

# Use of Paclitaxel-Eluting Technologies in the Femoropopliteal Segment Under Scrutiny Over Possible Link to Late All-Cause Mortality: Time to Panic or an Opportunity to Resurge?

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## Keywords

Drug-coated balloon, drug-eluting balloon, drug-eluting stent, mortality, paclitaxel

Since their market debut in 2009, paclitaxel-eluting technologies have established themselves as mainstay therapy for the endovascular treatment of femoropopliteal arterial disease. Since then, around 15 paclitaxel drug-coated balloons (DCBs) from different manufacturers and 2 paclitaxel drug-eluting stents (DES) have been granted Conformité Européenne mark and access to the European market, with 3 DCBs and 1 DES also receiving Food and Drug Administration approval for the United States market. Worth noting, the aggregate quantity of trials on DCBs and DES jointly constitutes the largest and strongest body of evidence ever produced for any endovascular therapy of peripheral artery disease. In particular, 3 DCBs and 2 DES are currently supported by broad and robust evidence, beyond just first-in-human trials, consisting of rigorous, independently adjudicated randomized pivotal trials and large real-world datasets.<sup>1-10</sup> The most recently released practice guidelines from the Society for Cardiovascular Angiography and Interventions have therefore elected DCB as first line endovascular therapy with the highest level of recommendation (I-A) for a wide array of indications in the femoropopliteal segment.<sup>11</sup>

Also noteworthy, several “no-class-effect” claims have been largely and consistently raised pertaining to paclitaxel-eluting technologies, specifically based on the multitude of observed technical differences and related outcome variances demonstrated in preclinical and clinical trials.<sup>12-16</sup> Although paclitaxel is the common denominator in all currently marketed DCBs and DES, substantial technical differences do in fact exist within individual categories of DCBs and DES as regards drug dose and excipients. Obviously even more differences exist across the two platforms.<sup>17-20</sup> Finally, the aforementioned clinical studies have informed and populated multiple meta-analyses that confirmed and reinforced DCB/DES efficacy compared to their bare balloon/stent counterparts.<sup>15,16,21-23</sup>

With all this in mind, we acknowledge the recent work by Katsanos et al.<sup>24</sup> The article, published in the *Journal of the American Heart Association* in December 2018, is a systematic review and meta-analysis of 28 randomized trials of paclitaxel-coated devices in the femoropopliteal arteries. The primary safety measure was all-cause death. The findings and conclusions were striking; the analysis concluded that there is an increased risk of all-cause death at 2 and 5 years following application of paclitaxel-coated balloons and stents.<sup>24</sup>

Before undertaking urgent and further investigations (as suggested by the authors), several important aspects come to our attention: (1) DCB and DES are taken here as a single homogenous device class in spite of substantial differences across device features, including paclitaxel dose, release kinetics, and likely different performance in terms of both efficacy and safety; (2) patient-level data are missing, this being a condition necessary to adequately inform the search of a mechanistic relation to death; and (3) death from all-cause is taken as the primary safety measure, ignoring the verdict of no relationship between patient death and the study devices as adjudicated by the clinical event committees in most of the studies.

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The authors finally state they could not find any plausible causality between death and paclitaxel used for the treatment of lower limb arterial disease. In truth, only 2<sup>25,26</sup> of 28 controlled trials in their meta-analysis had significantly higher all-cause mortality in their study arms. It is clear that, in the absence of patient-level data, any number of possible associations with death other than paclitaxel may not have been properly investigated and accounted for to arrive at a certain vs hypothetical causality.<sup>27</sup>

While it is not the scope of this editorial to check the validity of the overall statistical method of this meta-analysis,<sup>21</sup> we urge expert biostatisticians to do so. Until that is accomplished and rigorous clarity is achieved, we encourage clinicians to continue appraising the reliability of each device and individual trial on its own merits and limitations and to continue relying on those individual DCBs and DES that offer rigorous and quality evidence of good outcomes.

More than ever before, clinical research should continue with a deeper look into long-term clinical events from broad real-world studies. It is not time to panic but to react and fully resurge.

### Declaration of Conflicting Interests

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