

<https://helda.helsinki.fi>

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

Björkman, Patrick

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>

cc_by_nc_nd

draft

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

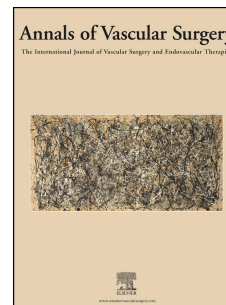
This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Journal Pre-proof

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

Patrick Björkman, M.D., Ph.D, Eeva-Maija Weselius, M.D, Ph.D, Maarit Venermo, M.D., Ph.D



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>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Inc.

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

2

3 Patrick Björkman, M.D., Ph.D.

4 Eeva-Maija Weselius, M.D, Ph.D.

5 Maarit Venermo, M.D., Ph.D.

6

7

8 Helsinki University Hospital, Abdominal Center, Dept. of Vascular Surgery

9

10 Corresponding author: PB

11 patrick.bjorkman@hus.fi

12

13 Original research

14 Word count: 2149 excluding abstract and references

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) ¹⁻⁵. The THUNDER-trial reported lasting benefit in terms
67 of patency and TLR-rates both in the mid- and long-term ^{6,7}. Furthermore, the
68 LEVANT-trials demonstrated non-inferiority and safety over a maximum of two
69 years of follow-up ^{8,9}. The IN.PACT SFA-trial included 330 patients, and reported
70 clear TLR-benefit from use of DCB ^{10,11}. These results have further been
71 confirmed in a systematic review by Katsanos et al. ¹², although clinical
72 improvement and benefit as improvement in clinical parameters, such as ABI or
73 walking distance, have been questioned by others ¹³.

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 ¹⁴. 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 methodology¹⁵. 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^{16,17}.

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^{18,19}. In
91 addition, we participated in the multicenter FINNPTX-trial comparing open
92 synthetic femoropopliteal bypass (BSX) to drug-eluting stents²⁰. 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/mm² 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 ($p=.73$)²¹. 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-group²². It has been hypothesized that paclitaxel
239 embolization might play a role, although no hard evidence in humans exists in
240 support of this^{23,24}. 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, $P=.03$.^{5,25} 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

267 **References**

268

- 269 1. Werk M, Langner S, Reinkensmeier B et al. Inhibition of restenosis in
270 femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral
271 paclitaxel randomized pilot trial. *Circulation* 2008; 118:1358-65.
- 272 2. Werk M, Albrecht T, Meyer DR et al. Paclitaxel-coated balloons reduce
273 restenosis after femoro-popliteal angioplasty: evidence from the randomized
274 PACIFIER trial. *Circ Cardiovasc Interv.* 2012 Dec;5(6):831-40
- 275 3. Dake MD, Ansel GM, Jaff MR et al. Paclitaxel-eluting stents show superiority to
276 balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-
277 month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 2011; 4:495-
278 504.
- 279 4. Dake MD, Ansel GM, Jaff MR et al. Sustained safety and effectiveness of
280 paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the
281 Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol* 2013;
282 61:2417-27.
- 283 5. Dake MD, Ansel GM, Jaff MR et al. Durable Clinical Effectiveness With
284 Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the
285 Zilver PTX Randomized Trial. *Circulation* 2016; 133:1472,83; discussion 1483.
- 286 6. Tepe G, Zeller T, Albrecht T et al. Local delivery of paclitaxel to inhibit
287 restenosis during angioplasty of the leg. *N Engl J Med* 2008; 358:689-99.

- 288 7. Tepe G, Schnorr B, Albrecht T et al. Angioplasty of femoral-popliteal arteries
289 with drug-coated balloons: 5-year follow-up of the THUNDER trial. *JACC*
290 *Cardiovasc Interv* 2015; 8:102-8.
- 291 8. Scheinert D, Duda S, Zeller T et al. The LEVANT I (Lutonix paclitaxel-coated
292 balloon for the prevention of femoropopliteal restenosis) trial for
293 femoropopliteal revascularization: first-in-human randomized trial of low-dose
294 drug-coated balloon versus uncoated balloon angioplasty. *Jacc: Cardiovascular*
295 *Interventions* 2014; 7:10-9.
- 296 9. Rosenfield K, Jaff MR, White CJ et al. Trial of a Paclitaxel-Coated Balloon for
297 Femoropopliteal Artery Disease. *N Engl J Med* 2015; 373:145-53.
- 298 10. Tepe G, Laird J, Schneider P et al. Drug-coated balloon versus standard
299 percutaneous transluminal angioplasty for the treatment of superficial femoral
300 and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA
301 randomized trial. *Circulation* 2015; 131:495-502.
- 302 11. Laird JR, Schneider PA, Tepe G et al. Durability of Treatment Effect Using a
303 Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT
304 SFA. *J Am Coll Cardiol.* 2015 Dec 1;66(21):2329-2338
- 305 12. Katsanos K, Geisler BP, Garner AM et al. Economic analysis of endovascular
306 drug-eluting treatments for femoropopliteal artery disease in the UK. *BMJ Open.*
307 2016 May 9;6(5):e011245.

