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1 **AN EXPERIMENTAL STUDY OF PACLITAXEL EMBOLISATION DURING DRUG-**  
2 **COATED BALLOON ANGIOPLASTY**

3

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35

36 **ABSTRACT**

37 **Objective:** Drug-Coated Balloons (DCB) improve the patency of femoro-popliteal angioplasty  
38 but remain debatable in infrapopliteal lesions since Paclitaxel (PTX) particles embolisation was  
39 suspected. The aim of this study was to compare experimentally five DCBs in terms of distal  
40 embolism of PTX.

41 **Methods:** Twenty-five New Zealand rabbits were divided into five groups according to the  
42 DCB used: Lutonix® (Bard), In.Pact® (Medtronic), Passeo-18 Lux® (Biotronik), Ranger®  
43 (Boston Scientific) and Stellarex® (Spectranetics) (n=5 in each group). After ligation of the  
44 right common iliac artery, a 4x40 mm DCB was inflated in the infrarenal aorta for 180 seconds.  
45 Rabbits were euthanized two hours after the DCB inflation. The infrarenal aorta, a blood sample  
46 and three left hind leg muscles [tensor fasciae latae (TFL), vastus lateralis (VL) and tibialis  
47 anterior (TA) muscles] were harvested for blind measurement of PTX concentrations and  
48 histological analysis (PTX emboli count).

49 **Results:** In the TA muscle (the most distal one), concentrations of PTX were significantly lower  
50 for the Ranger® (0.067 ng/mg) than for the Lutonix® (0.342 ng/mg;  $p=0.008$ ), In.Pact® (0.370  
51 ng/mg;  $p=0.012$ ) and Passeo-18-Lux® (0.160 ng/mg;  $p=0.021$ ) DCBs. Similarly,  
52 concentrations of PTX were significantly lower for the Passeo-18-Lux® than for the In.Pact  
53 ( $p=0.028$ ). Concentrations of PTX were not significantly different between DCBs in TFL and  
54 VL muscles. Concentrations of PTX were found to be significantly higher in the plasmas, lower  
55 in the aortas and on the DCBs after use with the Lutonix® than with the 4 others DCBs.  
56 Histological analysis revealed evidence of embolised PTX crystals in small arterioles of all  
57 muscle tissue samples without any significant difference between the DCBs.

58 **Conclusions:** This study suggests some differences regarding distal embolisation profiles  
59 between the five assessed DCBs. Although clinical implications remain to be demonstrated, our

60 results may have implications while choosing a DCB, especially in a critical limb ischemia

61 setting.

62

63 **What this study adds:**

64 This experimental study is one of the first to compare five different drug-coated balloons. It  
65 provides the demonstration that differences in drug-coated balloons designs translate into  
66 differences in terms of embolisation and vessel wall penetration profiles. Although clinical  
67 implications remain to be demonstrated, our results may have implications while choosing a  
68 drug-coated balloon, especially in a critical limb ischemia setting.

69 **INTRODUCTION**

70 There is now body of proof that drug coated balloons (DCB) improve the results of lower limb  
71 plain balloon angioplasty (PBA) for femoro-popliteal disease (1-15). As a result, the recent  
72 European Society of Cardiology/European Society for Vascular Surgery ESC/ESVS concluded  
73 that DCBs may be considered for short lesions (<25 cm) (Class IIb, Level A) or in in-stent  
74 restenosis (Class IIb, Level B) (16). Their main action is to reduce cellular proliferation  
75 secondary to the initial angioplasty injury through paclitaxel (PTX) deposition in the arterial  
76 wall (17). This deposition in the arterial wall is driven by a balloon platform, a carrier (or  
77 excipient) and a local amount of PTX. In particular, a certain quantity of crystalline PTX form  
78 is required to keep solid-phase PTX reservoirs in the arterial wall for sustained anti-proliferative  
79 effects (18-20).

80 At the same time, drug nanocrystals may act as solid thrombi with a subsequent risk of  
81 embolisation and thrombosis. Concerning cases of diffuse distal fibrinoid necrosis were  
82 reported following DCB use at the femoro-popliteal level (21-22), in which the responsibility  
83 of PTX emboli was demonstrated. Similarly, one large randomised controlled trial comparing  
84 PBA + DCBs to PBA alone in the tibial arteries for critical limb ischemia had to be stopped  
85 prematurely because of a trend towards an increased major amputation rate at 12 months in the  
86 DCB group (23). One suspected cause was PTX particles downstream effects in the distal  
87 arterial bed, which could lead to microvessel occlusions and non-healing wounds (19). This  
88 DCB is not available anymore for bellow-the-knee use.

