



Commentary

Paclitaxel in endovascular devices: Identikit of a “serial killer”?

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Death does not concern us, because as long as we exist, death is not here. And when it does come, we no longer exist.

Epicurus

Recent developments in the management of peripheral artery disease have been momentous, and a key advance has been the introduction of drug-coated balloons, which capitalise on the mechanical effects of angioplasty balloons, and on the pharmacologic effects of anti-restenotic drugs [1,2]. Indeed, single reports from randomized trials and pooled estimates from meta-analyses have clearly showed that paclitaxel-coated balloons reduce the risk of restenosis and repeat revascularization, while improving patency, limb salvage, and freedom from claudication [3,4].

A bomb was however dropped in the endovascular arena in late 2018 by Katsanos and colleagues, who pooled available trials on paclitaxel-coated balloons and paclitaxel-eluting stents for endovascular therapy, and strongly hinted at an increased risk of death when using these devices [5]. A heated debate has followed suite, with device companies updating previous reports from controlled studies of drug-coated devices, further weakening the case in favor of paclitaxel, and the US Food and Drug Administration convening a panel of experts and recommending caution when considering the use of these devices [6].

It is thus not unexpected nor useless that other investigators have sought to confirm and expand the findings reported by Katsanos et al. In this issue of *EClinicalMedicine*, Klumb and colleagues provide the results of a carefully conducted meta-analysis, comparing paclitaxel-coated balloons vs. standard balloons for the treatment of femoro-popliteal lesions [7]. They included 14 trials, totalling 2504 patients, treated with 8 different types of paclitaxel-coated balloons, with drug density ranging between 2.0 to 3.5 $\mu\text{g}/\text{mm}^2$, and follow-up between 1 and 3 years. Trial validity was quite variable, with some studies of high quality and others of suboptimal quality. In addition, quantitative results were not consistent and homogeneous, as testified by the significant tests for statistical heterogeneity. Yet, both fixed and random effect analyses showed that paclitaxel-coated balloons provided important clinical benefits, ranging from prevention of restenosis and repeat revascularization to functional class improvement. A detailed analysis exploring potential sources of heterogeneity highlighted ankle-brachial index at baseline, lesion length, predilation strategy, and paclitaxel density as potentially important moderators. In particular, higher paclitaxel density was associated with fewer repeat revascularizations. Undoubtedly, these findings would support the liberal use of paclitaxel-coated balloons.

Yet, what about deaths? Should paclitaxel be acquitted from all charges? Or should we still consider this drug, and any device coated with it, a potential “killer”? Unfortunately, the very same careful analysis conducted by Klumb et al. showed that paclitaxel-coated balloons conferred an increased risk of death, especially at 24 months of follow-up. Whereas nominal statistical significance

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was not reached when using a random effect model (i.e. a mathematical approach which gives more weight to small and imprecise studies and less weight to large and more precise ones), a fixed effect model suggested a strong and significant increase in the risk of death. In particular, the authors estimated a fixed-effect number-needed-to-harm of 26 (95% confidence interval 16–79). In the best-case scenario, this would translate in 1 person's death every 79 treated with paclitaxel-coated balloons, and, in the worst case scenario, in 1 patient's death every 16 receiving such devices. Without question, these findings would call for a global moratorium or ban of paclitaxel-coated balloons, similarly to what adverse reports do, for instance, for electronic cigarettes and other modified risk products [8]. This has not yet happened, but some authorities have indeed called for such extreme measures.

Opinions are still quite polarized, and supporters of paclitaxel-coated devices argue that the mechanism underlying a potential lethal effect of these devices is lacking. Indeed, plausibility is one of the 9 Bradford Hill's criteria for epidemiologic evidence of a causal relationship, but its absence does not negate causation per se [9]. Moreover, it is noticeable that paclitaxel density correlates with revascularization prevention as well as mortality, showing thus another and quite important Bradford Hill's criterion: biologic gradient. The other similarly important criteria, which should be considered in the paclitaxel debate, are strength, consistency, specificity, temporality, coherence, experiment, and analogy. Yet, application and applicability of these additional criteria has been limited, and so uncertainty persists on the actual association between fatality and paclitaxel devices.

In summary, it appears even clearer that paclitaxel-coated devices provide important benefits when used for endovascular therapy, especially in terms of restenosis and revascularization prevention, but may possibly increase fatality. While awaiting more definitive data from ongoing studies, we recommend an extremely selective use of such devices (if any use at all), keeping in mind that other devices, devoid of paclitaxel, may still be used as effectively and more safely [10]. Indeed, paclitaxel coating is probably more potent than other coatings (e.g. sirolimus), but possibly so potent that it may jeopardize safety.

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Drs. Biondi-Zoccai, Frati, Giordano and Versaci have nothing to disclose.

CRedit authorship contribution statement

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