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EDITORIAL

Paclitaxel Eluting Endovascular Technology and Long-Term Mortality: Safety Concern or a Reminder of an Obvious Literature Gap?

The use of drug eluting endovascular technologies in the form of a drug coated balloon (DCB) or drug eluting stent (DES) has greatly increased in recent years. The European Society for Vascular Surgery (ESVS) guidelines recommend that DCB or DES may be considered for the treatment of short atherosclerotic lesions.[1] This is based on industry funded randomised controlled trials (RCTs) reporting that drug eluting devices may be associated with better patency rates compared with standard percutaneous transluminal angioplasty (PTA) in the femoropopliteal (F-P) segment.[2] These RCTs, however have several limitations; a number of well designed multicentre effectiveness RCTs with long-term follow up are ongoing.[3–5]

In this context, the meta-analysis of published RCTs by Katsanos et al.,[6] which suggests that the use of paclitaxel based devices in F-P intervention may be associated with increased long-term mortality risk, has raised questions among the endovascular community. Katsanos et al. performed a thorough review of the literature using widely accepted methodology. Despite there being no differences at one year, the authors reported a significantly higher mortality at two and five years. Interestingly, the weighted two year and five year all cause mortality in the paclitaxel group was not dissimilar to that observed among conservatively managed claudicants in contemporary cohort studies.[7]

Despite the robust meta-analytical methodology, these findings should be interpreted with caution. Historical evidence suggests that coronary paclitaxel eluting stents may be associated with late stent thrombosis and cardiovascular events,[8,9] but these observations are based on multicentre, well conducted, RCTs with long-term follow up. This is not the case in the F-P literature. The RCTs included in the meta-analysis under question were powered using a patency based primary endpoint, typically at six or 12 months, and were not specifically designed to detect late clinical events. Combining results from these small efficacy studies to support or refute an all cause mortality hypothesis poses a potential methodological pitfall. In fact, "small study effect" is the most common type of bias in meta-analyses; as discussed by experienced methodologists, conclusions arising from the synthesis of such RCTs should be approached with caution.[10]

Furthermore, to make a definitive causal association between paclitaxel based devices and mortality, the use of patient level data is mandatory. Few of the currently available paclitaxel F-P RCTs report causes of death after the first year, and no patient level data were available to Katsanos et al., which prohibits in depth analyses or exploration of alternative hypotheses relating to mortality. Lack of patient level open access data is a wider issue across the cardiovascular literature, impeding meaningful clinical interpretation.[11] More than anything, this meta-analysis has unmasked deficiencies in the currently available industry sponsored paclitaxel F-P RCTs, such as design and sample size calculations based on arbitrary patency driven endpoints, short follow up duration, underrepresentation of patients with critical ischaemia, and patient level data being unavailable to researchers. These factors should be taken into consideration when interpreting this information.

Nevertheless, the meta-analysis by Katsanos et al. has shed light on a potential, although not fully established, association between paclitaxel and late mortality. It is now important to adopt robust mechanisms, in line with the IDEAL framework recommendations,[12] to fully investigate this observation using high quality data, before widely implementing these endovascular innovations into routine practice. To do so, the ongoing high quality effectiveness RCTs should be completed, individual institutions should review their outcomes following the use of paclitaxel eluting devices and share their findings publicly, and manufacturers of paclitaxel eluting technology should be encouraged to make their patient level data openly accessible to researchers. Until then, the potential risks and benefits of paclitaxel eluting devices should be judged on an individual basis and discussed with patients prior to their treatment.

REFERENCES

1 Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. Editor's choice – 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.

2 Katsanos K, Spiliopoulos S, Karunanithy N, Krokidis M, Sabharwal T, Taylor P. Bayesian network meta-analysis of nitinol stents, covered stents, drug-eluting stents, and drug-coated balloons in the femoropopliteal artery. *J Vasc Surg* 2014;**59**:1123–33 e8.

3 Hunt BD, Popplewell MA, Davies H, Meecham L, Jarrett H, Bate G, et al. BAlloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3): study protocol for a randomised controlled trial. *Trials* 2017;**18**:224.

4 Menard MT, Farber A, Assmann SF, Choudhry NK, Conte MS, Creager MA, et al. Design and rationale of the best endovascular versus Best Surgical Therapy for Patients with critical Limb Ischemia (BEST-CLI) trial. *J Am Heart Assoc* 2016;**5**.

https://doi.org/10.1016/j.ejvs.2019.01.030

5 SWEDEPAD. *The SWEDEPAD trials*. 2019. Available from: http://www.ucr.uu.se/swedepad/.
6 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**:e011245.
7 Kumakura H, Kanai H, Hojo Y, Iwasaki T, Ichikawa S. Long-term survival and fate of the leg in de novo intermittent claudication. *Eur Heart J Qual Care Clin Outcomes* 2017;**3**:208–15.
8 Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (clinical evaluation of the Xience V Everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv* 2013;**6**:914–22.
9 Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;**362**:1663–74.
10 Fanelli D, Costas R, Ioannidis JP. Meta-assessment of bias in science. *Proc Natl Acad Sci U S A* 2017;**114**:3714–9.
11 BMJ. *Open data*. 2019. Available from: https://www.bmj.com/open-data.
12 McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009;**374**:1105–12.

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