89 Since DCBs are different regarding balloon platform, excipient, PTX formulation and dosage,  
90 the aim of this study was to compare experimentally five DCBs in terms of distal embolisation  
91 of paclitaxel.

92 **MATERIALS AND METHODS**

93 This study was conducted in accordance with the requirements and guidelines of the European  
94 Union legislation and the French Animal Protection Act. The animal experiments were  
95 approved by the French animal protection committee (Project n° 2016101009413104 – V8  
96 #8423) and took place in the UMR 1148 lab (Inserm-Paris7 - Denis Diderot University, Xavier  
97 Bichat Hospital, Paris, France), as well as histological analyses. Paclitaxel dosages were  
98 performed in the mass spectrometry platform MasSpecLab (UMR 1173, Inserm-Paris11 -  
99 Faculty of Health Sciences Simone Veil, Versailles Saint-Quentin-en-Yvelines University,  
100 Paris-Saclay University, Montigny-le-Bretonneux, France).

### 101 **Animals**

102 Twenty-five 6-month-old New Zealand male white rabbits (CEGAV, Saint-Mars d'Egrenne,  
103 France) were used for the present study. They were fed with a normal diet and could drink ad  
104 libitum. An acclimatisation period of one week was respected before the procedure to decrease  
105 the stress of animals.

### 106 **Drug-coated balloons**

107 All DCBs used were coated with PTX and were provided free of charge by DCB companies.

108 The study was performed between March 2017 and August 2017.

109 The following DCBs were assessed: Lutonix® (Bard), In.Pact® (Medtronic), Ranger® (Boston  
110 Scientific), Stellarex® (Spectranetics) and Passeo 18 Lux® (Biotronik) (Table 1). All DCBs  
111 had a diameter of 4 mm and a 40-mm length. These dimensions were chosen because they were  
112 available for all the balloons and aortic diameter is around 3.5 mm in rabbits.

### 113 **Experimental design**

114 Rabbits were divided in 5 groups, according to the DCB used: the Lutonix® group (n=5), the  
115 In.Pact® group (n=5), the Ranger® group (n=5), the Stellarex® group (n=5) and the Passeo  
116 18-Lux® group (n=5). One DCB was used for each animal.



117 General anesthesia was induced with intramuscular xylazine at a dose of 20 mg/kg, ketamine  
118 hydrochloride at a dose of 4.5 mg/kg and acepromazine at a dose of 1 mg/kg. The intramuscular  
119 injections were done in the right thigh. In a first step, a laparotomy was done and the aorto-iliac  
120 vessels were dissected from the renals to the iliac bifurcations. The external aortic diameter was  
121 measured. The right common iliac artery was ligated at its origin with a non-absorbable 5-0  
122 nylon suture. Aim of this maneuver was to direct all the aortic flow toward the left side for  
123 precise measurement of the downstream PTX emboli following DCB inflation in the aorta.  
124 Abdomen was further closed with a 4-0 Polypropylene running suture. In a second step, arterial  
125 access was obtained via the right common carotid artery through neck cut-down. The common  
126 carotid was clamped. An oblique arteriotomy was performed to allow retrograde insertion of  
127 an angiography catheter (Vertebral Radifocus® Glidecath® 4 French - Hydrophilic  
128 Angiographic Catheter; Terumo, Leuven, Belgium), a guidewire [0.035 wires (Terumo  
129 Glidewire® Hydrophilic Coated Guidewire Straight 180 cm, Terumo Leuven, Belgium) for  
130 Lutonix®, In.Pact® and Stellarex® and 0.018 wires (V-18™ ControlWire™ Guidewire, 150  
131 cm, Boston Scientific) for Ranger® and Passeo 18-Lux®] and a short sheath (Radifocus®  
132 Introducer II Terumo, Leuven, Belgium). The diameter of the sheaths was 4 French for Passeo  
133 18-Lux®, 5 French for Lutonix®, In.Pact® and Ranger® and 6 French for Stellarex®. A 2000  
134 IU bolus of heparin was injected through the sheath. Baseline angiography was performed  
135 through the angiography catheter to locate the renal arteries. A guidewire was pushed down to  
136 the distal left limb vessels and a DCB was positioned in the infrarenal aorta. Navigation time  
137 between DCB insertion and inflation in the infrarenal aorta was inferior to 30 seconds. The  
138 DCB was then inflated in the infrarenal aorta just below the renal arteries with an inflation  
139 pressure of 10 atmospheres for 180 seconds. The DCB was collected following retrieval. Two  
140 hours after the DCB inflation, the rabbits were euthanized by an intravenous Pentobarbital  
141 injection at a dose of 120 mg/kg. The infrarenal aorta, a 10 cc blood sample and a sample of

142 three left hind leg muscles (Tensor Fasciae Latae, Vastus Lateralis and Tibialis Anterior  
143 muscles) were harvested for measurement of PTX concentrations. Another sample of the same  
144 three left hind leg muscles was harvested for histology.

