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2021-04

Björkman , P , Hietala , E-M & Venermo , M 2021 , ' No Difference in Mid-term and Long-Term Mortality After Vascular Paclitaxel Exposure ' , Annals of Vascular Surgery , vol. 72 , pp. 253-260 . https://doi.org/10.1016/j.avsg.2020.08.147

http://hdl.handle.net/10138/341671
https://doi.org/10.1016/j.avsg.2020.08.147

Journal Pre-proof

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PII: S0890-5096(20)30839-6

DOI: https://doi.org/10.1016/j.avsg.2020.08.147

Reference: AVSG 5357

To appear in: *Annals of Vascular Surgery*

Received Date: 1 July 2020

Revised Date: 21 August 2020

Accepted Date: 28 August 2020

Please cite this article as: Björkman P, Weselius EM, Venermo M, No difference in mid- to long-term mortality after vascular paclitaxel exposure, *Annals of Vascular Surgery* (2020), doi: https://doi.org/10.1016/j.avsg.2020.08.147.

No difference in mid- to long-term mortality after vascular paclitaxel exposure

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Original research

Word count: 2149 excluding abstract and references

Abstract

Objectives

Concern has been raised over potential paclitaxel-related increase in mortality following treatment with drug-coated balloons. We report mid- to long-term patient-level mortality in three trials from our institution.

Methods

Patient data from the DRECOREST I and II trials as well as the FINNPTX-trial were included for analysis. The DRECOREST I involved patients with stenosis in a bypass vein graft, and the DRECOREST II included patients with stenosis in a dialysis fistula. The FINNPTX –trial randomized patients to either a prosthetic bypass or drug-eluting stent for long femoropopliteal lesions. Since the present retrospective study addressed mortality related to intravascular paclitaxel exposure, and population data in Finland are comprehensive, we were able to include all patients exposed to paclitaxel in the three trials.

Mortality data were extracted from the population registry as well as patient records. Survival rates were analyzed for all trials pooled and separately. Late mortality was retrospectively analyzed and cross-referenced with national registry data.

Results

A total of 142 patients were included, 76 treated with paclitaxel eluting device and 66 without. Mean follow-up time for survivors was 3.9 years. Overall all-cause mortality was 31.7% during follow-up. In the DRECOREST I -trial 35.5% patients died in the paclitaxel group and 37.9% in the control group (p=.84). In

the DRECOREST II, overall mortality was 55.6% in paclitaxel group and 44.4% in the control group (p=.51). In the FINNPTX-trial 22.2% died in the paclitaxel group and 10.5% in the control group during follow-up (p=.30). No single cause of death was overrepresented. The most common causes of death in both groups were cardiovascular death, 59.3% in the paclitaxel group and 52.4% in the control group (p=.733) followed by malignancy (14.8% vs. 14.3% in the groups respectively).

Conclusions

No significant difference was seen in the overall analysis between paclitaxel and control group. A statistically non-significant elevated late mortality in the FINNPTX-trial after paclitaxel exposure was observed. However, the numbers in the individual trials are small, and should be interpreted in the context of future patient-level meta-analysis.

1. Introduction

Paclitaxel is a cytostatic and cytotoxic drug that has, in its solvent-based form, for many years been used in cancer treatment. During the last decade, we have seen a significant increase in the use of paclitaxel-coated and eluting devices in peripheral arterial disease, where the drug is aimed at preventing restenosis due to intimal hyperplasia at the treated sites. Drug-coated balloons (DCB) and drug-eluting stents (DES) have mainly been studied and approved for use in femoropopliteal occlusive disease, where remarkable benefit in patency and target-lesion revascularization (TLR) has been observed when drug eluting technology has been compared with conventional devices in several randomized controlled trials (RCT) [1-5]. The THUNDER-trial reported lasting benefit in terms of patency and TLR-rates both in the mid- and long-term [6,7]. Furthermore, the LEVANT-trials demonstrated non-inferiority and safety over a maximum of two years of follow-up [8,9]. The IN.PACT SFA-trial included 330 patients, and reported clear TLR-benefit from use of DCB [10,11]. These results have further been confirmed in a systematic review by Katsanos et al. [12], although clinical improvement and benefit as improvement in clinical parameters, such as ABI or walking distance, have been questioned by others [13].

