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EDITORIAL: HOT TOPIC

No Increased Mortality Risk Following Paclitaxel Treatment in a Large Swedish Registry Based Randomised Controlled Trial — Reassuring Patient Safety

The *Swedish Drug Elution Trial in Peripheral Arterial Disease* (SWEDEPAD) has reported an interim safety analysis in the New England Journal of Medicine[1] showing that use of paclitaxel does NOT lead to excess mortality at mean 2.5 years follow up. This is an extremely important and reassuring finding, after the systematic review and meta-analysis by Katsanos et al.[2] had cast severe doubts on drug eluting technology.

Randomised Controlled Trials (RCTs) offer the best methodology to assess the effects of new interventions, but they do have important limitations.[3] Selection bias is common, and usually they do not represent the entire population at risk. In addition, RCTs are expensive, and often their results arrive late, so they are sometimes no longer relevant. Observational data may have more obvious limitations, but they can be very representative if collected within systematic registries ('real world'). A hybrid solution is to randomise patients within population based registries, and the first ever registry based RCT (RRCT) was published in 2013.[4]

SWEDEPAD is the first RRCT within the Swedvasc registry. Its original aim was to find out whether drug elution technology affected amputation rates in patients with chronic limb threatening ischaemia (CLTI), and quality of life (QoL) in patients with intermittent claudication (IC). Based on the sample size calculation the study planned to randomise 3 700 patients, 2 400 with CLTI and 1 300 with IC.

When, in December 2018, the Katsanos systematic review[2] suggested an increased mortality after paclitaxel administration at medium term follow up, inclusion into SWEDEPAD was immediately halted on December 10, 2018. At that time 2 289 patients had been randomised: 1 480 with CLTI, and 809 with IC. Although not pre-planned in the analysis plan, the trial data and safety monitoring committee recommended an interim analysis of all cause mortality as soon as a minimum follow up was reached in a large proportion of the patients.

The SWEDEPAD investigators have now found that after a mean follow up of 2.5 years:[1] as expected in this population, mortality was high, with 574 deaths overall (25%). Of 2 289 randomised patients, 1 457 had been followed for two years, 789 for three years, and 282 for four years. Interestingly, there was no difference in mortality between the treatment groups, either for CLTI or for IC, at any follow up interval. Mortality at the end of follow up was, for drug coated vs. non-drug coated devices, for patients with CLTI 249 [33.4%] *vs.* 243 [33.1%], and for those with IC 44 [10.9%] *vs.* 38 [9.4%], respectively.

Although the title of the paper (*"Mortality with Paclitaxel-coated Devices in Peripheral Artery Disease"*)[1] may suggest otherwise, these results are quite reassuring. In contrast to the Katsanos meta-analysis, which analysed aggregate data of several heterogeneous RCTs (some of them underpowered) with variable follow up,[2] SWEDEPAD is a large, homogeneous and population based, i.e. representative, RCT. Not even the slightest trend towards an increased mortality among the paclitaxel treated patients was shown. Of note, no other drug than paclitaxel was used in the drug eluting balloons and stents. Furthermore, for mortality not a single patient was lost to follow up in this large study. This is explained by the fact that the same personal identity number that was used in the trial is also used in healthcare and the population registry. The latter captures all deaths in the country with a maximum delay of two weeks and adds this information to Swedvasc through automatic cross matching. Since death is not reported by the treating surgeons or radiologists, the risk of "alternative facts" is minimised.

It is important to note that no outcomes other than mortality were reported in this interim analysis. Enrolment into the study has been re-initiated, although the Covid-19 pandemic presently delays the inclusion rate. We look forward to learning about the main outcomes of this study: amputations, re-interventions and QoL, which will inform us whether drug eluting techniques have clinical benefits and risks. In the meantime, we can feel safe using paclitaxel coated devices in the sense that there is not an increased mortality risk. But it remains to be shown whether this treatment has any clinical advantages, and if it is cost effective.

This paper adds robust evidence to previous reports from observational data. Behrendt CA et al.[5] performed two propensity score analyses (sometimes named "the poor man's RCT") in a large insurance fund database in Germany. They could not identify any increased mortality among patients treated with paclitaxel coated devices, either after intervention in the femoropopliteal,[6] or in the below the knee[6] segments.

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The Global CLTI Guidelines[7] could not give firm recommendations regarding the use of drug eluting devices. Hopefully, we will have more data in future guidelines. In the meantime, vascular surgeons and interventionists will have to lean on personal experience, rule of thumb and budget restrictions, when deciding whether or not to use this technology. At least we need no longer worry that we harm our patients, and the fact that recruitment into the SWEDEPAD trial has restarted is good news for future knowledge.

REFERENCES

1 Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, et al. Mortality with paclitaxel-coated devices in peripheral artery Disease. *N Engl J Med* 2020.

2 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.

3 Mani K, Björck M. Alternatives to randomised controlled trials for the poor, the impatient and when evaluating emerging technologies. *Eur J Vasc Endovasc Surg* 2019;**57**:598–9.

4 Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gugnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013 Oct 24;**369**:1587–97.

5 Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, et al. Editor's choice - long term survival after femoropopliteal artery revascularisation with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg* 2020;**59**:587–96.

6 Heidemann F, Peters F, Kuchenbecker J, Kreutzburg T, Sedrakyan A, Marschall U, et al. Long term outcomes after revascularisations below the knee with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg* 2020;**60**:549–58.

7 Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Joint guidelines of the society for vascular surgery; European society for vascular surgery; world federation of vascular societies. *Eur J Vasc Endovasc Surg* 2019;**58**:S1–109.

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