#### 145 **Paclitaxel analysis**

146 Blood samples were centrifuged at 2000 G for 15 minutes, to obtain the supernatant that was  
147 again centrifuged at 2000 G for 10 minutes to purify the plasma. With the exception of the  
148 DCBs, aortas, muscles and blood samples were frozen at -20°C.

149 The PTX concentrations were assessed using a standardized method of high-performance liquid  
150 chromatography (HPLC) tandem mass spectrometry. Dosages were performed blindly by a  
151 single operator (SGD). Briefly, 50 µL of internal standard (docetaxel 1 mg/L) and 1 mL of  
152 methyl tert-butyl ether(MTBE)/hexane (50/50 v/v) were added to 100 µL of plasma or 25 mg  
153 of tissue samples (aorta and muscles). Plasma samples were agitated for 20 minutes and tissue  
154 samples were crushed for 20 minutes. Then, all the samples (tissue and blood samples) were  
155 centrifuged and supernatants were vacuum-evaporated. 100 µL of ammonium  
156 formate/methanol (20/80 v/v) were added to reconstitute the dry residues. Remaining PTX on  
157 the DCBs after use was analysed after extraction with 10 mL of methanol. Dilutions in the  
158 1/100<sup>th</sup> and in the 1/1000<sup>th</sup> were directly injected after adding 50 µL of internal standard. With  
159 each serie, a curve of calibration in 9 points going of 0.1 ng/mL in 1000 ng/mL was done. The  
160 samples were analysed with Ultimate 3000 on a Hypersil Gold C18 column (1.9 µm, 150 x 2.1)  
161 (Thermofisher, France) using 20/80 (v/v) ammonium formate 2mM/methanol as mobile phase.  
162 Paclitaxel detection was done with a Quantiva mass spectrometer operating with electrospray  
163 ionisation in the positive mode, with specific MRM transitions for PTX and internal standard.  
164 The lower and upper limits of quantification were 0.1 and 1000 ng/mL, respectively.

#### 165 **Histological analysis**

166 After euthanasia, one piece of 1 cm<sup>3</sup> of each tibialis anterior (TA), vastus lateralis (VL) and  
167 tensor fascia latae (TFL) muscles was isolated and fixed in formalin 10% during 24 hours for  
168 histological analysis. Briefly, Muscles were dehydrated, embedded in paraffin and 6 µm  
169 sections were cut. Sections were then deparaffinised in toluene and hydrated in ethanol baths.  
170 Several stains were used: hematoxylin-eosin or Masson's trichrome to explore the structure of  
171 muscles. The histological slides were scanned in using NanoZoomer 2.1 (Hamamatsu  
172 Photonics KK, Hamamatsu City, Japan). Histological analyses focused on paclitaxel crystals  
173 detection in the microvessels. Two slides were randomly studied for each muscle piece. In each  
174 slide, the number of arteries with paclitaxel crystals emboli was counted. This analysis was  
175 performed blindly.

#### 176 **Statistical analysis**

177 The Stata/SE software (Version 13.0 for Mac) was used for statistical analysis. Datas are given  
178 as median and interquartile range (IQR) for non-parametric distribution or mean ± standard  
179 deviation for parametric distribution. For global comparison of the five groups (independent  
180 nonparametric samples), the Kruskal-Wallis test was used. When the Kruskal-Wallis test was  
181 significant, differences were assessed by comparing groups two by two using the Mann-  
182 Whitney U-test. A *p*-value of less than 0.05 was considered to indicate statistical significance.

183

184

185 **RESULTS**

186 **Surgical procedures**

187 In total, complete procedures were achieved in 25 rabbits (weight  $3.84\pm 0.36$  kg, aortic diameter  
188  $3.6\pm 0.1$  mm). Inflation pressure of DCBs was  $10.3\pm 0.5$  atm for 180 seconds. Duration between  
189 DCB inflation in the infrarenal aorta and animal sacrifice was  $122.5\pm 11.2$  minutes. A  
190 retroperitoneal hematoma was found in one case during the autopsy but it did not lead to the  
191 death of the rabbit.

