Paclitaxel-Coated or Uncoated Devices: Significant Differences in Patient Populations and Mortality Led to Study Incomparability

Chenyang Zhang and Guosheng Yin

Authors’ affiliations:
Department of Statistics and Actuarial Science, University of Hong Kong, Hong Kong

Corresponding author:
Guosheng Yin, PhD
Patrick S C Poon Endowed Professor and Head
Department of Statistics and Actuarial Science
The University of Hong Kong
Pokfulam Road, Hong Kong SAR, China
Email: gyin@hku.hk
Tel: 852-3917-8313; Fax: 852-2858-9041

Conflicts of interest: The authors declare no potential conflict of interest.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

The SWEDEPAD trial reported an unplanned interim analysis to show no difference in the mortality rate between the paclitaxel-coated and uncoated groups (Nordanstig et al., 2020), which contradicts the long-term risk of paclitaxel-coated devices claimed by a meta-analysis (Katsanos et al., 2018). However, there existed significant differences in mortality rates between the SWEDEPAD trial and the trials included in the meta-analysis, which were caused by significant differences in the patient populations. As a result, the SWEDEPAD trial and meta-analysis results are not directly comparable. An updated meta-analysis including the SWEDPEPAD trial and all studies in the meta-analysis (Katsanos et al., 2018) shows marginal differences in mortality rates between the paclitaxel-coated and control groups at two years with Bayesian relative risk (RR) 1.39 (95% credible interval (CrI) [1.01, 2.39]) and frequentist RR 1.16 (95% confidence interval (CI) [0.99, 1.36]) and differences in mortality rates during the entire follow-up period with Bayesian RR 1.29 (95% CrI [1.01, 1.72]) and frequentist RR 1.13 (95% CI [0.99, 1.28]) under random-effects models. Given the relatively short follow-up thus far in the SWEDEPAD trial (with a mean follow-up of 2.49 years) and the paclitaxel-coated risk being long-term (e.g., 4 or 5 years), the interim results on the risk of paclitaxel-coated devices reported by the SWEDEPAD trial warrant further investigation.
1 Introduction

The SWEDEPAD trial\(^1\), which are investigating paclitaxel-coated versus uncoated devices in patients with peripheral artery disease (PAD), was temporarily suspended on December 2018 due to the potential long-term risk of paclitaxel-coated devices reported by a meta-analysis.\(^2\) An unplanned interim analysis of the SWEDEPAD trial showed no difference in the mortality rate between the paclitaxel-coated and uncoated groups at one year with a hazard ratio (HR) of 1.03 (95% CI [0.77, 1.37]) or during the entire follow-up period with an HR of 1.06 (95% CI [0.92, 1.22]). Based on these results, it was decided to resume enrollment in the SWEDEPAD trial on March 23, 2020. However, Figure 2 of the SWEDEPAD trial publication shows that the cumulative incidence curves of drug-coated devices constantly stayed above those of uncoated either for the overall population or subgroups of chronic limb threatening ischemia or intermittent claudication.\(^1\) The risk of paclitaxel-coated devices is known to be of long term,\(^2,^3\) while the SWEDEPAD trial has so far had a mean follow-up of 2.49 years which is still relatively short for evaluating long-term risk.

2 Methods and Results

2.1 Baseline Differences in Patient Populations

By pooling the numbers of deaths and patients from all studies included in the meta-analysis, we treat the combined data as a mega-trial,\(^2\) and compare the differences in mortality between the SWEDEPAD trial\(^1\) and mega-trial. For the paclitaxel-coated group, we found significant differences in the all-cause death rates at one year with relative risk (RR) 4.4 (95% CI [3.2, 6.0]) and during the entire study period with RR 3.7 (95% CI [3.1,
For the uncoated group (control), the mortality rate differences between the SWEDEPAD trial\(^1\) and mega-trial were also significant with RR 4.2 (95% CI [3.0, 5.9]) at one year, and RR 5.7 (95% CI [4.5, 7.2]) during the entire study period. All RRs comparing the SWEDEPAD trial\(^1\) and mega-trial\(^2\) are larger than 3.5 with p-values smaller than 0.0001, which could have attributed to incomparability between the SWEDEPAD trial\(^1\) and the trials included in the meta-analysis\(^2\). There are significant differences at the baseline in the patient populations between the SWEDEPAD trial and trials in meta-analysis: the former had 35% intermittent claudication (IC) and 65% chronic limb threatening ischemia (CLTI) while the latter had 89% IC and 11% CLTI.

