### Response to "Re Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: a Systematic Review and Meta-Analysis of Randomised Controlled Trials"

We thank Dr Coscas and colleagues for their interest in our recent paper documenting a substantially higher risk of major amputation following use of paclitaxel coated balloons in the infra-inguinal arteries.[1] The authors discuss the fact that the control arm in the PACUS trial had also received liquid paclitaxel at the treatment site. We would like to clarify that this has been noted and accounted for in our meta-analysis. First, as explained in the legend of Table 1, in the PACUS trial, DCB were randomised *vs.* a combination of high frequency low intensity intravascular ultrasound therapy and contrast dissolved liquid paclitaxel (1.0 μg/mm$^3$) delivered in the femoropopliteal treatment area under distal balloon occlusion and aspirated with a 50 mL syringe after 60 sec.[2] Second, the total dose of liquid paclitaxel in the control arm was accounted for in the multivariable dose response meta-analysis, that is the control liquid paclitaxel dose was incorporated in the reference control arm when the amputation log hazard was regressed on the nominal paclitaxel dose delivered from the DCB devices. Of note, the dose response meta-analysis demonstrated an accelerated amputation risk over increasing paclitaxel dose. Finally, in the sensitivity tests, the pooled HR was congruent across leave one out meta-analysis without any influential studies. The pooled estimate was HR 1.55 (95% CI 1.06 – 2.26; $p = .025$) when excluding the PACUS trial. Hence, the authors believe that the current findings are stable and robust.

#### REFERENCES

1 Katsanos K, Spiliopoulos S, Teichgraber U, Kitrou P, Del Giudice C, Bjorkman P, et al. Risk of major amputation following application of paclitaxel coated balloons in the lower limb arteries: a systematic review and meta-analysis of randomised controlled trials. *Eur J Vasc Endovasc Surg* 2022;**63**:661.
2 Gandini R, Del Giudice C. Local ultrasound to enhance paclitaxel delivery after femoral-popliteal treatment in critical limb ischaemia: the PACUS trial. *JACC Cardiovasc Interv* 2016;**9**:2147–53.

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