192 **Paclitaxel analysis**

193 In the TA muscle (the most distal muscle), concentrations of PTX were significantly lower for  
194 the Ranger® (0.067 ng/mg) DCB than for the Lutonix® (0.342 ng/mg;  $p=0.008$ ), In.Pact®  
195 (0.370 ng/mg;  $p=0.012$ ) and Passeo-18-Lux® (0.160 ng/mg;  $p=0.021$ ) DCBs. Similarly,  
196 concentrations of PTX were significantly lower for the Passeo-18-Lux® than for the In.Pact  
197 DCB ( $p=0.028$ ) (Tables 2 and 3, Figure 1).

198 Concentrations of paclitaxel were not significantly different between DCBs in TFL and VL  
199 muscles (Table 2, Figure 1).

200 In the plasmas, concentrations of PTX were significantly higher for Lutonix® (9.00 ng/mL)  
201 than In.Pact® (1.00 ng/mL;  $p=0.008$ ), Ranger® (0.05 ng/mL;  $p=0.007$ ), Stellarex® (0.08  
202 ng/mL;  $p=0.014$ ) and Passeo-18-Lux® (0.90 ng/mL;  $p=0.014$ ) and significantly lower for  
203 Ranger® than In.Pact® ( $p=0.011$ ) and Passeo-18-Lux® ( $p=0.011$ ) (Tables 2 and 4, Figure 1).

204 In the aortas, concentrations of PTX were significantly lower for Lutonix® (35.2 ng/mg) than  
205 In.Pact® (119.0 ng/mg;  $p=0.004$ ), Ranger® (568.0 ng/mg;  $p=0.009$ ), Stellarex® (113.5 ng/mg;  
206  $p=0.038$ ) and Passeo-18-Lux® (77.0 ng/mg;  $p=0.030$ ) (Tables 2 and 5, Figure 1).

207 Remnant amount of PTX after DCB use were significantly lower for Lutonix® (1364.1 µg)  
208 than In.Pact® (3643.5 µg;  $p=0.004$ ), Ranger® (2500.9 µg;  $p=0.017$ ) and Passeo-18-Lux®  
209 (2522.50 µg;  $p=0.017$ ) and significantly higher for In.Pact® than Lutonix® ( $p=0.004$ ),

210 Ranger® ( $p=0.032$ ), Stellarex® (1335.85 µg;  $p=0.016$ ) and Passeo-18-Lux® ( $p=0.016$ ) (Tables  
211 2 and 6, Figure 1).

## 212 **Histological analysis**

213 Histological analysis of muscle tissue samples revealed evidence of embolised PTX with some  
214 crystals in small arterioles with all DCBs (Figure 2). PTX crystals were identified in one to  
215 eight arteries per slide, with a mean of  $4.30 \pm 2.08$  emboli. The number of PTX emboli was not  
216 significantly different between the DCBs ( $p=0.141$ ).

217

## 218 **DISCUSSION**

219 The present study was designed to evaluate the embolic profiles of the five main DCBs used in  
220 our country. To assess downstream tissue PTX emboli and PTX distribution during and  
221 immediately after DCB use, the muscle tissue samples, the aorta, the plasma and the DCBs used  
222 were analysed. Histological analysis showed some PTX crystals in several muscle tissue  
223 samples, highlighting the reality of distal embolisation after inflation of DCBs in the arteries.  
224 We found some significant differences in terms of concentrations of PTX in the muscles  
225 between the five DCBs, which can be explained by the differences between the PTX  
226 formulations (crystalline, microcrystalline or amorphous), the technique of PTX deposition  
227 (pulverization or micro-pipetting), the balloon state during PTX deposition (inflated or  
228 deflated), the dose of PTX on the DCBs and the excipient (Table 1). Crystals enter the arterial  
229 wall and serves as long term PTX reservoir, allowing sustained anti-proliferative effects (18),  
230 but distal embolisation of crystalline PTX can cause fibrinoid necrosis with serious clinical  
231 consequences (21-22). Moreover, the antiproliferative effects may have an impact on wound  
232 healing in the setting of ischemic ulcers, especially when ulcers are secondary to below-the-  
233 knee lesions (24).

234 Endovascular treatment became the first-line therapy in peripheral vascular disease but the 1-  
235 year primary patency of PBA can be as low as 50% in the femoro-popliteal segment, with  
236 subsequent target lesion reinterventions (TLR) (1-15). DCBs are now considered a valuable  
237 alternative to stents because they decrease the rate of restenosis by intimal hyperplasia without  
238 leaving a permanent scaffold in place. Several randomised controlled trials (RCTs) (1-15)  
239 concluded that primary patency and TLR were better after DCB angioplasty than PBA in  
240 femoro-popliteal disease. Cost-effectiveness studies also support DCB use. However, results of  
241 RCTs are more heterogeneous when looking at infrapopliteal lesions. Of note, bioresorbable  
242 scaffolds could be use in association with DCBs in the future (25-26) to avoid permanent  
243 scaffolding of the treated arteries.

