Systematic Meta-analysis—A Scientific Gold Standard for All Therapies?

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In contrast to a meta-analysis by Katsanos et al,[1] the meta-analysis by Al Halabi et al[2] in this issue the *Journal of Critical Limb Ischemia* examined paclitaxel-coated drug-coated balloon (DCB) angioplasty in infrapopliteal artery lesions and found significant benefits for the use of DCB regarding freedom from target-lesion revascularization (TLR), late lumen loss, and complete wound healing, and no difference in all-cause mortality, major amputation, and amputation-free survival.

However, we should be asking if meta-analyses of randomized controlled trials (RCTs) should be considered an appropriate method to evaluate the efficacy and safety of DCB angioplasty. RCTs are considered to be the highest scientific evidence (level 1a) when evaluating a therapy. The rationale for conducting a systematic review and meta-analysis is to overcome study cohort size limitations of individual studies by pooling data in an attempt to identify even small differences in effectiveness and/or safety of a new therapy compared with an established standard therapy. If a meta-analysis results in an effectiveness benefit, then a class effect is considered. Safety analysis of a drug-releasing device must include the safety of the device application and the drug delivered. However, drug safety analysis must include potential additional exposure of the same drug during follow-up. How do these assumptions apply to the present meta-analysis?

Efficacy. What is the value of pooling data for identifying a potential class effect if there is obviously none? The IN.PACT Amphirion DCB (Medtronic) was voluntarily withdrawn from the market when the 1-year analysis of the IN.PACT Deep study missed its 1-year efficacy goal.[3] However, this DCB type was used in 3 of 10 studies included in the present meta-analysis, including the largest of the included trials.[4-6] A second DCB brand, the Passeo-18 Lux (Biotronik) was used in 2 of the studies, again without proof of efficacy.[7] Finally, the Lutonix 14 DCB (Bard) tested in the second-largest RCT was not approved by the United States Food and Drug Administration, again due to a lack of efficacy.[8] Thus, only 3 studies remain that showed superior efficacy over plain old balloon angioplasty. As such, the conclusion from the meta-analysis that "DCB use in infrapopliteal arteries is superior to PTA in improving clinical outcomes, angiographic results, and ..." is misleading in the sense of suggesting a class effect for DCB efficacy in infrapopliteal interventions. The coating technology of DCBs designed for below-the-knee (BTK) interventions seems to be even more important compared with those designed for treating femoropopliteal lesions. For BTK interventions, each individual balloon brand has to show technical superiority over a control device, which is usually the plain, uncoated balloon in terms of either reducing late lumen loss and/or TLR rate, or increasing vessel patency. Without a technical benefit, clinical benefits can hardly be expected.

Safety. None of the published meta-analyses had access to individual patient data regarding total paclitaxel dose exposure during follow-up. Therefore, drug safety is only reliably assessed for the periprocedural period, and it is obvious that no acute systemic paclitaxel toxicity exists following DCB angioplasty of infrapopliteal arteries. However, the 2 major safety endpoints of the meta-analysis are all-cause mortality and major amputation. As for both endpoints, a potential side effect of the paclitaxel coating is that it is essential to calculate the life-time total paclitaxel dose exposed to each individual patient. This includes not only those patients who were initially treated with a paclitaxel-coated balloon, but also those whose index therapy was uncoated balloon angioplasty and then received paclitaxel-coated device therapy during follow-up. In a single-center study from Bad Krozingen, comprising 576 patients with BTK interventions, including 269 patients treated with uncoated devices without crossover to a paclitaxel-coated device during follow-up and 307 patients with DCB angioplasty, more than half of the patients treated with DCB underwent at least 1 additional intervention with a paclitaxel-coated device during a mean follow-up of 46 ± 33 months.[9] The cumulative total paclitaxel dose was about 2.5 times higher than the index

paclitaxel dose, without a negative impact on all-cause mortality. As the meta-analysis included only information about the paclitaxel dose during the index intervention, the second conclusion that "DCB use in infrapopliteal arteries is..., with no increase in all-cause mortality or major amputations" must also be interpreted with caution.

In conclusion, considering systematic review and meta-analysis of RCTs as the scientific gold standard only holds true if the analysis applies to an appropriate patient population with access to complete endpoint-related data. Nevertheless, in opposition to the previous meta-analysis published by Katsanos et al, the current meta-analysis could not confirm a decrease in the combined endpoint of amputation-free survival.[1]

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