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# BMJ Open

## Financial impact of Heparin-bonded polytetrafluoroethylen grafts (Propaten®) for below the knee bypass in patients with critical limb ischemia

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Manuscripts

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3 1 **TITLE PAGE**

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6 2 **Financial impact of Heparin-bonded polytetrafluoroethylen grafts (Propaten<sup>®</sup>) for below**  
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8 3 **the knee bypass in patients with critical limb ischemia**

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3 22 **ABSTRACT**  
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8 **Objectives:** To evaluate the budget impact of progressive replacement of crude  
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10 polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten<sup>®</sup>) for below-the-knee  
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12 (BTK) bypass in patients with critical limb ischemia (CLI).  
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15 **Design:** From a review of the scientific literature we calculated a theoretical BTK primary  
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17 patency for Propaten<sup>®</sup> grafts. Using the French hospital expenditure database (PMSI), we  
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19 retrospectively estimated a rehospitalization rate for crude PTFE grafts. From these data, a  
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21 model was created to assess the budget impact of a progressive replacement from crude PTFE  
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23 grafts to Propaten<sup>®</sup> grafts over a 5-year horizon. We performed a univariate sensitivity  
24  
25 analysis to assess the robustness of our results.  
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29 **Setting:** French National Health Insurance (FNHI) perspective.  
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33 **Participant:** Patient with CLI.  
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36 **Main outcome measures:** Budget impact of progressive replacement of crude PTFE grafts  
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38 by Propaten<sup>®</sup>.  
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41 **Results:** Data extraction from the PMSI revealed that 656 patients were treated with PTFE  
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43 grafts in 2011 in French public hospitals for a BTK bypass. Assuming a survival rate of  
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45 76.8 %, observed reintervention rate for crude PTFE grafts at 24 months from the PMSI was  
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47 35.1%. The mean rehospitalization cost was €10 689. The budget impact analysis based on  
48  
49 these data found a net cumulative 5-year payer budget reduction of €112 420, under the  
50  
51 assumption of a 75.6 % primary patency for Propaten<sup>®</sup> grafts for a projected population of  
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53 3 215 patients of which 801 received a Propaten<sup>®</sup> graft.  
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3 43 **Conclusions:** Based on a literature review and a retrospective nationwide data extraction, we  
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5 44 modelled a budget impact analysis that showed a positive impact on the national health  
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7 45 insurance budget of the replacement of crude PTFE grafts by Propaten<sup>®</sup> grafts in below-knee  
8  
9 46 surgical bypasses. This supports the enactment of a reimbursement policy by the FNHI. Our  
10  
11 47 model can be used in other countries with a DRG-based reimbursement system.  
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13  
14 48 **Keywords:** Critical limb ischemia, Bypass Heparin-bonded graft, Below the knee, Budget  
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16 49 impact analysis  
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3 50 **Strengths and limitations of this study**  
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- 6 51 • This paper presents a budget impact analysis in real life of a progressive replacement of  
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8 52 crude polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten®) for  
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10 53 below-the-knee (BTK) bypass in patients with critical limb ischemia (CLI) using the  
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12 54 French hospital expenditure (PMSI) database.  
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14  
15 55 • PMSI database allows for studies with exhaustive data on the French population, thus  
16  
17 56 producing results with a high statistical power and negligible sampling fluctuations.  
18  
19 57 • However, only patients with critical limb ischemia and initially treated by crude PTFE  
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21 58 in public hospital could be identified in the PMSI database, underestimating the results  
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23 59 of the study.  
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26 60 • Clinical factors potentially influencing patterns of practice, non-hospital consumption of  
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28 61 cares, and non-reimbursable items and medicines could not be analyzed.  
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## 62 INTRODUCTION

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65 Patients with critical limb ischemia (CLI) are at risk of limb amputation. Consequently, a  
66 revascularization should be performed as soon as possible in order to save the limb (1). To  
67 realize the revascularization, two options should be considered: endovascular or open repair.

68 So far, despite the lack of consensus, open repair could be recommended in a first line of  
69 treatment to re-vascularize CLI patients (2) or performed in a second line of treatment in case  
70 of failure of endovascular repair (3). In the event of open surgery, a vein should be used as  
71 conduit to perform the bypass, especially in the case of infrapopliteal lesions. A suitable vein  
72 is one of the main factors that determine the clinical success of open revascularization for  
73 below the knee (BTK) popliteal and distal bypass (1). Unfortunately, a suitable venous  
74 conduit is not available in more than 20% of the cases (2). In these patients, prosthesis such as  
75 crude polytetrafluoroethylene (PTFE) graft demonstrated worse clinical and morphological  
76 results and more severe consequences in case of occlusion (4,5). Consequently, there is still a  
77 room for improvement in CLI patients in the absence of a suitable conduit and in whom  
78 endovascular repair failed. In these patients, prostheses with heparin-bound to the luminal  
79 surface could improve crude prosthesis results. In 2011, Lindholt et al. reported the results of  
80 a multicenter randomized trial comparing heparin-bound PTFE (Propaten<sup>®</sup>, Flagstaff, AZ,  
81 USA) grafts with those of crude PTFE grafts (6). In total, 546 patients had 1-year follow-up  
82 (crude PTFE: 272; Propaten<sup>®</sup>: 274). Propaten<sup>®</sup> graft significantly reduced the overall risk of  
83 primary graft failure by 37% at one year from the intervention. Specifically, risk reduction  
84 reached 50% in femoropopliteal bypass for patients with CLI. Moreover, after 5 years,  
85 patients receiving Propaten<sup>®</sup> grafts for CLI were more likely to have a patent graft than those  
86 with crude PTFE grafts.(7)

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3 87 However, to date, the financial impact of Propaten<sup>®</sup> use on health care spending was not  
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5 88 assessed. Using data from the literature and from the French hospital expenditure database  
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7 89 (PMSI), we assess the financial impact of a progressive replacement of crude PTFE by  
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9 90 Propaten<sup>®</sup> on a 5-year timeline from the payer perspective, for BTK bypass in patients with  
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11 91 CLI.  
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## 92 METHODS

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### 95 Analytic Overview

96 We combined clinical data based on a review from the literature and retrospective data about  
97 hospital stays from the PMSI to feed a cost model from a third party payer perspective and to  
98 perform a budget impact analysis. No change in our clinical practice and no randomization  
99 occurred. As our model was based on an observational retrospective analysis of data,  
100 according to the French legislation (articles L.1121-1 paragraph 1 and R1121-2, Code de la  
101 Santé Publique), approval of an ethics committee was not required for use of the data in an  
102 epidemiologic study.

103

### 104 Source population

105 From a retrospective analysis on hospital stays during 2011 using the PMSI, we identified  
106 patients who were admitted for a BTK bypass surgery, where a crude PTFE graft was used. In  
107 France, only CLI patients have this surgery, where using a crude PTFE graft is the usual  
108 choice (French medical information agency –ATIH– online data)(8). Therefore, no analysis  
109 was conducted on other types of grafts. Propaten<sup>®</sup> grafts were not available in France in 2011.  
110 Patients having been operated upon for a BTK bypass surgery in the two years prior were  
111 excluded as well as patients under 18 years old. The data included the reference of the  
112 diagnosis related groups (DRGs), the type of bypass grafts used, the duration of stays, the  
113 time spent in reanimation or intensive care unit as well as the patient's comorbidities.

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115 **The population model (Table 1)**

116 First at all, the follow up of the source population was determined. Rehospitalization in  
 117 relation to the crude PTFE was determined by a retrospective analysis on hospital stays for  
 118 our source population during the 24 months following the initial surgery. The follow up of the  
 119 source population was adjusted according for 2-year mortality and contralateral  
 120 reintervention.(9,10). Loss of patency was defined by a hospital stay for a lower limb  
 121 reintervention hereafter called the first rehospitalization. These lower limb interventions  
 122 included angioplasties, major amputations, thrombectomies, ablations of vascular grafts, stent  
 123 placements and in situ fibrinolysis.

124 **Table 1:** Values fed to the model and their sources.

Clinical Data	Values	Sources
First rehospitalization rate due to graft of interest	35.1% (177/504)	French rehospitalization data, adjusted for mortality (10) and contralateral reintervention (De Vries et al (1998) (9))
Pooled primary patency for Propaten grafts:	75.6%	Own calculations (Appendix A)
Cost Estimates	Values	Sources
Mean initial intervention cost	€12 290	Own calculations (PMSI-based)
Rehospitalization mean cost (one rehospitalization)	€10 689	Own calculations (PMSI-based)
Propaten initial additional cost	€627	GORE <sup>®</sup>
ePTFE reimbursement tariff	€639	FNHI online data (8)
Market Data	Values	Sources
Initial Market Penetration	15%	NA
Annual Market Penetration Increase	5%	NA
Population growth	-1.0%	ATIH (7)

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126 Regarding the Propaten<sup>®</sup> population, the 2-year primary patency was determined according a  
 127 review of the literature. A review found 7 studies on Propaten<sup>®</sup> with either 2-year BTK  
 128 primary patency or both BTK femoropopliteal and femorocrural 2-year BTK primary patency.

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3 129 One study was excluded because it focused exclusively on diabetics (11). Another was found  
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5 130 to have an outlying rate of renal insufficiency.(12). In total, 5 studies were included in our  
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7 131 estimation and the mean 2-year BTK primary patency for Propaten<sup>®</sup> was 75.6 %.(13–17)  
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### 133 **Retrospective cost estimation for crude PTFE grafts**

134 As we aimed to estimate the budget impact of an official reimbursement policy, we conducted  
135 our budget impact analysis from the payer perspective (French National Health Insurance,  
136 FNHI) and estimated costs only from this perspective. Only direct medical costs, covering in-  
137 patient treatment, were considered. Costs were estimated by the 2015 official tariffs applied to  
138 the relevant DRGs, for both initial and further hospitalizations. The tariffs provide the amount  
139 paid by the FNHI to a hospital with respect to each stay, procedure duration and potential  
140 additional costs, i.e. hospital costs that are reimbursed in addition to the DRG tariff (e.g.  
141 intensive care).

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### 143 **Simulated cost estimation for Propaten<sup>®</sup> grafts**

144 We estimated the costs for the initial Propaten<sup>®</sup> procedure using the mean initial intervention  
145 cost (MIIC) for crude PTFE grafts added to the cost difference between Propaten<sup>®</sup> graft's  
146 market price and the reimbursed tariff for crude PTFE grafts. The mean rehospitalizations  
147 cost (MRC) for crude PTFE was used to estimate the mean cost for Propaten<sup>®</sup>  
148 rehospitalizations. Every bypass graft used during rehospitalization stays was assumed to be a  
149 crude PTFE graft.