244 The DEBATE-BTK study (27) found lower restenosis and TLR rates after DCB use in diabetic  
245 patients with critical limb ischemia (CLI). In contrast, the BIOLUX P-II (28) and IN.PACT  
246 DEEP (23) studies showed no significant differences between DCB and PBA in terms of  
247 restenosis, TLR and occlusion. Of interest, the IN.PACT DEEP study (23) had to be stopped  
248 prematurely because of a trend towards increase of major amputation rate at 12 months in  
249 patients treated with DCB (8.8% vs 3.6%;  $p=0.080$ ). One suspected cause was PTX particles  
250 embolism in distal arteries, which could lead to arterial occlusion and non-healing wounds.  
251 Kolodgie et al. (19) compared Lutonix® and In.Pact® balloons in terms of distal embolisms in  
252 swine. Although the embolism rate was low in both groups, differences were found between  
253 DCBs (In.Pact® 15.4% vs Lutonix® 7.7%;  $p=0.04$ ). In our study, we also found higher PTX  
254 concentrations in the TA muscle after In.Pact® DCB use, but embolisation rates after Lutonix®  
255 were also concerning. In contrast, Ranger® use was associated with significantly lower  
256 embolisation rates. This may be explained by the characteristics of Ranger® DCB excipient  
257 and coating. The citrate ester is known to be hydrophobic and lipophilic. A hydrophobic coating  
258 may provide substantial protection against PTX loss while navigating and inflating the DCB.

259 At the same time, the sorbitol used as the excipient of the Lutonix® is known to be highly  
260 soluble in water (29) which may facilitates excipient and PTX downstream washing while  
261 navigating and inflating this DCB. The In.Pact® balloon has a hydrophobic coating with the  
262 urea but uses higher concentrations of macrocrystalline PTX, which could also be responsible  
263 of higher rates of distal PTX concentrations. Macrocrystals could be more susceptible to  
264 occlude distal microvessels and be detected in the muscles.

265 Regarding aortic penetration of the PTX, our study highlights significant lower rates of PTX  
266 when using the Lutonix® balloon and higher (but non significant) PTX concentrations with the  
267 Ranger® DCB. The lipophilic features of the Ranger® DCB could explain the satisfactory PTX  
268 diffusion in the artery wall. One hypothesis to explain the disappointing results of the Lutonix®  
269 DCB could be that a lot of PTX is lost during the navigation before the arrival on the target  
270 artery, as underlined by the high levels of PTX found in the plasma. In contrast, with the  
271 Ranger® balloon, the lipophilic effect keeps the PTX in the artery wall because of the presence  
272 of cellular lipids in the arterial wall. Although we did not use an atherosclerosis model in rabbits  
273 used for this study, fatty streak can be found in the intima as early as during childhood in  
274 humans, with the presence of T cells and sometimes foam cells. (30)

275 The clinical relevance of the detected doses of PTX remains to be elucidated. The PTX  
276 concentrations detected in the muscle samples are low and may have no negative impact in  
277 terms of wound healing. Recently, the results of the Global Lutonix® DCB Below-the-Knee  
278 (BTK) Registry in patients with Rutherford class 3 to 5 and  $\geq 70\%$  stenosis of native BTK  
279 arteries were reported with high rates of freedom from primary safety events and freedom from  
280 amputation at 6 months (31). Similar results were found with the Lutonix Global SFA  
281 (Superficial Femoral Artery) Registry at 12 and 24 months (32) and with the In.Pact® DCB  
282 (29). Although our study found significantly more distal emboli after Lutonix® and In.Pact®  
283 inflations, the results of the above-mentioned clinical registries (31-33) showed that these two

284 DCBs are relatively safe in a clinical setting. Of note, the most severe patients (Rutherford 6)  
285 were excluded. The question regarding the impact of distal PTX embolisation on ulcers healing  
286 remains therefore to be determined.