In a recent meta-analysis, Katsanos *et al* reported consistent and lasting late mortality after treatment with paclitaxel DCBs across nearly 30 RCTs [14]. The striking finding was that the difference in mortality was not visible in the first year following treatment, but becomes clear and remarkable after that with an astonishing 95% rise in the DCB-group at 5 years. Furthermore, the effect seemed dose-dependent with lower odds ratios for low-dose DCBs compared to

higher dose balloons. However, the dose-dependency in the analysis has been contested due to weak methodology[15]. The meta-analysis did not report on patient specific causes of death for the majority of included trials, and the possible causal correlation remains unresolved. Considering mortality after treatment of stenotic lesions with DCB in vascular accesses of hemodialysis patients, published data so far has not demonstrated increased mortality after the use of DCB[16,17].

In recent years, two paclitaxel-related RCTs have been conducted at our institution. These are the DRECOREST I and II –trials, in which DCBs were compared to plain balloons in vein grafts and dialysis fistulas, respectively[18,19]. In addition, we participated in the multicenter FINNPTX-trial comparing open synthetic femoropopliteal bypass (BSX) to drug-eluting stents [20]. The 2-year mortality data of DRECOREST I and FINNPTX-trials were included in the recent meta-analysis by Katsanos.

This paper reports on the updated late mortality and causes of death for the three aforementioned trials. The aim of this report is to publish patient-level mortality data with extended follow-up from previously published RCTs for possible future meta-analysis.

2. Materials and Methods

2.1 Included trials

In the DRECOREST I –trial, patients with significant stenosis or restenosis in femoropopliteal or femorodistal vein grafts requiring PTA were randomized between March 2013 and December 2015. All bypasses had been performed using translocated, non-reversed and valvulectomized vein. The autogenous grafts included both single-segment and spliced great saphenous and arm veins. Grafts were measured with duplex-ultrasound for diameter, cross-section area and peak systolic velocity ratio (PSVR). A PSVR of 2.5 was defined as threshold for intervention. Lesions <15 mm from an anastomosis were excluded. The lesion was crossed with a guide wire and thereafter predilated with a conventional angioplasty balloon before randomization. It was then redilated with DCB or traditional balloon (control group) according to allocation. This trial used a balloon with a paclitaxel coating of 3.5 μg/mm^2 with urea as excipient (Medtronic IN.PACT, Medtronic, Minneapolis, MN, USA). All patients, except those on warfarin, received dual antiplatelet therapy postoperatively (ASA 100 mg + **c**lopidogrel 75 mg). This was continued for 3 months. Patients on warfarin received concurrent ASA 50 mg for three months. A vascular nurse performed follow-up at 1, 6, and 12 months. The follow-up examination included clinical evaluation for symptoms, ankle brachial index (ABI) and toe pressure (TP) measurements, as well as duplex ultrasound assessment of the graft and the index lesion. As the studied intervention aims only at graft patency, the threshold for reintervention was set as a PSVR of >2.5 regardless of clinical findings. 57 cases were ultimately included in the statistical analysis. Baseline characteristics and technical details of the interventions, such as dilatation time and balloon size, were similar in both groups. During the original study period, six patients

died, of which four were in the DCB group. There was one major amputation in the control group.

The setup for the DRECOREST II-trial was similar, but addressed stenosis in dialysis fistulas. Inclusion was done between March 2013 and February 2016. A 3.5 µg/mm^2 DCB was used. 36 patients were randomized. Five patients died during the original follow-up, of which four were in the control group. These four in the control group died with an open AVF on average at 145 (100-180) days after the intervention, whereas the one in the DCB group died unrelated to any reintervention at 240 days after the index intervention. Two patients from the control group were lost to follow-up: **o**ne due to withdrawal of consent after randomization, and the other for unknown reasons after re-revascularization. Interestingly, patency rates in the DCB-groups were significantly worse in the immediate term, suggesting potential damage to the fistula from the DCB.