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56 151 **Budget impact model:**  
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8 152 Our budget impact analysis premised the enactment by the French Health Authorities of a  
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10 153 FNHI reimbursement policy, i.e. additional costs from the initial procedure would be charged  
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12 154 solely to the FNHI. Our base case for the budget impact model used the estimates from our  
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14 155 literature review to simulate a rehospitalization rate for the Propaten<sup>®</sup> implantation for the  
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16 156 2011 PMSI-extracted population. No analysis was conducted on 2-year secondary patency  
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18 157 mainly because of the lack of PMSI data on limb side. Total hospital reimbursement costs for  
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20 158 both procedures were calculated by adding the initial intervention costs with subsequent  
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22 159 rehospitalizations costs. Each year for 5 years, a new cohort of patients entered the model for  
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24 160 duration of 2 years, starting with the 2011 population. The number of patients decrease by a  
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26 161 flat 1.0% annually, i.e. the mean decrease rate between 2011 and 2014 for the DRG  
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28 162 representing 95% of our population as informed in ATIH online data (8). We hypothesized  
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30 163 that the enactment of a reimbursement policy by French Health authorities would result in an  
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32 164 initial market penetration rate of 15% for Propaten<sup>®</sup> grafts, with a subsequent annual increase  
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34 165 of 5 percentage points, meaning that after 5 years, 35% of the grafts in this indication would  
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36 166 be Propaten<sup>®</sup> grafts. Numerical values corresponding to the hypotheses we made are  
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38 167 presented in Table 1. We based our sensitivity analysis on variation one by one of relevant  
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40 168 variables in order to assess the weight of each hypothesis on the overall behavior of the  
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42 169 model.(18).  
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3 170 **RESULTS**

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10 173 **Retrospective database analysis for crude PTFE grafts (Figure 1)**

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12 174 The retrospective data from the national expenditure database revealed 656 patients with CLI  
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14 175 treated with crude PTFE grafts for a BTK bypass surgery during year 2011. Over the 24  
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16 176 months after their initial surgery, 189 patients were hospitalized for a total of 278  
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18 177 rehospitalizations considered related to loss of primary patency or contralateral limb  
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20 178 reinterventions. The 2-year rehospitalization rate for crude PTFE grafts in our population was  
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22 179 37.5%. We estimated the actual primary patency at 64.9%, because of the high reported  
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24 180 intervention rate on contralateral limbs.(9,19,20) With Propaten<sup>®</sup>, assuming a patency rate of  
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26 181 75.6% at 2 years, we predict 123 rehospitalisations.

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34 183 **Costs of treatment using crude PTFE and Propaten<sup>®</sup>**

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36 184 The MIIC from the payer perspective was €12 290 per patient (Total initial intervention costs:  
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38 185 €8 062 382). Most patients (99%) belonged to the DRG for major revascularization surgeries  
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40 186 (DRG 05C10). The MRC from the payer perspective was €10 689. When subsequent  
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42 187 rehospitalizations were pooled, the MRC rose to €15 437. Two-year total hospitalization cost  
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44 188 from the national insurance perspective for the 656 patients with crude PTFE grafts was  
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46 189 €10 988 513.

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50 190 Postulating treatment with only Propaten<sup>®</sup> grafts for the 656 patients from 2011, 2-year total  
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52 191 hospital reimbursement costs would have been €10 822 598.

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193 **Budget Impact Analysis (Figure 2)**

194 Under the base case assumptions (Table 1), we calculated a difference in MIIC of €502 173 in  
 195 favor of crude PTFE grafts over a 5-year period (Table 2).

196 **Table 2:** Budget impact comparison. A *plus* sign indicates an increase in costs, a *minus* sign  
 197 shows savings.

Year	ePTFE alone	Propaten + ePTFE					Cost difference	
	Total costs (€)	ePTFE grafts	Propaten grafts	Initial additional cost (€)	Rehospitalizations	Rehospitalizations avoided		Total cost (€)
1	€9 008 321	558	98	€61 439	85	4	€9 027 006	€18 685
2	€9 857 540	519	130	€81 501	167	9	€9 837 500	€-20 040
3	€9 762 422	482	161	€100 936	162	12	€9 735 095	€-27 327
4	€9 672 648	446	191	€119 744	158	15	€9 637 408	€-35 240
5	€9 570 583	409	221	€138 552	154	17	€9 522 086	€-48 498
Total	€47 871 515	2 414	801	€502 174	726	57	€47 759 095	€-112 420

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199 We projected a cumulative population of 3 215 patients over 5 years, of which 801 would  
 200 have received a Propaten<sup>®</sup> graft. At 5 years, we would have avoided 57 rehospitalizations,  
 201 resulting in saving costs of €614 593 in favor of Propaten<sup>®</sup> grafts. The amount of savings due  
 202 to fewer rehospitalizations offset the difference in MIIC as soon as the 2<sup>nd</sup> year. Assuming a  
 203 15% market penetration during the 1<sup>st</sup> year and then 5% fixed market penetration (35% over  
 204 the 5 years), the total difference between the observed crude PTFE and simulated Propaten<sup>®</sup> +  
 205 PTFE courses was estimated at €112 420, in favor of Propaten<sup>®</sup> grafts, from the FNHI  
 206 perspective. Outcomes in term of reduction costs and Propaten<sup>®</sup> additional costs are presented  
 207 in Figure 2.

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3 209 **Sensitivity analysis (Figure 3)**

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5 210 Primary patency for Propaten<sup>®</sup> had a strong impact on budget results. Using the lower rate of  
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7 211 primary patency at 2 years (worst case), the additional cost was €486 140. On the contrary,  
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9 212 using the higher patency rate (best case), the saving was €636 160. For PTFE grafts, a  
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11 213 primary patency closer to the values found in the literature (47%) increased the savings  
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13 214 allowed by Propaten<sup>®</sup> grafts. (4). The market price for Propaten<sup>®</sup> grafts (initial intervention  
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15 215 additional cost) had comparatively little impact on the 5-year budget balance and so did MRC  
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17 216 when including further rehospitalizations. A cheaper graft or a higher MRC led to higher 5-  
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24 218 **DISCUSSION**

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31 221 Our model-based analysis showed the 5-year budget impact for the diffusion of Propaten<sup>®</sup> in  
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33 222 replacement of crude PTFE to be cost-saving. This is a strong economic incentive in favor of  
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35 223 both a widespread use and the enactment of a reimbursement policy for Propaten<sup>®</sup> grafts.  
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39 224 Our modeling approach was founded on a set of assumptions that deserve mention.

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42 225 The centralized structure of the French Health Information system allows for low-cost studies  
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44 226 with exhaustive data on the French population, thus producing results with a high statistical  
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46 227 power and negligible sampling fluctuations.  
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50 228 Few articles on Propaten<sup>®</sup> grafts presented 2-year primary patency for BTK bypasses in the  
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52 229 general population, and the level of their clinical evidence was limited. Furthermore no article  
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54 230 presented specific results on BTK bypasses in critically ischemic patients, and two articles  
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56 231 had better BTK than above-the-knee results. This usually is not the case in lower limb  
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3 232 bypasses, and could be partially explained by important sampling fluctuations due to their  
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5 233 small sample sizes. This very fact gave them a low weight in our estimation of the 2-year  
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7 234 primary patency. As there was no other available data, we chose to use reasonably  
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9 235 unfavorable hypotheses in our analyses to compensate for these shortcomings and thus  
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11 236 strengthen the overall conclusion.

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14 237 As our sensitivity analysis showed, our conclusions are tied to both the effectiveness of  
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16 238 Propaten<sup>®</sup> grafts and the comparative lack of effectiveness of crude PTFE grafts. The  
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18 239 observed 2-year primary patency for crude PTFE grafts is about 35% higher than usually  
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20 240 described (4). Most clinical studies follow their patients more thoroughly than it is the case in  
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22 241 daily care. This is the cause of a follow-up bias in our study, due to the use of reintervention  
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24 242 as a measure of loss of patency, which overestimate the patency for crude PTFE grafts. Indeed,  
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26 243 in the case of an occluded graft, reintervention and/or amputation are not systematically  
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28 244 performed because the patient is asymptomatic or because a palliative treatment is decided.  
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30 245 These types of health consumptions are not logged in the PMSI database and as we used  
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32 246 intervention-specific codes, we estimated the 2-year primary patency for crude PTFE grafts  
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34 247 using only patients with lower limb vascular surgical interventions. The patients lost because  
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36 248 of our method of follow-up would only ramp up the costs of the crude PTFE course of action.

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39 249 We used hospital reimbursement costs only, as they are likely to be cost-drivers in a surgical  
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41 250 course of action. Unavailable costs included those for non-hospital medical consultations and  
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43 251 care, which are likely to decrease with a more effective Propaten<sup>®</sup> graft. Likewise, the  
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45 252 exclusion of readmissions past the first one may only have lessened the difference in costs  
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47 253 between the two types of grafts. It was anyhow not an option to use these readmissions, given  
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49 254 the uncertainty on limb side and the lack of available data.  
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3 255 Finally, even though we based our model on French data and tariffication, it can be used for  
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5 256 any DRG-based system to estimate the budget impact of Propaten<sup>®</sup> reimbursement.  
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## 10 11 258 **CONCLUSION**

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20 261 At current times of resource allocation rationalization, every innovation in healthcare must  
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22 262 pass tests of both clinical and economic value. Propaten<sup>®</sup> grafts have shown their clinical  
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24 263 effectiveness, but had yet to be proven economically attractive.

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27 264 In this paper, we used existing clinical proof to show that Propaten<sup>®</sup> grafts in patients with  
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29 265 CLI needing a BTK bypass would be financially beneficial for the French NHI in most cases.

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31 266 The decision to specifically reimburse Propaten<sup>®</sup> at its market price dictates the extent of its  
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33 267 use throughout France, as few hospitals can afford it in a DRG-based system, which does not  
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35 268 allow them to benefit directly from the increased primary patency. Based on our hypotheses  
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37 269 and analysis we conclude that a reimbursement policy would benefit both the French NHI and  
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39 270 the patients. Our model allows performing of the same analysis in other countries using local  
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41 271 cost and clinical effectiveness data providing they have a similar reimbursement system.