- 308 13. Kayssi A, Al-Atassi T, Oreopoulos G et al. Drug-eluting balloon angioplasty
309 versus uncoated balloon angioplasty for peripheral arterial disease of the lower
310 limbs. *Cochrane Database Syst Rev* 2016; (8):CD011319.
- 311 14. Katsanos K, Spiliopoulos S, Kitrou P et al. Risk of Death Following Application
312 of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the
313 Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials *J*
314 *Am Heart Assoc.* 2018 Dec 18; 7(24): e011245.
- 315 15. FDA Center for Devices and Radiological Health, US Food and Drug
316 Administration. August 7, 2019 update: treatment of peripheral arterial disease
317 with paclitaxel-coated balloons and paclitaxel-eluting stents potentially
318 associated with increased mortality. [https://www.fda.gov/medical-](https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel)
319 [devices/letters-health-care-providers/august-7-2019-update-treatment-](https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel)
320 [peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel](https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel). Published
321 2019
- 322 16. Kennedy SA, Mafeld S, Baerlocher MO et al. Drug-Coated Balloon Angioplasty
323 in Hemodialysis Circuits: A Systematic Review and Meta-Analysis. *J Vasc Interv*
324 *Radiol* 2019 Apr;30(4):483-494
- 325 17. Trerotola SO, Saad TF, Roy-Chaudhury P et al. The Lutonix AV Randomized
326 Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year
327 Results and Subgroup Analysis. *J Vasc Interv Radiol* 2020 Jan;31(1):1-14

- 328 18. Bjorkman P, Kokkonen T, Alback A et al. Drug-Coated versus Plain Balloon
329 Angioplasty in Bypass Vein Grafts (the DRECOREST I-Study). *Ann Vasc Surg.*
330 2019 Feb;55:36-44.
- 331 19. Bjorkman P, Weselius EM, Kokkonen T et al. Drug-Coated Versus Plain
332 Balloon Angioplasty In Arteriovenous Fistulas: A Randomized, Controlled Study
333 With 1-Year Follow-Up (The Drecorest Ii-Study). *Scand J Surg.* 2019
334 Mar;108(1):61-66
- 335 20. Bjorkman P, Auvinen T, Hakovirta H et al. Drug-Eluting Stent Shows Similar
336 Patency Results as Prosthetic Bypass in Patients with Femoropopliteal Occlusion
337 in a Randomized Trial. *Ann Vasc Surg.* 2018 Nov;53:165-170
- 338 21. Zeller T, Baumgartner I, Scheinert D et al. Drug-eluting balloon versus
339 standard balloon angioplasty for infrapopliteal arterial revascularization in
340 critical limb ischemia: 12-month results from the IN.PACT DEEP randomized
341 trial. *J Am Coll Cardiol* 2014; 64:1568-76.
- 342 22. Schneider PA, Laird JR, Doros G, et al. Mortality Not Correlated With
343 Paclitaxel Exposure *J Am Coll Cardiol.* 2019 May, 73 (20) 2550-2563.
- 344 23. Gongora CA, Shibuya M, Wessler JD et al. Impact of Paclitaxel Dose on Tissue
345 Pharmacokinetics and Vascular Healing: A Comparative Drug-Coated Balloon
346 Study in the Familial Hypercholesterolemic Swine Model of Superficial Femoral
347 In-Stent Restenosis. *JACC Cardiovasc Interv.* 2015 Jul;8(8):1115-1123
- 348 24. Yazdani S, Pacheco E, Nakano M et al. Vascular, downstream, and
349 pharmacokinetic responses to treatment with a low dose drug-coated balloon in

350 a swine femoral artery model. Catheter Cardiovasc Interv. 2014 Jan 1;83(1):132-

351 40

352 25. Correction to: Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in

353 the Femoropopliteal Artery 5-Year Results of the Zilver PTX Randomized Trial.

354 Circulation. 2019 Feb 19;139(8):e42.

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	

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

DRECOREST II (AVF)