In the FINNPTX multicenter trial, patients were randomized between 2011 and 2014, follow-up ended in 2016 at six hospitals in Finland. 5-25 cm SFA-occlusions were eligible for inclusion. Clinical manifestations varied from claudication to rest pain (Rutherford class II-IV). Patients were randomized to endovascular recanalization and DES or prosthetic above-knee femoropopliteal bypass 2:1 (DES:BSX). Bypass surgery was performed with a 6 mm heparin-bonded polytetrafluoroethylene (PTFE) graft. In the stent group, the occlusion was recanalized and crossed before deployment of a Zilver PTX drug-eluting stent (Cook Medical Inc., Bloomington, IN, USA). Primary outcome measure was overall stent or graft patency. Follow-up was performed by clinical evaluation

supplemented with ankle-brachial index (ABI), toe pressure (TP) and duplex ultrasound at 1, 6, 12, and 24 months postoperatively. 46 patients were randomized in the different centers. Baseline characteristics were well balanced between the study groups. Five patients were excluded due to immediate technical failure, i.e. unsuccessful recanalization. These were salvaged by distal and/or venous bypass, and were thus not eligible for intention-to-treat analysis. No deaths or major amputations were seen in either group during 12-month follow-up. One patient in the DES group died at 24 months from procedure. The individual trials were reviewed by the Ethics Committee of Helsinki University Hospital at the time of their design, and all patients gave written informed consent.

2.2 Analysis

In this analysis, the dates and causes of death were updated from the patient records as well as from the Cause of Death –registry of Statistics Finland until 30April2019. This means that also deaths of those who were lost to follow-up in the original trials could be included. The primary endpoint was death due to any cause. The study populations were cross-referenced with population registries to detect deaths and causes of death, and thus no patients were lost to follow-up with regard to overall mortality. Data were analyzed for the three trials pooled, as well as each trial separately.

Statistical analysis was performed with SPSS v.24 (IBM, Armonk, VA, USA). Log-rank (Mantel-Cox) calculations were used for survival analysis. Risk ratio (RR) was defined as the ratio of cumulative incidences. There were no missing mortality data.

3. Results

Since this study addresses all-cause mortality, we were able to include also those patients who were excluded from the initial studies, but still exposed to paclitaxel. This yielded a total of 142 patients, 76 treated with paclitaxel eluting device and 66 without. Mean follow-up time for survivors in the three trials was 3.9 (range 2.9-7.1) years being the longest in the FINNPTX-trial (7.1 years), followed by DRECOREST I (4.7 years) and DRECOREST II (3.5 years). Overall all-cause mortality was 31.7 % during follow-up. In the DRECOREST I -trial (bypass grafts), 11 (35.5%) patients died in the paclitaxel group and 11 (37.9%) in the control group (p=.84). In the DRECOREST II (AVFs), overall mortality was 18 (55.6%) in paclitaxel group and 8 patients (44.4%) in the control group (p=.51). In the FINNPTX-trial (stent vs. bypass), 6 patients (22.2%) died in the paclitaxel group and 2 patients (10.5%) in the control group (p=.30). Distribution of patients and death rates across the trials is listed in table 1 and Figures 1-4 and table 2 illustrate cumulative mortality as a function of time. The most common cause of death in the both groups was cardiovascular death 59.3% in the paclitaxel group and 52.4% in the control group (p=.73) followed by malignancy (14.8% vs. 14.3% in the groups respectively). All causes of death in the trials are listed in table 3.

There were no major amputations in the FINNPTX cohort up to five years. In the DRECOREST I –trial there were 3 major amputations in both groups.

Population registry data in Finland is comprehensive, so the authors are confident in that all deaths were detected.

4. Discussion

4.1 Context

In this retrospective analysis of three RCTs, we cannot demonstrate a statistically significant difference in late mortality between paclitaxel-coated products and control products. We can, however, see an elevated relative risk for mortality after paclitaxel exposure in the FINNPTX-trial, even though nothing in the analysis of causes of death at the individual level suggested the relation of deaths with paclitaxel. Thus, considering that the number of patients in the FINNPTX-trial was so low that a false positive result is somewhat likely. On average, the patients in the bypass trial (DRECOREST I) and especially in the AVF trial (DRECOREST II) were affected by more comorbidities and therefore had already a shorter life expectancy compared with relatively fit claudicants in the FINNPTX-trial. This difference in baseline population prognosis confounds interpretation of the mortality data for the separate trials, especially when pooled together.