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44 272 Future research ought to focus on directly comparing crude PTFE and Propaten<sup>®</sup> grafts in  
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46 273 order to confirm its probable cost-effectiveness dominance.  
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3 274 **ACKNOWLEDGEMENTS**  
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10 277 The data extracted from the PMSI was supplied by the French Medical Information Agency

11 278 (ATIH) and was used under agreement with the French data protection authority (CNIL) with

12  
13 279 the authorization numbers DE-2011-066 and 2015-064. Only authorized and discretion-bound

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17 280 personnel handled this data.  
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20 281 The model was created using Microsoft<sup>®</sup> Excel<sup>®</sup>.  
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282 **COMPETING INTERESTS AND FUNDING**

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284

285 This research was carried out with financial support from GoreTex<sup>®</sup>.

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3 290 DATA SHARING STATEMENT  
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5 291 Data sharing: no additional data available.  
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## 292 REFERENCES

- 293 1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-  
294 Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J*  
295 *Vasc Endovasc Surg.* 2007;33(1, Supplement):S1–75.
- 296 2. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al.  
297 Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011  
298 ACCF/AHA Guideline Recommendations) A Report of the American College of  
299 Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.  
300 *Circulation.* 2013 Apr 2;127(13):1425–43.
- 301 3. Setacci C, de Donato G, Teraa M, Moll FL, Ricco J-B, Becker F, et al. Chapter IV:  
302 Treatment of Critical Limb Ischaemia. *Eur J Vasc Endovasc Surg.* 2011 Dec;42,  
303 Supplement 2:S43–59.
- 304 4. Albers M, Battistella VM, Romiti M, Rodrigues AAE, Pereira CAB. Meta-analysis of  
305 polytetrafluoroethylene bypass grafts to infrapopliteal arteries1. *J Vasc Surg.* 2003  
306 Jun;37(6):1263–9.
- 307 5. Jackson MR, Belott TP, Dickason T, Kaiser WJ, Modrall JG, Valentine RJ, et al. The  
308 consequences of a failed femoropopliteal bypass grafting: Comparison of saphenous  
309 vein and PTFE grafts. *J Vasc Surg.* 2000 Sep;32(3):498–505.
- 310 6. Lindholt JS, Gottschalksen B, Johannesen N, Dueholm D, Ravn H, Christensen ED, et al.  
311 The Scandinavian Propaten® trial - 1-year patency of PTFE vascular prostheses with  
312 heparin-bonded luminal surfaces compared to ordinary pure PTFE vascular prostheses -  
313 a randomised clinical controlled multi-centre trial. *Eur J Vasc Endovasc Surg Off J Eur*  
314 *Soc Vasc Surg.* 2011 May;41(5):668–73.
- 315 7. Lindholt JS, Houlind K, Gottschalksen B, Pedersen CN, Ravn H, Viddal B, et al. Five-  
316 year outcomes following a randomized trial of femorofemoral and femoropopliteal  
317 bypass grafting with heparin-bonded or standard polytetrafluoroethylene grafts. *Br J*  
318 *Surg.* 2016 Sep;103(10):1300–5.
- 319 8. Statistics from the French Medical Information Agency (ATI H [Internet]. ScanSanté.  
320 [cited 2016 Jan 8]. Available from: <http://www.scansante.fr/>
- 321 9. de Vries SO, Donaldson MC, Hunink MGM. Contralateral symptoms after unilateral  
322 intervention for peripheral occlusive disease. *J Vasc Surg.* 1998 Mar;27(3):414–21.
- 323 10. Martini R, Andreozzi GM, Deri A, Cordova R, Zulian P, Scarpazza O, et al. Amputation  
324 rate and mortality in elderly patients with critical limb ischemia not suitable for  
325 revascularization. *Aging Clin Exp Res.* 2012 Jun;24(3 Suppl):24–7.
- 326 11. Dorigo W, Pulli R, Castelli P, Dorrucchi V, Ferilli F, De Blasis G, et al. A multicenter  
327 comparison between autologous saphenous vein and heparin-bonded expanded  
328 polytetrafluoroethylene (ePTFE) graft in the treatment of critical limb ischemia in  
329 diabetics. *J Vasc Surg.* 2011 Nov;54(5):1332–8.

- 1  
2  
3 330 12. Lösel-Sadée H, Alefelder C. Heparin-bonded expanded polytetrafluoroethylene graft for  
4 331 infragenicular bypass: five-year results. *J Cardiovasc Surg (Torino)*. 2009  
5 332 Jun;50(3):339–43.
- 6  
7 333 13. Walluscheck KP, Bierkandt S, Brandt M, Cremer J. Infrainguinal ePTFE vascular graft  
8 334 with bioactive surface heparin bonding. First clinical results. *J Cardiovasc Surg (Torino)*.  
9 335 2005 Aug;46(4):425–30.
- 10  
11 336 14. Peeters P, Verbist J, Deloose K, Bosiers M. Results with heparin bonded  
12 337 polytetrafluoroethylene grafts for femorodistal bypasses. *J Cardiovasc Surg (Torino)*.  
13 338 2006 Aug;47(4):407–13.
- 14  
15  
16 339 15. Dorigo W, Di Carlo F, Troisi N, Pratesi G, Innocenti AA, Pulli R, et al. Lower limb  
17 340 revascularization with a new bioactive prosthetic graft: early and late results. *Ann Vasc*  
18 341 *Surg*. 2008 Jan;22(1):79–87.
- 19  
20 342 16. Dorrucchi V, Griselli F, Petralia G, Spinamano L, Adornetto R. Heparin-bonded  
21 343 expanded polytetrafluoroethylene grafts for infragenicular bypass in patients with critical  
22 344 limb ischemia: 2-year results. *J Cardiovasc Surg (Torino)*. 2008 Apr;49(2):145–9.
- 23  
24 345 17. Daenens K, Schepers S, Fourneau I, Houthoofd S, Nevelsteen A. Heparin-bonded  
25 346 ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses:  
26 347 1- and 2-year results. *J Vasc Surg*. 2009 May;49(5):1210–6.
- 28  
29 348 18. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al.  
30 349 Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012  
31 350 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014 Jan;17(1):5–  
32 351 14.
- 33  
34 352 19. Shah AP, Klein AJ, Sterrett A, Messenger JC, Albert S, Nehler MR, et al. Clinical  
35 353 outcomes using aggressive approach to anatomic screening and endovascular  
36 354 revascularization in a veterans affairs population with critical limb ischemia. *Catheter*  
37 355 *Cardiovasc Interv*. 2009 Jul;74(1):11–9.
- 38  
39 356 20. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-Eluting Balloon in  
40 357 Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) A  
41 358 Randomized Trial in Diabetic Patients With Critical Limb Ischemia. *Circulation*. 2013  
42 359 Aug 6;128(6):615–21.

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60362 **FIGURE**

363 Figure 1: Patients extraction process using the French expenditure database and obtainment of  
364 observed and simulated 2-year data

365 Figure 2: Budget impact comparison. A *plus* sign indicates an increase in costs, a *minus* sign  
366 shows savings

367 Figure 3: Tornado diagram representing the variation of the 5-year budget balance depending  
368 on 5 hypotheses. A negative balance indicates a cost-save.

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3 369 **CONTRIBUTORSHIP STATEMENT**

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5 370 Simon Vergnaud: Conception and Design, Analysis and interpretation, Data collection,  
6 371 Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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10 373 Valéry-Pierre Riche: Conception and Design, Analysis and interpretation, Data collection,  
11 374 Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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15 376 Philippe Tessier: Conception and Design, Analysis and interpretation, Data collection, Writing  
16 377 the manuscript, Critical revision of the manuscript, Statistical Analysis

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20 379 Nicolas Mauduit: Analysis and interpretation, Data collection, Writing the manuscript, Critical  
21 380 revision of the manuscript

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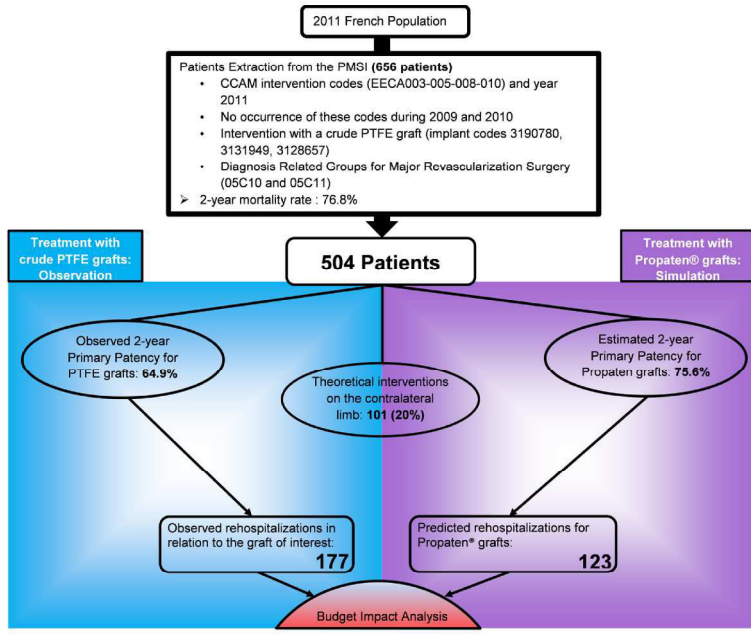
24  
25 382 Adrien Kaladji: Analysis and interpretation, Writing the manuscript, Critical revision of the  
26 383 manuscript

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30 385 Yann Gouëffic: Conception and Design, Analysis and interpretation, Writing the manuscript,  
31 386 Critical revision of the manuscript, Statistical Analysis, Obtaining funding



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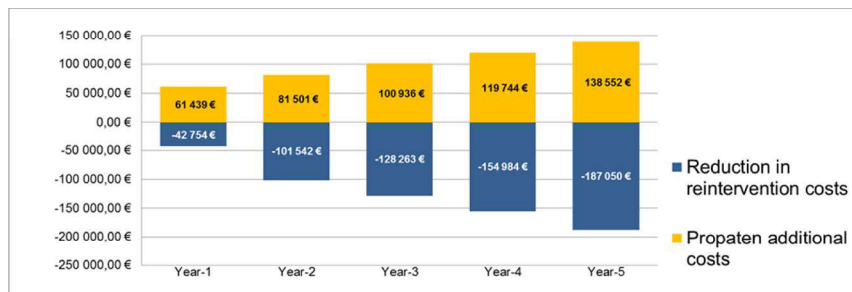


Patients extraction process using the French expenditure database and obtainment of observed and simulated 2-year data

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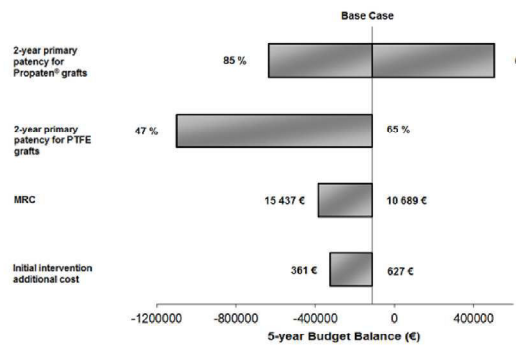


Budget impact comparison. A plus sign indicates an increase in costs, a minus sign shows savings.

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Tornado diagram representing the variation of the 5-year budget balance depending on 4 hypotheses. A negative balance indicates a cost-save.

