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## No Difference in Mid-term and Long-Term Mortality After Vascular Paclitaxel Exposure

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

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12

13 Original research

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15 Abstract

16 Objectives

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

20

21 Methods

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

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

34

35 Results

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

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

47

#### 48 Conclusions

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

54

## 55 **1. Introduction**

56

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

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

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

87

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

95

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

100

## 101 **2. Materials and Methods**

### 102 2.1 Included trials

103

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



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

130

131 The setup for the DRECOREST II-trial was similar, but addressed stenosis in  
132 dialysis fistulas. Inclusion was done between March 2013 and February 2016. A  
133  $3.5 \mu\text{g}/\text{mm}^2$  DCB was used. 36 patients were randomized. Five patients died  
134 during the original follow-up, of which four were in the control group. These four  
135 in the control group died with an open AVF on average at 145 (100-180) days  
136 after the intervention, whereas the one in the DCB group died unrelated to any  
137 reintervention at 240 days after the index intervention. Two patients from the  
138 control group were lost to follow-up: one due to withdrawal of consent after  
139 randomization, and the other for unknown reasons after re-revascularization.  
140 Interestingly, patency rates in the DCB-groups were significantly worse in the  
141 immediate term, suggesting potential damage to the fistula from the DCB.

142

143 In the FINNPTX multicenter trial, patients were randomized between 2011 and  
144 2014, follow-up ended in 2016 at six hospitals in Finland. 5-25 cm SFA-  
145 occlusions were eligible for inclusion. Clinical manifestations varied from  
146 claudication to rest pain (Rutherford class II-IV). Patients were randomized to  
147 endovascular recanalization and DES or prosthetic above-knee femoropopliteal  
148 bypass 2:1 (DES:BSX). Bypass surgery was performed with a 6 mm heparin-  
149 bonded polytetrafluoroethylene (PTFE) graft. In the stent group, the occlusion  
150 was recanalized and crossed before deployment of a Zilver PTX drug-eluting  
151 stent (Cook Medical Inc., Bloomington, IN, USA). Primary outcome measure was  
152 overall stent or graft patency. Follow-up was performed by clinical evaluation

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

164

## 165 2.2 Analysis

166 In this analysis, the dates and causes of death were updated from the patient  
167 records as well as from the Cause of Death –registry of Statistics Finland until  
168 30April2019. This means that also deaths of those who were lost to follow-up in  
169 the original trials could be included. The primary endpoint was death due to any  
170 cause. The study populations were cross-referenced with population registries to  
171 detect deaths and causes of death, and thus no patients were lost to follow-up  
172 with regard to overall mortality. Data were analyzed for the three trials pooled,  
173 as well as each trial separately.

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

178

179 **3. Results**

180 Since this study addresses all-cause mortality, we were able to include also those  
181 patients who were excluded from the initial studies, but still exposed to  
182 paclitaxel. This yielded a total of 142 patients, 76 treated with paclitaxel eluting  
183 device and 66 without. Mean follow-up time for survivors in the three trials was  
184 3.9 (range 2.9-7.1) years being the longest in the FINNPTX-trial (7.1 years),  
185 followed by DRECOREST I (4.7 years) and DRECOREST II (3.5 years). Overall all-  
186 cause mortality was 31.7 % during follow-up. In the DRECOREST I -trial (bypass  
187 grafts), 11 (35.5%) patients died in the paclitaxel group and 11 (37.9%) in the  
188 control group ( $p=.84$ ). In the DRECOREST II (AVFs), overall mortality was 18  
189 (55.6%) in paclitaxel group and 8 patients (44.4%) in the control group ( $p=.51$ ).  
190 In the FINNPTX-trial (stent vs. bypass), 6 patients (22.2%) died in the paclitaxel  
191 group and 2 patients (10.5%) in the control group ( $p=.30$ ). Distribution of  
192 patients and death rates across the trials is listed in table 1 and Figures 1-4 and  
193 table 2 illustrate cumulative mortality as a function of time. The most common  
194 cause of death in the both groups was cardiovascular death 59.3% in the  
195 paclitaxel group and 52.4% in the control group ( $p=.73$ ) followed by malignancy  
196 (14.8% vs. 14.3% in the groups respectively). All causes of death in the trials are  
197 listed in table 3.

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

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

202

## 203 4. Discussion

### 204 4.1 Context

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

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

228 were 85.8%, 84.2%, and 88.2%, respectively ( $p=.73$ )<sup>21</sup>. There was no significant  
229 difference in all-cause mortality between DCB and PTA through 5 years.

230

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

235

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

249

#### 250 4.2 Limitations

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

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

260

## 261 **5. Conclusions**

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

266

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355 .

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	

<b>Mean FU for survivors (years)</b>	<b>Paclitaxel</b>	<b>Deaths</b>	<b>%</b>	<b>Control</b>	<b>Deaths</b>	<b>%</b>	<b>Relative risk</b>	<b>p-value (<math>\chi^2</math>)</b>
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