CLTI is an advanced stage of PAD. Compared with intermittent claudication, CLTI has a negative prognosis within a year after the initial diagnosis, with a 1-year amputation rate of approximately 12% and mortality rates of 50% at 5 years and 70% at 10 years.\(^4\) The baseline prognosis difference could be a main cause of observed differences in mortality rates between the studies.

### 2.2 Updated Meta-Analysis

We conducted an updated meta-analysis which included the SWEDEPAD trial\(^1\) and all studies in the meta-analysis\(^2\). The number of deaths by two years of the SWEDEPAD trial\(^1\) was estimated by multiplying the estimated two-year cumulative incidence rate and the total number of patients. For each study in the meta-analysis\(^2\), we took the results with the longest follow-up as those for the entire study period. The R packages ‘meta’ and ‘bayesmeta’ were used to formulate frequentist and Bayesian random-effects models, respectively.
As shown in Table 1, both frequentist and Bayesian random-effects models demonstrate no difference in one-year all-cause death rates between paclitaxel-coated and uncoated arms, indicating no short-term risk of paclitaxel-coated devices. At two years or during the entire follow-up period, the frequentist random-effects model yields marginally insignificant differences in all-cause death rates with two-year RR 1.16 (95% CI [0.99, 1.36], P=0.063), and the entire follow-up RR 1.13 (95% CI [0.99, 1.28], P=0.065).

However, the Bayesian random-effects model yields an RR of 1.39 (95% credible interval (CrI) [1.01, 2.39]) at two years and an RR of 1.29 (95% CrI [1.01, 1.72]) during the entire follow-up period, which suggests significant risk of paclitaxel-coated devices with longer-term follow-ups. The posterior probabilities for the death rate of the paclitaxel-coated arm being higher than that of the control arm were around 0.98 at two years and during the entire follow-ups, with Bayes factors larger than 40. This provides strong evidence for the long-term mortality risk of paclitaxel-coated devices.

3. Conclusion

The SWEDEPAD trial\(^1\) enrolled 2289 patients, which is about half of the total number of patients included in the meta-analysis\(^2\). Although one study with such a large sample size and insignificant results was added, the new meta-analysis still yields marginally significant differences in the mortality rates at two years and during the entire follow-up. Moreover, with a mean follow-up of only 2.49 years, the results of the SWEDEPAD trial warrant further investigation, because the risk from paclitaxel-coated devices is long-term.\(^5\)
References

1. Nordanstig J, James S, Andersson M, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. N Engl J Med 2020;383:2538-2546.

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. Beckman JA, White CJ. Paclitaxel-coated balloons and eluting stents: is there a mortality risk in patients with peripheral artery disease? Circulation 2019;140:1342-51.

4. Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. J Vasc Surg 2010;51:230-41.

5. Rocha-Singh KJ, Duval S, Jaff MR, et al. Mortality and paclitaxel-coated devices: an individual patient data meta-analysis. Circulation 2020;141:1859-69.
Table 1. Relative risk and interval estimates of the meta-analysis including the SWEDEPAD trial\textsuperscript{1} and all studies in the meta-analysis\textsuperscript{2}.

|                     | Follow-up period |          |          |          |
|---------------------|------------------|----------|----------|----------|
|                     | One year         | Two years| Entire follow-up |
| Frequentist         | Random-effects   | 1.04 [0.84, 1.28] * | 1.16 [0.99, 1.36] | 1.13 [0.99, 1.28] |
|                     | \( P \) value    | 0.713    | 0.063    | 0.065    |
| Bayesian            | Random-effects   | 1.04 [0.77, 1.41] | 1.39 [1.01, 2.39] | 1.29 [1.01, 1.72] |
|                     | Posterior probability of (\( RR > 1 \)) | 0.613 | 0.978 | 0.980 |

*Relative risk (\( RR \)) with 95% confidence interval (frequentist) or equal-tailed credible interval (Bayesian) in the brackets.