287 The other question that can be raised is the level of PTX concentration needed in the arterial  
288 wall to be effective on intimal proliferation. In our study, the Lutonix® DCB had the lowest  
289 PTX concentrations in the aorta and a lower efficiency could be suspected. The Lutonix® DCB  
290 was assessed in a well-conducted large randomised trial, the LEVANT II trial (4), and showed  
291 its superiority compared to the PBA. However, primary patency rates reported with the  
292 Lutonix® DCB in the LEVANT II trial appear lower than those reported with the 4 other tested  
293 balloons in specific randomised trial (1,2,12,13), although no head-to-head comparison has  
294 been published to date. A prospective trial directly comparing relevant clinical outcomes with  
295 the DCBs available in the femoro-popliteal segment would be needed. An analysis of the  
296 amputated or debrided tissues could assess the importance of distal PTX embolisation in  
297 humans.

298 This study has several limitations. First, we used healthy rabbits without atherosclerosis for this  
299 study. Rabbits were chosen for the experiments because they have a similar vascular anatomy  
300 when compared to humans but it is known that PTX delivery during the DCB inflation is  
301 different between healthy and atherosclerotic arteries (34). It may be valuable to repeat this  
302 work in atherosclerotic models. Second, our number of rabbits in each group is small which  
303 can lead to a lack of power. This may explain substantial but non-significant differences  
304 between groups. Third, we inflated DCBs in the aorta, not in below-the-knee arteries. Flows  
305 may be different between these arterial levels and influence the embolisation rate. Fourth,, we  
306 did not analyse the amount of PTX lost on the sheath during DCB insertion. However the  
307 amount of PTX lost in the sheath may vary according to the type of sheath used. Fifth, rabbits  
308 were sacrificed two hours after DCB inflation but PTX effects are not only limited to the first



309 hours following PTX delivery (17, 35-36). Studies with a longer follow-up may highlight  
310 different results. Finally, we only assessed the DCBs available on the French market at the time  
311 the study was performed. A larger study including all currently available DCBs may bring  
312 additional and valuable information.

313

#### 314 **CONCLUSION**

315 This study suggests some differences regarding distal embolisation profiles between the five  
316 assessed DCBs. The Ranger® and the Stellarex® DCBs seem to have the best profiles with  
317 low distal PTX concentrations, reasonable plasma PTX loss and satisfactory aortic penetration.  
318 In contrast the Lutonix® DCB had the most disappointing features. Although clinical  
319 implications remain to be demonstrated, our results may have implications while choosing a  
320 DCB, especially in a critical limb ischemia setting.

321

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330

331 **Conflicts of interest:**

332 Raphael Coscas has been consultant for Medtronic Inc., Spectranetics Inc. and Bard Inc.

333 Other authors do not disclose any conflict of interest.

334

335

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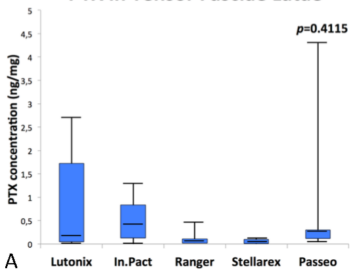
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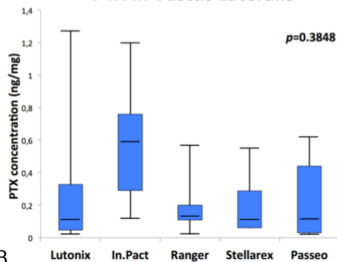