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# BMJ Open

## Budget impact analysis of heparin-bonded polytetrafluoroethylen grafts (Propaten®) against standard polytetrafluoroethylen grafts for below the knee bypass in patients with critical limb ischemia in France.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017320.R1
Article Type:	Research
Date Submitted by the Author:	20-Oct-2017
Complete List of Authors:	Vergnaud, Simon; Centre Hospitalier Universitaire de Nantes Riche, Valéry-Pierre; CHU de Nantes, Research Direction Tessier, Philippe; Universite de Nantes - Faculte de Medicine Mauduit, Nicolas; CHU de Nantes Kaladji, Adrien; Centre Hospitalier Universitaire de Rennes Gouëffic, Yan ; Universite de Nantes - Faculte de Medicine; Inserm-UN, Laboratoire de Physiopathologie de la Résorption Osseuse
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Health economics
Keywords:	Critical limb ischemia, Bypass, Heparin-bonded graft, Below the knee, Budget impact analysis

SCHOLARONE™  
Manuscripts

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3 1 **TITLE PAGE**

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6 2 **Budget impact analysis of heparin-bonded polytetrafluoroethylen grafts (Propaten®) against**  
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8 3 **standard polytetrafluoroethylen grafts for below the knee bypass in patients with critical limb**  
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10 4 **ischemia in France**

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9 27 **Words count: 3 053**

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3 28 **ABSTRACT**  
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8 29 **Objectives:** To evaluate the budget impact of progressive replacement of standard  
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10 30 polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten<sup>®</sup>) for below-the-knee  
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12 31 (BTK) bypass in patients with critical limb ischemia (CLI).  
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15 32 **Design:** From a review of the scientific literature we calculated a theoretical BTK primary  
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17 33 patency for Propaten<sup>®</sup> grafts. Using the French hospital expenditure database (PMSI), we  
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19 34 retrospectively estimated a rehospitalization rate for standard PTFE grafts. From these data, a  
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21 35 model was created to assess the budget impact of a progressive replacement from standard  
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23 36 PTFE grafts to Propaten<sup>®</sup> grafts over a 5-year horizon. We performed an univariate sensitivity  
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25 37 analysis to assess the robustness of our results.  
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29 38 **Setting:** French National Health Insurance (FNHI) perspective.  
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32 39 **Participant:** Patients with CLI.  
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35 40 **Main outcome measures:** Budget impact analysis  
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38 41 **Results:** Data extraction from the PMSI revealed that 656 patients were treated with PTFE  
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40 42 grafts in 2011 in French public hospitals for a BTK bypass. Assuming a 2-year survival rate  
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42 43 of 76.8 %, observed reinterventions rate for standard PTFE grafts at 24 months from the  
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44 44 PMSI was 35.1%. The mean rehospitalization cost was €10 689. The budget impact analysis  
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46 45 based on these data found a net cumulative 5-year payer budget reduction of €112 420 in  
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48 46 favor of Propaten<sup>®</sup>, under the assumption of a 75.6 % primary patency for Propaten<sup>®</sup> grafts  
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50 47 for a projected population of 3 215 patients of which 801 received a Propaten<sup>®</sup> graft.  
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3 48 **Conclusions:** Our budget impact analysis showed a positive impact on the national health  
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5 49 insurance budget of the replacement of standard PTFE grafts by Propaten® grafts for below  
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7 50 the knee bypass in patients with CLI in France. This supports the enactment of a  
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9 51 reimbursement policy by the FNHI.  
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3 **52 Strengths and limitations of this study**  
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6 53 • The budget impact analysis provides further evidence to adopt and to reimburse the  
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8 54 device for decision-makers.  
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10 55 • PMSI database allows for studies with exhaustive data on the French population, thus  
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12 56 producing results with a high statistical power and negligible sampling fluctuations.  
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14 57 • However, only patients with critical limb ischemia and initially treated by standard  
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16 58 PTFE in public hospital could be identified in the PMSI database, underestimating the  
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18 59 results of the study.  
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21 60 • Clinical factors potentially influencing patterns of practice, office-based consumption of  
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23 61 cares, and non-reimbursable items and medicines could not be analyzed.  
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## 62 INTRODUCTION

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65 Patients with critical limb ischemia (CLI) are at risk of limb amputation. Consequently, a  
66 revascularization should be performed as soon as possible in order to save the limb (1). To  
67 realize the revascularization, two options should be considered: endovascular or open repair.

68 So far, despite the lack of consensus, open repair could be recommended in a first line of  
69 treatment to re-vascularize CLI patients (2) or performed in a second line of treatment in case  
70 of failure of endovascular repair (3). In the event of open surgery, a vein should be used as  
71 conduit to perform the bypass, especially in the case of infrapopliteal lesions. A suitable vein  
72 is one of the main factors that determine the clinical success of open revascularization for  
73 below the knee (BTK) popliteal and distal bypass (1). Unfortunately, a suitable venous  
74 conduit is not available in more than 20% of the cases (2). In these patients, prosthesis such as  
75 standard polytetrafluoroethylene (PTFE) graft demonstrated worse clinical and morphological  
76 results and more severe consequences in case of occlusion (4,5). Consequently, there is still a  
77 room for improvement in CLI patients in the absence of a suitable conduit and in whom  
78 endovascular repair failed. In these patients, prostheses with heparin-bound to the luminal  
79 surface could improve standard prosthesis results. In 2011, Lindholt et al. reported the results  
80 of a multicenter randomized trial comparing heparin-bound PTFE (Propaten<sup>®</sup>, Flagstaff, AZ,  
81 USA) grafts with those of standard PTFE grafts (6). In total, 546 patients had 1-year follow-  
82 up (standard PTFE: 272; Propaten<sup>®</sup>: 274). Propaten<sup>®</sup> graft significantly reduced the overall  
83 risk of primary graft failure by 37% at one year from the intervention. Specifically, risk  
84 reduction reached 50% in femoropopliteal bypass for patients with CLI. Moreover, after 5  
85 years, patients receiving Propaten<sup>®</sup> grafts for CLI were more likely to have a patent graft than  
86 those with standard PTFE grafts.(7)

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3 87 However, to date, the financial impact of Propaten<sup>®</sup> use on health care spending was not  
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5 88 assessed. Using data from the literature and from the French hospital expenditure database  
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7 89 (PMSI), we assess the financial impact of a progressive replacement of standard PTFE by  
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9 90 Propaten<sup>®</sup> on a 5-year timeline from the payer perspective, for BTK bypass in patients with  
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11 91 CLI.  
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## 92 **METHODS**

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### 95 **Analytic Overview**

96 Our aim was to compare the usual course of action taken by French surgeons for BTK bypass  
97 surgery, using standard PTFE grafts, to a similar course of action using Propaten<sup>®</sup> grafts, in  
98 order to assess the latter's economical impact. We combined clinical data based on a review  
99 from the literature and retrospective data about hospital stays from the PMSI to feed a cost  
100 model from a third party payer perspective and to perform a budget impact analysis. No  
101 change in our clinical practice and no randomization occurred. As our model was based on an  
102 observational retrospective analysis of data, according to the French legislation (articles  
103 L.1121-1 paragraph 1 and R1121-2, Code de la Santé Publique), approval of an ethics  
104 committee was not required for use of the data in an epidemiologic study.

105

### 106 **Evidence acquisition**

107 Our search strategy was based on Preferred reporting items for systematic reviews and Meta-  
108 analyses (PrisMa) guidelines, with the help of PrisMa statement and explanation &  
109 elaboration documents (8). We used Medline register to conduct our bibliography. The  
110 following terms were added to the search builder using Mesh: below the knee, bypass,  
111 surgery, Propaten<sup>®</sup>, grafts, 2-years, primary patency, critical limb ischemia. One study was  
112 excluded because it focused exclusively on diabetics (9). Another was found to have an  
113 outlying rate of renal insufficiency (10). Indeed, we considered that outlying rate of diabetes  
114 and renal insufficiency could alter too much the outcomes in regards to perioperative  
115 outcomes and pattern of atherosclerotic disease (11), (12). We assigned each study a weight,

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116 based solely on the size of its sample and the location of the anastomoses (Table 1), assuming  
117 a fixed-effect model. Our estimate of the 2-year BTK primary patency for Propaten® grafts  
118 was 75.6%, ranging from 70.8% to 85%.

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119 **Table 1:** Detailed review of the literature of the Propaten<sup>®</sup> patency rate at 2-years

Study	Date	Authors	Patients (n)	2-year Primary Patency
Lower limb revascularization with a new bioactive Prosthetic graft: Early and late results	2008	Dorigo et al. (13)	34	80.0%
Results with heparin-bonded polytetrafluoroethylene grafts for femorodistal bypasses	2006	Peeters et al.(14)	41	72.0%
Infrainguinal ePTFE vascular graft with bioactive surface heparin bonding	2005	Walluscheck et al. (15)	17	81.0%
Heparin-bonded expanded polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb ischemia: 2-year results	2008	Dorrucci et al. (16)	20	85.0%
Heparin-bonded ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses: 1- and 2-year results	2009	Daenens et al. (17)	57	83.0%
Heparin-bonded expanded PTFE femoropopliteal bypass grafts outperform expanded PTFE grafts without heparin in a long-term comparison	2016	Samson et al. (18)	42	71.0%

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3 121 **Source population**

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5 122 From a retrospective analysis on hospital stays during 2011 using the PMSI, we identified  
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7 123 patients who were admitted for a BTK bypass surgery, where a standard PTFE graft was used.  
8  
9 124 In France, only CLI patients have this surgery, where using a standard PTFE graft is the usual  
10  
11 125 choice (French medical information agency –ATIH– online data)(19). Therefore, no analysis  
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13 126 was conducted on other types of grafts. Propaten<sup>®</sup> grafts were not available in France in 2011.  
14  
15 127 Patients under 18 years old were excluded. Patients having been operated upon for a BTK  
16  
17 128 bypass surgery in the two years prior were excluded as well as to exclude reinterventions  
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19 129 from index cases. The data included the reference of the diagnosis related groups (DRGs), the  
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21 130 type of bypass grafts used, the duration of stays, the time spent in intensive care unit as well  
22  
23 131 as the patient’s comorbidities. Patients were followed for 24 months.(20)  
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30 133 **The population model (Table 2)**

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32 134 First of all, the follow up of the source population was determined. Rehospitalization in  
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34 135 relation to the standard PTFE was determined by a retrospective analysis on hospital stays for  
35  
36 136 our source population during the 24 months following the initial surgery. The follow up of the  
37  
38 137 source population was adjusted for 2-year mortality and contralateral reintervention.(21,22).  
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40 138 Loss of patency was defined by a hospital stay for a lower limb reintervention hereafter called  
41  
42 139 the first rehospitalization. These lower limb interventions included angioplasties, major  
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44 140 amputations, thrombectomies, ablations of vascular grafts, stent placements and in situ  
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46 141 fibrinolysis.  
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142 **Table 2:** Values fed to the model and their sources.