Publication of the meta-analysis by Katsanos, has given rise to a large debate on the safety of paclitaxel technology. This meta-analysis immediately influenced large randomized trials, such as the Swedepad and Basil-2 trials, which ceased inclusion until further evidence is available. The same phenomenon was seen in several clinics, as paclitaxel eluting devices were abandoned in fear of elevated mortality. Conversely, several manufacturers made their own analysis on the late results suggesting that the signal in the Katsanos meta-analysis is not real. In the meta-analysis of 1980 patients in IN-PACT trials, survival analysis was performed in three paclitaxel dose groups: 5,019.0; 10,007.5; and 19,978.2 mg. Rates of freedom from all-cause mortality between the 3 groups through 5 years

were 85.8%, 84.2%, and 88.2%, respectively (p=.73) [21]. There was no significant difference in all-cause mortality between DCB and PTA through 5 years.

The biological hypothesis of the late mortality associated with paclitaxel remains unclear. In this analysis, we could not identify overrepresentation of any single cause of death in the paclitaxel groups. As in earlier publications, the difference between the groups in the FINNPTX-trial only becomes visible at around 2 years.

To date, there have been but few concerns about the safety of paclitaxel. The IN.PACT DEEP –trial was aborted due to an unexplained rise in major amputations in the DCB-group[22]. It has been hypothesized that paclitaxel embolization might play a role, although no hard evidence in humans exists in support of this [23,24]. Elevated late mortality rates after paclitaxel exposure have been noticed in many of the published trials, but these have consistently been rebutted as non-procedure related, either by safety committees or by authors themselves. For DES, the ZILVER PTX –trial provided 5-year patency and mortality rates after deployment of the ZILVER stent. While the first publication showed a higher mortality rate in the control group, this was corrected in an subsequent erratum; at five years overall mortality was 6.9% for the primary DES group and 10.2% for the PTA group, P=.03. [5,25] The deaths were not deemed as procedure related.

4.2 Limitations

Our study has several limitations. First of all, the number of patients is low and thus the power is limited. Secondly, two kinds of devices have been used in

altogether three trials and the patient population is heterogeneous due to the differences in the inclusion criteria in the three trials. On the other hand, our follow-up is comprehensive with no dropouts and all deaths as well causes of death are included. The authors wish to further emphasize that the sole purpose of this analysis was to analyze paclitaxel exposure, which justifies the heterogeneous mix of internally homogeneous trials, whose only common denominator was indeed paclitaxel.

5. Conclusions

There is no statistically significant elevated late mortality in the trials after paclitaxel exposure, although the relative risk after DES was increased. However, the numbers in the individual trials are small, and the results need to be interpreted in the context of future patient-level meta-analysis.

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356

357 **Figure Legends**

358 Fig 1-4. Kaplan-Meier survival plots for all trials and each trial separately. No
359 cases were lost to follow-up regarding mortality.

360 Table 1. Survival data for the included trials

361 Table 2. Life tables for the included trials

362 Table 3. Causes of death for all trials pooled

Table 3

Cause of Death	Paclitaxel	Control	Total
	%	%	%
Cardiovascular	59.3	52.4	56.3
Malignancy (any)	14.8	14.3	14.6
Infection	11.1	19.0	14.6
Diabetes	7.4	9.5	8.3
Other	3.7	0.0	2.1
Unknown	3.7	4.8	4.2

Table2

Cumulative deaths	Paclitaxel	Control	
DRECOREST I	N=31	N=29	Median FU for survivors = 4.7 yrs (3.2 - 5.7)
1y	1	4	
2y	4	6	
3y	7	6	
4y	7	6	
5y	7	7	
DRECOREST II	N=18	N=18	Median FU for survivors = 3.5 yrs (2.9 - 5.0)
1y	4	2	
2y	8	4	
3y	10	9	
4y	10	10	
5y	10	11	
FINNPTX	N=27	N=19	Median FU for survivors = 5.6 yrs (3.9 - 7.1)
1y	0	0	
2y	2	1	
3y	3	1	
4y	3	1	
5y	6	2	

Mean FU for survivors (years)	**Paclitaxel**	**Deaths**	**%**	**Control**	**Deaths**	**%**	**Relative risk**	**p-value** (χ^2)
4.7 (3.2-5.7)	31	11	35.5	29	11	37.9	0.94	0.844
3.5 (2.9-5.0)	18	10	55.6	18	8	44.4	1.25	0.505
5.6 (3.9-7.1)	27	6	22.2	19	2	10.5	2.11	0.303