### PTX in Tensor Fasciae Latae



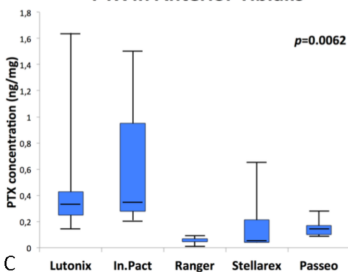
A

### PTX in Vastus Lateralis



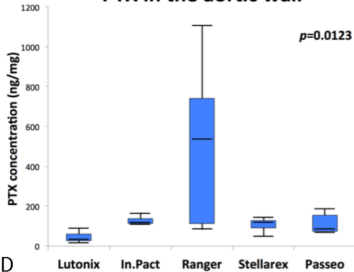
B

### PTX in Anterior Tibialis



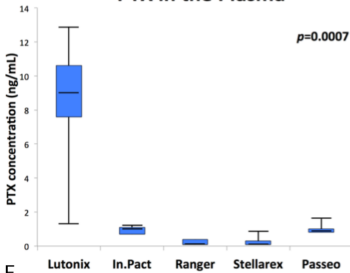
C

### PTX in the aortic wall



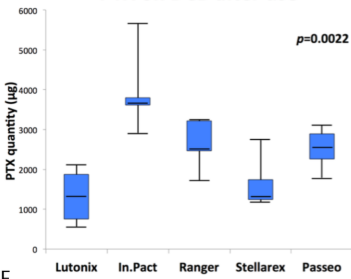
D

### PTX in the Plasma



E

### PTX on DCB after use



F

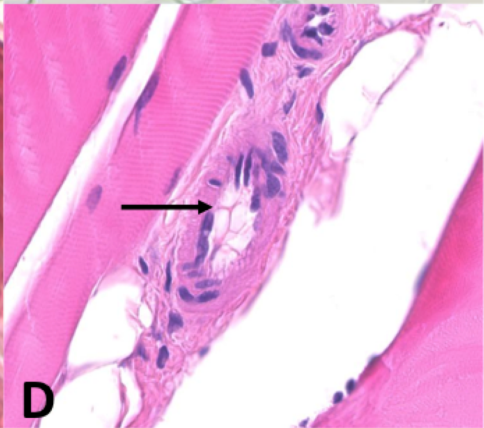
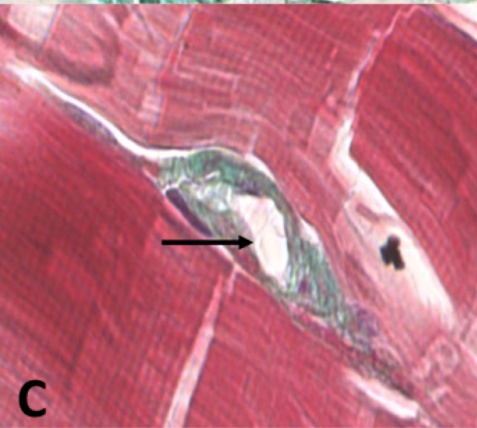
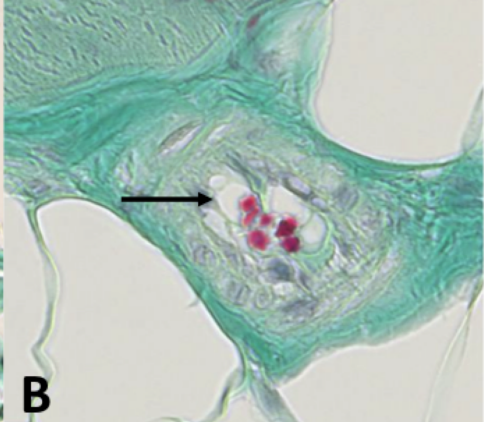
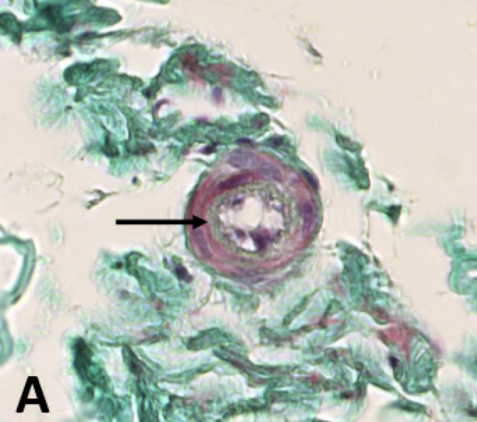


Table 1: Features of the main DCBs available in France.

PTX: Paclitaxel; BTHC: Butyryl-tri-n-hexyl citrate.

	<b>Lutonix Bard</b>	<b>IN.Pact Medtronic</b>	<b>Ranger Boston</b>	<b>Stellarex Spectranetics</b>	<b>Passeo-18 Lux Biotronik</b>
<b>PTX Dose (<math>\mu\text{g}/\text{mm}^2</math>)</b>	2	3,5	2	2	3
<b>Excipient</b>	Polysorbate Sorbitol	Urea	Citrate ester	Polyethylene glycol	BTHC
<b>PTX Formulation</b>	Hybrid (Crystalline + amorphous)	Crystalline	Microcrystalline	Hybrid (Microcrystalline + amorphous)	Microcrystalline
<b>Technique of PTX deposition</b>	Pulverization	Micro-pipetting	Pulverization	Pulverization	Micro-pipetting
<b>Balloon state during PTX deposition</b>	Inflated	Inflated	Deflated	Inflated	Deflated

Table 2: Paclitaxel concentrations (median with interquartile ranges) in muscles, aortic wall, plasma and DCB used, per group. *p*-values correspond to the results of the Kruskal-Wallis test. A *p*<0.05 indicate a significant difference between at least two groups for the variable assessed.