Clinical Data	Values	Sources
First rehospitalization rate due to graft of interest	35.1% (177/504)	French rehospitalization data, adjusted for mortality (22) and contralateral reintervention (21)
Added primary patency for Propaten grafts:	75.6%	Own calculations (Evidence acquisition)
Cost Estimates		
Mean initial intervention cost	€12,290	Own calculations (PMSI-based)
Rehospitalization mean cost (one rehospitalization)	€10,689	Own calculations (PMSI-based)
Propaten initial additional cost	€627	WL Gore®
PTFE reimbursement tariff	€639	FNHI online data (19)
Market Data		
Initial Market Penetration	15%	De Cock (23)
Annual Market Penetration Increase	5%	De Cock (23)
Population growth	-1.0%	ATIH (19)

143 **PMSI: french hospital expenditure database; PTFE: polytetrafluoroethylen; FNHI:**  
 144 **french national health insurance**

#### 146 **Retrospective cost estimation for standard PTFE grafts**

147 As we aimed to estimate the budget impact of an official reimbursement policy, we conducted  
 148 our budget impact analysis from the payer perspective (French National Health Insurance,  
 149 FNHI) and estimated costs only from this perspective. Only direct medical costs, covering in-  
 150 patient treatment, were considered. Costs were estimated by the 2015 official tariffs applied to  
 151 the relevant DRGs, for both initial and further hospitalizations. The tariffs provide the amount  
 152 paid by the FNHI to a hospital with respect to each stay, procedure duration and potential  
 153 additional costs, i.e. hospital costs that are reimbursed in addition to the DRG tariff (e.g.  
 154 intensive care). Variability was estimated for both initial and subsequent interventions using a  
 155 bootstrap technique, with a resampling of 100 random samples of 100 patients.



156

**157 Cost estimation for Propaten<sup>®</sup> grafts**

158 We estimated the costs for the initial Propaten<sup>®</sup> procedure using the mean initial intervention  
159 cost (MIIC) for standard PTFE grafts added to the cost difference (€627) between Propaten<sup>®</sup>  
160 graft's market price and the reimbursed tariff for standard PTFE grafts. The mean  
161 rehospitalizations cost (MRC) for standard PTFE was used to estimate the mean cost for  
162 Propaten<sup>®</sup> rehospitalizations. Every bypass graft used during rehospitalization stays was  
163 assumed to be a standard PTFE graft.

164

**165 Budget impact model:**

166 Our budget impact analysis premised the enactment by the French Health Authorities of a  
167 FNHI reimbursement policy, i.e. additional costs from the initial procedure would be charged  
168 solely to the FNHI. Our base case for the budget impact model used the estimates from our  
169 literature review to estimate a rehospitalization rate for the Propaten<sup>®</sup> implantation for the  
170 2011 PMSI-extracted population. No analysis was conducted on 2-year secondary patency  
171 mainly because of the lack of PMSI data on limb side. Total hospital reimbursement costs for  
172 both procedures were calculated by adding the initial intervention costs with subsequent  
173 rehospitalizations costs. Each year for 5 years, a new cohort of patients entered the model for  
174 duration of 2 years, starting with the 2011 population. The number of patients decrease by a  
175 flat 1.0% annually, i.e. the mean decrease rate between 2011 and 2014 for the DRG  
176 representing 95% of our population as informed in ATIH online data (19). We hypothesized  
177 that the enactment of a reimbursement policy by French Health authorities would result in an  
178 initial market penetration rate of 15% for Propaten<sup>®</sup> grafts, with a subsequent annual increase  
179 of 5 percentage points, meaning that after 5 years, 35% of the grafts in this indication would

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3 180 be Propaten<sup>®</sup> grafts (23). Numerical values corresponding to the hypotheses we made are  
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5 181 presented in Table 2. We based our sensitivity analysis on variation one by one of relevant  
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7 182 variables in order to assess the weight of each hypothesis on the overall behavior of the  
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9 183 model.(24).

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## 15 185 **Sensitivity analysis**

### 18 186 *Univariate analysis*

21 187 We tested the sensitivity of our results to the main hypotheses used in our model by  
22  
23 188 estimating the budget impact for a range of values. The tested parameters were the 2-year  
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25 189 BTK primary patencies for Propaten<sup>®</sup> and standard PTFE grafts, the mean cost of  
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27 190 rehospitalization and the additional cost of the initial intervention for Propaten<sup>®</sup> grafts. For  
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29 191 Propaten<sup>®</sup> grafts' patency, we used the 2-year primary patency for standard PTFE grafts  
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31 192 found in our population as low end of the range, and the highest reported primary patency (16)  
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33 193 as high end. For PTFE grafts' patency, we used the 2-year primary patency for standard PTFE  
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35 194 grafts found in our population as the high end of the range, and the value found in the  
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37 195 literature (4) as the low end. For the mean cost of rehospitalizations, we used the low and high  
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39 196 values of our 95% confidence interval as low and high ends of the range. Finally, we used  
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41 197 arbitrary values to test for the sensitivity of our results to the price of the Propaten<sup>®</sup> graft.

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### 48 199 *Scenario analysis*

51 200 We estimated the 5-year budget impact in three additional scenarios, describing one  
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53 201 alternative plausible situation and the two extremes. These extreme scenarios are described in

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3 202 Table 3, and either favored (best case) or disfavored (worst case) Propaten® grafts, based on  
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5 203 2-year BTK primary patency for Propaten® grafts, mean cost of rehospitalizations and 2-year  
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7 204 BTK primary patency for standard PTFE grafts. The alternative plausible scenario assumed  
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9 205 that a maximum patency would decrease the mean cost of rehospitalizations.

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12 206 **Table 3:** Worst and best case of the scenario analysis.

	Base case	Best case	Worst case
PTFE	64,9%	47,0%	64,9%
Propaten	75,6%	85,0%	64,9%

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## 208 RESULTS

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### 211 Retrospective database analysis for standard PTFE grafts (Figure 1)

212 The retrospective data from the national expenditure database revealed 656 patients with CLI  
213 treated with standard PTFE grafts for a BTK bypass surgery in 2011. Two years later, 152  
214 patients died and 504 patients were still alive. Among these 504 patients, 189 patients were  
215 re-hospitalized at 2-years. According the literature (21,25,26), we estimated that 12 patients  
216 have been operated only from the contralateral limb. Consequently, 177 patients were  
217 hospitalized at 2 years for a BTK surgical intervention on the limb of interest, resulting in a  
218 rehospitalization rate of 35.1%, or a 2-year primary patency of 64.9% for standard PTFE  
219 grafts. In the assumed group (treatment with Propaten<sup>®</sup> grafts) the estimated patency rate was  
220 75.6% at 2 years (Table 1) and we predict 123 rehospitalisations for the Propaten<sup>®</sup> grafts  
221 group.

222

### 223 Costs of treatment using standard PTFE and Propaten<sup>®</sup>

224 The MIIC from the payer perspective was €12 290 (95%CI : €11 118 - €13 386) per patient  
225 (Total initial intervention costs: €8 062 382). Most patients (99%) belonged to the DRG for  
226 major revascularization surgeries (DRG 05C10). The MRC from the payer perspective was  
227 €10 689 (95%CI : € 9 464 - € 12 072) . Two-year total hospitalization cost from the national  
228 insurance perspective for the 656 patients with standard PTFE grafts was €9 008 321.  
229 Assuming treatment with only Propaten<sup>®</sup> grafts for the 656 patients from 2011, 2-year total  
230 hospital reimbursement costs would have been €9 130 998. Assuming treatment with only

231 Propaten<sup>®</sup> grafts for the 656 patients from 2011, 2-year total hospital reimbursement costs  
232 would have been 10 822 598 €.

233

#### 234 **Budget Impact Analysis (Table 4)**

235 Under the base case assumptions (Table 2), we calculated a difference in MIIC of 502 173 €  
236 in favor of standard PTFE grafts over a 5-year period (Table 4).

237 **Table 4:** Budget impact comparison. A *plus* sign indicates an increase in costs, a *minus* sign  
238 shows savings.

Year	PTFE alone	Propaten + PTFE					Total cost (€)	Cost difference
	Total costs (€)	PTFE grafts	Propaten grafts	Initial additional cost (€)	RH	RH avoided		
1	€9 008 321	558	98	€61 439	85	4	€9 027 006	€18 685
2	€9 857 540	519	130	€81 501	167	9	€9 837 500	€-20 040
3	€9 762 422	482	161	€100 936	162	12	€9 735 095	€-27 327
4	€9 672 648	446	191	€119 744	158	15	€9 637 408	€-35 240
5	€9 570 583	409	221	€138 552	154	17	€9 522 086	€-48 498
Total	€47 871 515	2 414	801	€502 173	726	57	€47 759 095	€-112 420

239 PTFE: polytetrafluoroethylen; RH: Rehospitalization

240 We projected a cumulative population of 3 215 patients over 5 years, of which 801 would  
241 have received a Propaten<sup>®</sup> graft. At 5 years, we would have avoided 57 rehospitalizations,  
242 resulting in a saving costs of €614 593 in favor of Propaten<sup>®</sup> grafts. The amount of savings  
243 due to fewer rehospitalizations offset the difference in MIIC as soon as the 2<sup>nd</sup> year.  
244 Assuming a 15% market penetration during the 1<sup>st</sup> year and then 5% fixed market penetration  
245 (35% over the 5 years), the total difference between the observed standard PTFE and assumed

246 Propaten<sup>®</sup> + PTFE courses was estimated at €112 420 , in favor of Propaten<sup>®</sup> grafts, from the  
 247 FNHI perspective.

248

## 249 Sensitivity analysis (Figure 2)

### 250 *Univariate analysis*

251 Primary patency for Propaten<sup>®</sup> had a strong impact on budget results. Using the lower rate of  
 252 primary patency at 2 years (worst case), the additional cost was €486 140. On the contrary,  
 253 using the higher patency rate (best case), the saving was €636 160. For PTFE grafts, a  
 254 primary patency closer to the values found in the literature (47%) increased the savings  
 255 allowed by Propaten<sup>®</sup> grafts (4). The market price for Propaten<sup>®</sup> grafts (initial intervention  
 256 additional cost) had comparatively little impact on the 5-year budget balance and so did MRC  
 257 when including further rehospitalizations. A cheaper graft or a higher MRC led to higher 5-  
 258 year savings.

### 259 *Scenario analysis (Table 5)*

260 Our worst and best case showed the variability of the budget impact of Propaten<sup>®</sup> grafts with  
 261 a difference of more than 2.4 million euros.

262 **Table 5:** Results of the scenario analysis.