	<b>Lutonix®</b>	<b>In.Pact®</b>	<b>Ranger®</b>	<b>Stellarex®</b>	<b>Passeo 18-Lux®</b>	<b><i>p</i>-value</b>
<b>Tensor of Fascia Lata (ng/mg)</b>	0.162 (0.436-2.211)	0.450 (0.013-0.840)	0.092 (0.014-0.110)	0.047 (0.006-0.106)	0.290 (0.120-0.300)	<b><i>0.4115</i></b>
<b>Vastus lateralis (ng/mg)</b>	0.108 (0.322-0.395)	0.610 (0.290-0.760)	0.140 (0.110-0.200)	0.132 (0.062-0.375)	0.110 (0.030-0.440)	<b><i>0.3848</i></b>
<b>Tibialis anterior (ng/mg)</b>	0.342 (0.225-0.451)	0.370 (0.280-0.950)	0.067 (0.047-0.067)	0.055 (0.041-0.360)	0.160 (0.100-0.170)	<b><i>0.0062</i></b>
<b>Plasma (ng/mL)</b>	9.00 (7.50-10.80)	1.00 (0.70-1.10)	0.05 (0.05-0.40)	0.08 (0.05-0.50)	0.90 (0.80-1.00)	<b><i>0.0007</i></b>
<b>Aortic wall (ng/mg)</b>	35.2 (27.2-66.8)	119.0 (113.0-137.0)	568.0 (113.0-740.0)	113.5 (76.5-132.5)	77.0 (75.0-155.0)	<b><i>0.0123</i></b>
<b>DCB after use (µg)</b>	1364.1 (587.5-2013.0)	3643.5 (3613.1-3803.8)	2500.9 (2467.8-3214.3)	1335.85 (1219.9-2075.1)	2522.50 (2259.0-2896.1)	<b><i>0.0022</i></b>

Table 3: *p*-values from the Mann-Whitney U-tests regarding comparisons of PTX concentrations in the Tibialis Anterior muscles between the groups. A *p*<0.05 indicate a significant difference between the two groups for the PTX concentration in the Tibialis Anterior muscle.

<b>Group / Tibialis Anterior</b>	<b>Lutonix®</b>	<b>In.Pact®</b>	<b>Ranger®</b>	<b>Stellarex®</b>
<b>In.Pact®</b>	0.792	-	-	-
<b>Ranger®</b>	<b>0.008</b>	<b>0.012</b>	-	-
<b>Stellarex®</b>	0.165	0.110	0.902	-
<b>Passeo-18-Lux®</b>	0.052	<b>0.028</b>	<b>0.021</b>	0.268

Table 4: *p*-values from the Mann-Whitney U-tests regarding comparisons of PTX concentrations in the plasmas between the groups. A *p*<0.05 indicate a significant difference between the two groups for the PTX concentration in the plasma.

<b>Group / Plasma</b>	<b>Lutonix®</b>	<b>In.Pact®</b>	<b>Ranger®</b>	<b>Stellarex®</b>
<b>In.Pact®</b>	<b>0.008</b>	-	-	-
<b>Ranger®</b>	<b>0.007</b>	<b>0.011</b>	-	-
<b>Stellarex®</b>	<b>0.014</b>	0.064	0.893	-
<b>Passeo-18-Lux®</b>	<b>0.014</b>	0.916	<b>0.011</b>	0.082

Table 5: *p*-values from the Mann-Whitney U-tests regarding comparisons of PTX concentrations in the aortic walls between the groups. A *p*<0.05 indicate a significant difference between the two groups for the PTX concentration in the aortic wall.

<b>Group / Aortic wall</b>	<b>Lutonix®</b>	<b>In.Pact®</b>	<b>Ranger®</b>	<b>Stellarex®</b>
<b>In.Pact®</b>	<b>0.004</b>	-	-	-
<b>Ranger®</b>	<b>0.009</b>	0.463	-	-
<b>Stellarex®</b>	<b>0.038</b>	0.556	0.286	-
<b>Passeo-18-Lux®</b>	<b>0.030</b>	0.548	0.095	0.905

Table 6: *p*-values from the Mann-Whitney U-tests regarding comparisons of PTX quantities on DCBs after use between the groups. A *p*<0.05 indicate a significant difference between the two groups for the PTX quantities on DCBs after use.

<b>Group / Aortic wall</b>	<b>Lutonix®</b>	<b>In.Pact®</b>	<b>Ranger®</b>	<b>Stellarex®</b>
<b>In.Pact®</b>	<b>0.004</b>	-	-	-
<b>Ranger®</b>	<b>0.017</b>	<b>0.032</b>	-	-
<b>Stellarex®</b>	0.762	<b>0.016</b>	0.111	-
<b>Passeo-18-Lux®</b>	<b>0.017</b>	<b>0.016</b>	0.841	0.111