	Base case	Best case	Worst case
PTFE	64,9%	47,0%	64,9%
Propaten	75,6%	85,0%	64,9%
MRC	€10 689,00	€12 072,00	€9 464,00
5-year Budget Impact	-€112 419,75	€1 942 406,40	-€502 173,60

263 PTFE: polytetrafluoroethylen; MRC: mean rehospitalizations cost.

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3 264 **DISCUSSION**

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10 267 Our model-based analysis showed the 5-year budget impact for the diffusion of Propaten<sup>®</sup> in  
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12 268 replacement of standard PTFE to be cost-saving. This is a strong economic incentive in favor  
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14 269 of both a widespread use and the enactment of a reimbursement policy for Propaten<sup>®</sup> grafts.  
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18 270 Our modeling approach was founded on a set of assumptions that deserve mention.  
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20 271 The centralized structure of the French Health Information system allows for low-cost studies  
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22 272 with exhaustive data on the French population, thus producing results with a high statistical  
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24 273 power and negligible sampling fluctuations.  
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28 274 Few articles on Propaten<sup>®</sup> grafts presented 2-year primary patency for BTK bypasses in the  
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30 275 general population, and the level of their clinical evidence was limited. We excluded two  
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32 276 articles because of the epidemiological profile (diabetes, renal failure) of their populations,  
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34 277 which were associated with higher morbimortality and lower patency rates overall. Usually  
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36 278 patients with BTK bypasses represent a homogeneous group of patients with critical limb  
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38 279 ischemia in comparison to above the knee bypass, which could be realized for claudicants or  
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40 280 CLI patients. Furthermore no article presented specific results on BTK bypasses in critically  
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42 281 ischemic patients, and two articles had better outcomes for BTK than above-the-knee  
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44 282 revascularization. This usually is not the case in lower limb bypasses, and could be partially  
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46 283 explained by important sampling fluctuations due to their small sample sizes. As there was no  
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48 284 other available data, we chose to use reasonably unfavorable hypotheses in our analyses to  
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50 285 compensate for these shortcomings and thus strengthen the overall conclusion.  
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3 286 As our sensitivity analysis showed, our conclusions are tied to both the effectiveness of  
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5 287 Propaten<sup>®</sup> grafts and the comparative lack of effectiveness of standard PTFE grafts. The  
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7 288 observed 2-year primary patency for standard PTFE grafts is about 35% higher than usually  
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9 289 described (4). Most clinical studies follow their patients more thoroughly than it is the case in  
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11 290 daily care. This is the cause of a follow-up bias in our study, due to the use of reintervention  
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13 291 as a measure of loss of patency, which overestimate the patency for standard PTFE grafts.  
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15 292 Indeed, in the case of an occluded graft, reintervention and/or amputation are not  
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17 293 systematically performed because the patient is asymptomatic or because a palliative  
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19 294 treatment is decided. These types of health consumptions are not logged in the PMSI database  
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21 295 and as we used intervention-specific codes, we estimated the 2-year primary patency for  
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23 296 standard PTFE grafts using only patients with lower limb vascular surgical interventions. The  
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25 297 patients lost because of our method of follow-up would only ramp up the costs of the standard  
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27 298 PTFE course of action.

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31 299 We used hospital reimbursement costs only, as they are likely to be cost-drivers in a surgical  
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33 300 course of action. Unavailable costs included those for non-hospital medical consultations and  
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35 301 care, which are likely to decrease with a more effective Propaten<sup>®</sup> graft. Likewise, the  
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37 302 exclusion of readmissions past the first one may only have lessened the difference in costs  
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39 303 between the two types of grafts. It was anyhow not an option to use these readmissions, given  
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41 304 the uncertainty on limb side and the lack of available data.

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45 305 Our scenario analysis showed the extent of the potential budget impact that would follow the  
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47 306 globalization of Propaten<sup>®</sup> use for BTK bypasses in France. Unfortunately, the uncertainty  
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49 307 around the 2-year primary patency translated to an extensive range for its budget impact. The  
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51 308 worst-case scenario assumed that Propaten<sup>®</sup> grafts were no more effective than standard



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3 309 PTFE grafts in our population, which is pessimistic, but for which the likelihood does not  
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5 310 seem quantifiable.  
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8 311 Finally, even though we based our model on French data and tariffication, it can be used for  
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10 312 any DRG-based system to estimate the budget impact of Propaten<sup>®</sup> reimbursement.  
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3 313 **CONCLUSION**  
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11 316 At current times of resource allocation rationalization, every innovation in healthcare must  
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13 317 pass tests of both clinical and economic value. Propaten<sup>®</sup> grafts have shown their clinical  
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15 318 effectiveness, but had yet to be proven economically attractive.  
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18 319 In this paper, we used existing clinical proof to show that Propaten<sup>®</sup> grafts in patients with  
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20 320 CLI needing a BTK bypass would be financially beneficial for the French NHI in most cases.  
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22 321 The decision to specifically reimburse Propaten<sup>®</sup> at its market price dictates the extent of its  
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24 322 use throughout France, as few hospitals can afford it in a DRG-based system, which does not  
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26 323 allow them to benefit directly from the increased primary patency. Based on our hypotheses  
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28 324 and analysis we conclude that a reimbursement policy would benefit both the French NHI and  
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30 325 the patients. Our model allows performing of the same analysis in other countries using local  
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32 326 cost and clinical effectiveness data providing they have a similar reimbursement system.  
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36 327 Future research ought to focus on directly comparing standard PTFE and Propaten<sup>®</sup> grafts in  
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38 328 order to confirm its probable cost-effectiveness dominance.  
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3 329 **ACKNOWLEDGEMENTS**

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10 332 The data extracted from the PMSI was supplied by the French Medical Information Agency  
11  
12 333 (ATIH) and was used under agreement with the French data protection authority (CNIL) with  
13  
14 334 the authorization numbers DE-2011-066 and 2015-064. Only authorized and discretion-bound  
15  
16  
17 335 personnel handled this data.

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20 336 The model was created using Microsoft<sup>®</sup> Excel<sup>®</sup>.

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3 337 **CONFLICT OF INTEREST**

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10 340 This research was carried out with financial support from WL Gore<sup>®</sup>.

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343 **REFERENCES**

344

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346 1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-  
347 Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J*  
348 *Vasc Endovasc Surg Off J Eur Soc Vasc Surg*. 2007;33 Suppl 1:S1-75.

349 2. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al.  
350 Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011  
351 ACCF/AHA Guideline Recommendations) A Report of the American College of  
352 Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.  
353 *Circulation*. 2013 Apr 2;127(13):1425–43.

354 3. Setacci C, de Donato G, Teraa M, Moll FL, Ricco J-B, Becker F, et al. Chapter IV:  
355 Treatment of Critical Limb Ischaemia. *Eur J Vasc Endovasc Surg*. 2011 Dec;42,  
356 Supplement 2:S43–59.

357 4. Albers M, Battistella VM, Romiti M, Rodrigues AAE, Pereira CAB. Meta-analysis of  
358 polytetrafluoroethylene bypass grafts to infrapopliteal arteries1. *J Vasc Surg*. 2003  
359 Jun;37(6):1263–9.

360 5. Jackson MR, Belott TP, Dickason T, Kaiser WJ, Modrall JG, Valentine RJ, et al. The  
361 consequences of a failed femoropopliteal bypass grafting: Comparison of saphenous  
362 vein and PTFE grafts. *J Vasc Surg*. 2000 Sep;32(3):498–505.

363 6. Lindholt JS, Gottschalksen B, Johannesen N, Dueholm D, Ravn H, Christensen ED, et  
364 al. The Scandinavian Propaten(®) trial - 1-year patency of PTFE vascular prostheses  
365 with heparin-bonded luminal surfaces compared to ordinary pure PTFE vascular

- 1  
2  
3 366 prostheses - a randomised clinical controlled multi-centre trial. *Eur J Vasc Endovasc*  
4 367 *Surg Off J Eur Soc Vasc Surg*. 2011 May;41(5):668–73.
- 5  
6  
7 368 7. Lindholt JS, Houlind K, Gottschalksen B, Pedersen CN, Ravn H, Viddal B, et al. Five-  
8 369 year outcomes following a randomized trial of femorofemoral and femoropopliteal  
9 370 bypass grafting with heparin-bonded or standard polytetrafluoroethylene grafts. *Br J*  
10 371 *Surg*. 2016 Sep;103(10):1300–5.
- 11  
12  
13 372 8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting  
14 373 Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*.  
15 374 2009 Jul 21;6(7):e1000097.
- 16  
17  
18 375 9. Dorigo W, Pulli R, Castelli P, Dorrucchi V, Ferilli F, De Blasis G, et al. A multicenter  
19 376 comparison between autologous saphenous vein and heparin-bonded expanded  
20 377 polytetrafluoroethylene (ePTFE) graft in the treatment of critical limb ischemia in  
21 378 diabetics. *J Vasc Surg*. 2011 Nov;54(5):1332–8.
- 22  
23  
24 379 10. Lösel-Sadée H, Alefelder C. Heparin-bonded expanded polytetrafluoroethylene graft for  
25 380 infragenicular bypass: five-year results. *J Cardiovasc Surg (Torino)*. 2009  
26 381 Jun;50(3):339–43.
- 27  
28  
29 382 11. Diehm N, Shang A, Silvestro A, Do D-D, Dick F, Schmidli J, et al. Association of  
30 383 Cardiovascular Risk Factors with Pattern of Lower Limb Atherosclerosis in 2659  
31 384 Patients Undergoing Angioplasty. *Eur J Vasc Endovasc Surg*. 2006 Jan;31(1):59–63.
- 32  
33  
34 385 12. Wasmuth S, Baumgartner I, Do D-D, Willenberg T, Saguner A, Zwahlen M, et al. Renal  
35 386 Insufficiency is Independently Associated with a Distal Distribution Pattern of  
36 387 Symptomatic Lower-limb Atherosclerosis. *Eur J Vasc Endovasc Surg*. 2010  
37 388 May;39(5):591–6.
- 38  
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3 389 13. Dorigo W, Di Carlo F, Troisi N, Pratesi G, Innocenti AA, Pulli R, et al. Lower limb  
4 390 revascularization with a new bioactive prosthetic graft: early and late results. *Ann Vasc*  
5 391 *Surg.* 2008 Jan;22(1):79–87.
- 6  
7  
8  
9 392 14. Peeters P, Verbist J, Deloose K, Bosiers M. Results with heparin bonded  
10 393 polytetrafluoroethylene grafts for femorodistal bypasses. *J Cardiovasc Surg Torino.*  
11 394 2006 Aug;47(4):407–13.
- 12  
13  
14  
15 395 15. Walluscheck KP, Bierkandt S, Brandt M, Cremer J. Infrainguinal ePTFE vascular graft  
16 396 with bioactive surface heparin bonding. First clinical results. *J Cardiovasc Surg Torino.*  
17 397 2005 Aug;46(4):425–30.
- 18  
19  
20  
21 398 16. Dorrucchi V, Griselli F, Petralia G, Spinamano L, Adornetto R. Heparin-bonded expanded  
22 399 polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb  
23 400 ischemia: 2-year results. 2008 Apr;49–2.
- 24  
25  
26  
27 401 17. Daenens K, Schepers S, Fourneau I, Houthoofd S, Nevelsteen A. Heparin-bonded  
28 402 ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses:  
29 403 1- and 2-year results. *J Vasc Surg.* 2009 May;49(5):1210–6.
- 30  
31  
32  
33 404 18. Samson RH, Morales R, Showalter DP, Lepore MR, Nair DG. Heparin-bonded  
34 405 expanded polytetrafluoroethylene femoropopliteal bypass grafts outperform expanded  
35 406 polytetrafluoroethylene grafts without heparin in a long-term comparison. *J Vasc Surg.*  
36 407 2016 Sep;64(3):638–47.
- 37  
38  
39  
40 408 19. Statistics from the French Medical Information Agency (ATIH [Internet]. ScanSanté.  
41 409 [cited 2016 Jan 8]. Available from: <http://www.scansante.fr/>
- 42  
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45 410 20. Conte MS. Understanding Objective Performance Goals for Critical Limb Ischemia  
46 411 *Trials. Semin Vasc Surg.* 2010 Sep;23(3):129–37.

- 1  
2  
3 412 21. de Vries SO, Donaldson MC, Hunink MGM. Contralateral symptoms after unilateral  
4 413 intervention for peripheral occlusive disease. *J Vasc Surg.* 1998 Mar;27(3):414–21.  
5  
6  
7 414 22. Martini R, Andreozzi GM, Deri A, Cordova R, Zulian P, Scarpazza O, et al. Amputation  
8 415 rate and mortality in elderly patients with critical limb ischemia not suitable for  
9 416 revascularization. *Aging Clin Exp Res.* 2012 Jun;24(3 Suppl):24–7.  
10  
11  
12  
13  
14 417 23. De Cock E, Sapoval M, Julia P, de Lissovoy G, Lopes S. A Budget Impact Model for  
15 418 Paclitaxel-eluting Stent in Femoropopliteal Disease in France. *Cardiovasc Intervent*  
16 419 *Radiol.* 2013 Apr;36(2):362–70.  
17  
18  
19  
20  
21 420 24. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al.  
22 421 Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012  
23 422 Budget Impact Analysis Good Practice II Task Force. *Value Health.* 2014 Jan;17(1):5–  
24 423 14.  
25  
26  
27  
28  
29  
30 424 25. Shah AP, Klein AJ, Sterrett A, Messenger JC, Albert S, Nehler MR, et al. Clinical  
31 425 outcomes using aggressive approach to anatomic screening and endovascular  
32 426 revascularization in a veterans affairs population with critical limb ischemia. *Catheter*  
33 427 *Cardiovasc Interv.* 2009 Jul;74(1):11–9.  
34  
35  
36  
37  
38  
39 428 26. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-Eluting Balloon in  
40 429 Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) A  
41 430 Randomized Trial in Diabetic Patients With Critical Limb Ischemia. *Circulation.* 2013  
42 431 Aug 6;128(6):615–21.  
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3 432 **FIGURE**

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10 435 Figure 1: Patients extraction process using the French expenditure database

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13 436 PTFE: polytetrafluoroethylen; BTK: below the knee

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18 438 Figure 2: Tornado diagram representing the variation of the 5-year budget balance depending  
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21 439 on 5 hypotheses. A negative balance indicates a cost-save.

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24 440 Costs are in euros (€). Positive costs indicate savings, negative costs indicate a cost increase.

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3 441 **AUTHOR'S CONTRIBUTION**  
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8 443 Simon Vergnaud: Conception and Design, Analysis and interpretation, Data collection,  
9 444 Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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13 446 Valéry-Pierre Riche: Conception and Design, Analysis and interpretation, Data collection,  
14 447 Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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18 449 Philippe Tessier: Conception and Design, Analysis and interpretation, Data collection, Writing  
19 450 the manuscript, Critical revision of the manuscript, Statistical Analysis

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23 452 Nicolas Mauduit: Analysis and interpretation, Data collection, Writing the manuscript, Critical  
24 453 revision of the manuscript

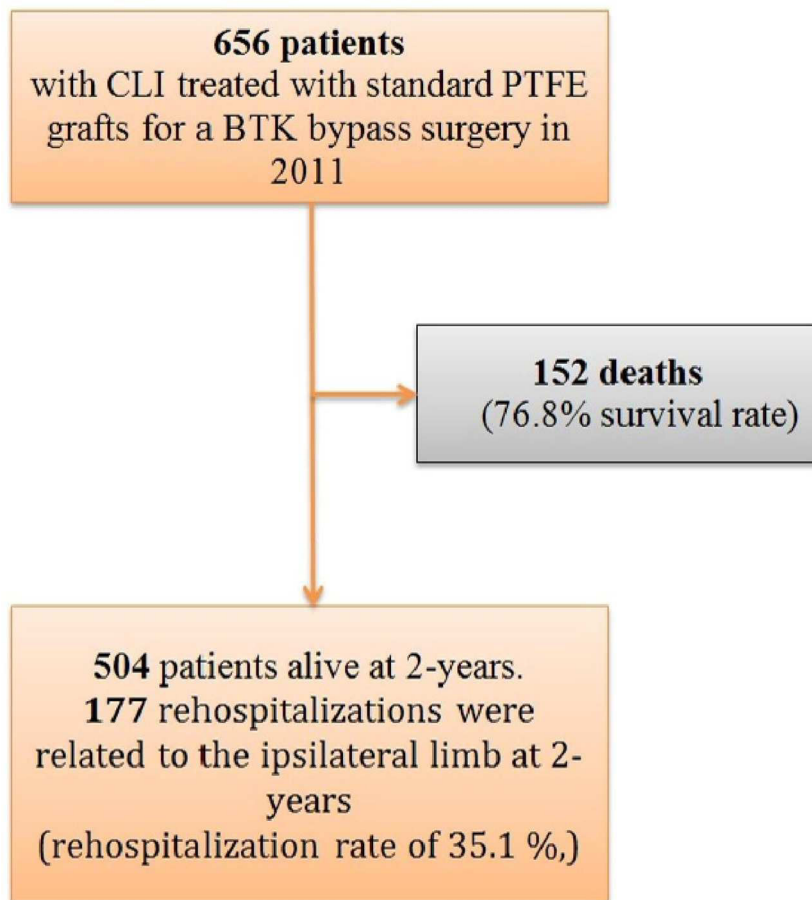
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28 455 Adrien Kaladji: Analysis and interpretation, Writing the manuscript, Critical revision of the  
29 456 manuscript

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33 458 Yann Gouëffic: Conception and Design, Analysis and interpretation, Writing the manuscript,  
34 459 Critical revision of the manuscript, Obtaining funding

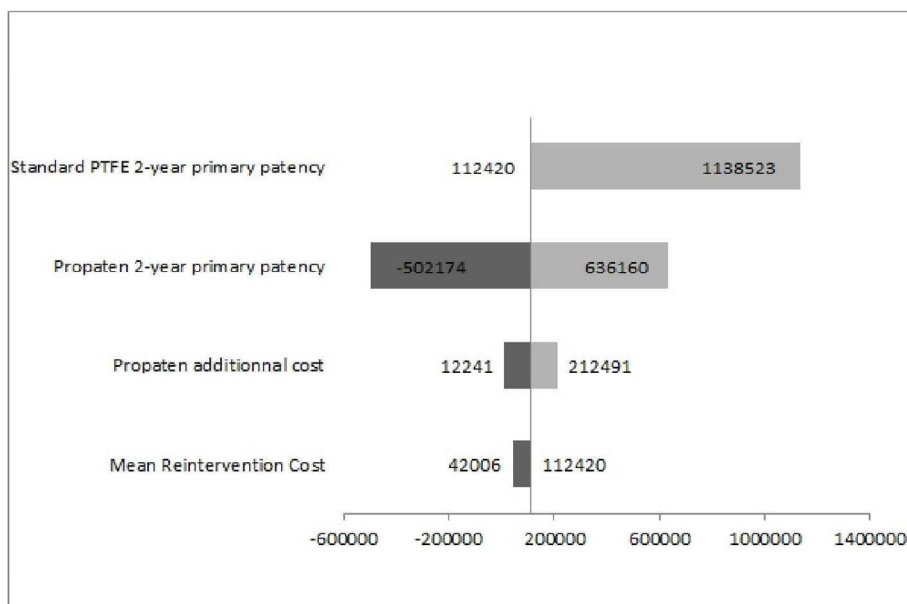
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Patients extraction process using the French expenditure database

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Tornado diagram representing the variation of the 5-year budget balance depending on 5 hypotheses. A negative balance indicates a cost-save

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		Line		Checklist-Criteria
<b>Study design</b>			<b>Study question</b>	
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		1.1	96-97	The research question is stated (e.g. are alternatives compared?)
		1.2	Intro	The (economic) importance of the research question is stated (both cost and effects?)
		1.3	100	The viewpoint(s) of the analysis are clearly stated and justified
	2			<b>Selection of alternatives</b>
		2.1	Intro	The rationale (Begründung) for choosing the alternatives compared is stated (alternatives omitted?)
		2.2	96-97	The alternatives being compared are clearly described
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		3.1	100	The form of economic evaluation used is stated
	3.2	Yes	The choice of form of economic evaluation is justified i.r.t. the questions addressed	
<b>Data collection</b>	4			<b>Effectiveness data</b>
		4.1	107-118	The source(s) of effectiveness estimates used are stated (effectiveness established?)
		4.2	133-144	Details of design and results of effectiveness study are given (if based on single study)
		4.3	107-118	Details of method of synthesis of estimates are given (if based on overview of effectiveness studies)
	5			<b>Benefit measurement and valuation</b>
		5.1	166-170	The primary outcome measure(s) for the economic evaluation are clearly stated
		5.2	NA	Methods to value health states and other benefits are stated
		5.3	121-131	Details of the subjects from whom valuations were obtained are given
		5.4	NA	Productivity changes (if included) are reported separately
		5.5	NA	The relevance of productivity changes to the study question is discussed
	6			<b>Costing</b>
		6.1	NA	Cost range is wide enough
		6.2	142-143	Quantities of resources are reported separately from their unit costs
		6.3	146-163	Methods for the estimation of quantities and unit costs are described
		6.4	142-143	Currency (Währung) and price data are recorded
		6.5	NA	Details of currency of price adjustments for inflation or currency conversion are given
	7			<b>Modelling</b>
		7.1	133-144	Details of any model used are given
		7.11	133-141	Is the Model used a decision analytic Model
		7.111	NA	The Model used is a Markov Modell
	7.112	133-141	The Model used is a decision tree	
	7.113	NA	The Numer of cycles is stated	
	7.114	174	The cycle length is stated	
	7.115	Yes	The correct assumption for the Model are choosen	
	7.116	118-119	The appropriate distribution for the Parameter of the Model are choosen	
	7.12	185-205	Is a Sensitivity Analysis in the Model implemented	

		7.121	119-120		The References for the used Distributions are stated
		7.122	115-120		The Calculation for the parameter of distribution are stated
		7.123	NA		A Monte Carlo Simulation is implemented
		7.2	165-183		The choice of model used and the key parameters on which it is based are justified
<b>Analysis and interpretation of Results</b>	8			<b>Adjustments for timing of costs and benefits</b>	
		8.1	173		Time horizon of costs and benefits is stated
		8.2	NA	No discount in BIA	The discount rate(s) is stated
		8.3	NA		The choice of rate(s) is justified
		8.4	NA		An explanation is given if costs or benefits are not discounted
	9			<b>Allowance for uncertainty</b>	
		9.1	NA		Details of statistical tests are given for stochastic data (incl. CI and p-values)
		9.11	209-221		Descriptive statistics
		9.12	233-247		Predictive Statistics
		9.2	185-205		The approach to sensitivity analysis is given
		9.3	185-205		The choice of variables for sensitivity analysis is justified
		9.4	262-263		The ranges over which the variables are varied are stated
	10			<b>Presentation of results and discussion</b>	
		10.1	Yes		Relevant alternatives are compared
		10.2	238-242		Incremental analysis is reported
		10.3	Yes		Major outcomes are presented in a disaggregated as well as aggregated form
		10.4	246-247		The answer to the study question is given
		10.5	Yes		Conclusions follow from the data reported
	10.6	NA		Comparison made with relevant other studies (regarding costs, effects, ICER)	
	10.7	311-312		Discussion on generalizability of results	
	10.8	327-328		Conclusions are accompanied by the appropriate caveats (incl. other important factors)	

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# BMJ Open

## Budget impact analysis of heparin-bonded polytetrafluoroethylen grafts (Propaten®) against standard polytetrafluoroethylen grafts for below the knee bypass in patients with critical limb ischemia in France.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017320.R2
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Date Submitted by the Author:	05-Dec-2017
Complete List of Authors:	Vergnaud, Simon; Centre Hospitalier Universitaire de Nantes Riche, Valéry-Pierre; CHU de Nantes, Research Direction Tessier, Philippe; Universite de Nantes - Faculte de Medicine Mauduit, Nicolas; CHU de Nantes Kaladji, Adrien; Centre Hospitalier Universitaire de Rennes Gouëffic, Yan ; Universite de Nantes - Faculte de Medicine; Inserm-UN, Laboratoire de Physiopathologie de la Résorption Osseuse
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Health economics
Keywords:	Critical limb ischemia, Bypass, Heparin-bonded graft, Below the knee, Budget impact analysis

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Manuscripts

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3 1 **TITLE PAGE**

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6 2 **Budget impact analysis of heparin-bonded polytetrafluoroethylen grafts (Propaten®) against**  
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8 3 **standard polytetrafluoroethylen grafts for below the knee bypass in patients with critical limb**  
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10 4 **ischemia in France**

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17 7 Simon Vergnaud<sup>1,3</sup>, Valéry-Pierre Riche<sup>1</sup>, Philippe Tessier<sup>1,2</sup>, Nicolas Mauduit<sup>3</sup>, Adrien  
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9 27 **Words count: 3 323**

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3 28 **ABSTRACT**  
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8 29 **Objectives:** To evaluate the budget impact of progressive replacement of standard  
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10 30 polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten<sup>®</sup>) for below-the-knee  
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12 31 (BTK) bypass in patients with critical limb ischemia (CLI).

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15 32 **Design:** From a review of the scientific literature we calculated a theoretical BTK primary  
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17 33 patency for Propaten<sup>®</sup> grafts. Using the French hospital expenditure database (PMSI), we  
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19 34 retrospectively estimated a rehospitalization rate for standard PTFE grafts. From these data, a  
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21 35 model was created to assess the budget impact of a progressive replacement from standard  
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23 36 PTFE grafts to Propaten<sup>®</sup> grafts over a 5-year horizon. We performed an univariate sensitivity  
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25 37 analysis to assess the robustness of our results.

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29 38 **Setting:** French National Health Insurance (FNHI) perspective.

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32 39 **Participant:** Patients with CLI.

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35 40 **Main outcome measures:** Budget impact analysis

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38 41 **Results:** Data extraction from the PMSI revealed that 656 patients were treated with PTFE  
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40 42 grafts in 2011 in French public hospitals for a BTK bypass. Assuming a 2-year survival rate  
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42 43 of 76.8 %, observed reinterventions rate for standard PTFE grafts at 24 months from the  
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44 44 PMSI was 35.1%. The mean rehospitalization cost was €10 689. The budget impact analysis  
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46 45 based on these data found a net cumulative 5-year payer budget reduction of €112 420 in  
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48 46 favor of Propaten<sup>®</sup>, under the assumption of a 75.6 % primary patency for Propaten<sup>®</sup> grafts  
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50 47 for a projected population of 3 215 patients of which 801 received a Propaten<sup>®</sup> graft.  
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3 48 **Conclusions:** Our budget impact analysis showed a positive impact on the national health  
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5 49 insurance budget of the replacement of standard PTFE grafts by Propaten® grafts for below  
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7 50 the knee bypass in patients with CLI in France. This supports the enactment of a  
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9 51 reimbursement policy by the FNHI.  
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3 **52 Strengths and limitations of this study**  
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6 53 • The budget impact analysis provides further evidence to adopt and to reimburse the  
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8 54 device for decision-makers.  
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10 55 • PMSI database allows for studies with exhaustive data on the French population, thus  
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12 56 producing results with a high statistical power and negligible sampling fluctuations.  
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14 57 • However, only patients with critical limb ischemia and initially treated by standard  
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16 58 PTFE in public hospital could be identified in the PMSI database, underestimating the  
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18 59 results of the study.  
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21 60 • Clinical factors potentially influencing patterns of practice, office-based consumption of  
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23 61 cares, and non-reimbursable items and medicines could not be analyzed.  
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## 62 INTRODUCTION

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65 Patients with critical limb ischemia (CLI) are at risk of limb amputation. Consequently, a  
66 revascularization should be performed as soon as possible in order to save the limb (1). To  
67 realize the revascularization, two options should be considered: endovascular or open repair.

68 So far, despite the lack of consensus, open repair could be recommended in a first line of  
69 treatment to re-vascularize CLI patients (2) or performed in a second line of treatment in case  
70 of failure of endovascular repair (3). In the event of open surgery, a vein should be used as  
71 conduit to perform the bypass, especially in the case of infrapopliteal lesions. A suitable vein  
72 is one of the main factors that determine the clinical success of open revascularization for  
73 below the knee (BTK) popliteal and distal bypass (1). Unfortunately, a suitable venous  
74 conduit is not available in more than 20% of the cases (2). In these patients, prosthesis such as  
75 standard polytetrafluoroethylene (PTFE) graft demonstrated worse clinical and morphological  
76 results and more severe consequences in case of occlusion (4,5). Consequently, there is still a  
77 room for improvement in CLI patients in the absence of a suitable conduit and in whom  
78 endovascular repair failed. In these patients, prostheses with heparin-bound to the luminal  
79 surface could improve standard prosthesis results. In 2011, Lindholt et al. reported the results  
80 of a multicenter randomized trial comparing heparin-bound PTFE (Propaten<sup>®</sup>, Flagstaff, AZ,  
81 USA) grafts with those of standard PTFE grafts (6). In total, 546 patients had 1-year follow-  
82 up (standard PTFE: 272; Propaten<sup>®</sup>: 274). Propaten<sup>®</sup> graft significantly reduced the overall  
83 risk of primary graft failure by 37% at one year from the intervention. Specifically, risk  
84 reduction reached 50% in femoropopliteal bypass for patients with CLI. Moreover, after 5  
85 years, patients receiving Propaten<sup>®</sup> grafts for CLI were more likely to have a patent graft than  
86 those with standard PTFE grafts.(7)

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3 87 However, to date, the financial impact of Propaten<sup>®</sup> use on health care spending was not  
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5 88 assessed. Using data from the literature and from the French hospital expenditure database  
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7 89 (PMSI), we assess the financial impact of a progressive replacement of standard PTFE by  
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9 90 Propaten<sup>®</sup> on a 5-year timeline from the payer perspective, for BTK bypass in patients with  
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## 92 **METHODS**

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### 95 **Analytic Overview**

96 Our aim was to compare the usual course of action taken by French surgeons for BTK bypass  
97 surgery, using standard PTFE grafts, to a similar course of action using Propaten<sup>®</sup> grafts, in  
98 order to assess the latter's economical impact. We combined clinical data based on a review  
99 from the literature and retrospective data about hospital stays from the PMSI to feed a cost  
100 model from a third party payer perspective and to perform a budget impact analysis. No  
101 change in our clinical practice and no randomization occurred. As our model was based on an  
102 observational retrospective analysis of data, according to the French legislation (articles  
103 L.1121-1 paragraph 1 and R1121-2, Code de la Santé Publique), approval of an ethics  
104 committee was not required for use of the data in an epidemiologic study.

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### 106 **Evidence acquisition**

107 Our search strategy was based on Preferred reporting items for systematic reviews and Meta-  
108 analyses (PrisMa) guidelines, with the help of PrisMa statement and explanation &  
109 elaboration documents (8). We used Medline register to conduct our bibliography. The  
110 following terms were added to the search builder using Mesh: below the knee, bypass,  
111 surgery, Propaten<sup>®</sup>, grafts, 2-years, primary patency, critical limb ischemia. One study was  
112 excluded because it focused exclusively on diabetics (9). Another was found to have an  
113 outlying rate of renal insufficiency (10). Indeed, we considered that outlying rate of diabetes  
114 and renal insufficiency could alter too much the outcomes in regards to perioperative  
115 outcomes and pattern of atherosclerotic disease (11), (12). We assigned each study a weight ,

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116 assuming a fixed-effect model. (Table 1). Our estimate of the 2-year BTK primary patency for  
117 Propaten<sup>®</sup> grafts was 75.6%, ranging from 70.8% to 85%.

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118 **Table 1:** Detailed review of the literature of the Propaten<sup>®</sup> patency rate at 2-years

Study	Date	Authors	Patients (n)	2-year Primary Patency
Lower limb revascularization with a new bioactive Prosthetic graft: Early and late results	2008	Dorigo et al. (13)	34	80.0%
Results with heparin-bonded polytetrafluoroethylene grafts for femorodistal bypasses	2006	Peeters et al.(14)	41	72.0%
Infrainguinal ePTFE vascular graft with bioactive surface heparin bonding	2005	Walluscheck et al. (15)	17	81.8%
Heparin-bonded expanded polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb ischemia: 2-year results	2008	Dorrucci et al. (16)	20	85.0%
Heparin-bonded ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses: 1- and 2-year results	2009	Daenens et al. (17)	57	83.0%
Heparin-bonded expanded PTFE femoropopliteal bypass grafts outperform expanded PTFE grafts without heparin in a long-term comparison	2016	Samson et al. (18)	42	71.4%

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## 120 **Source population**

121 From a retrospective analysis on hospital stays during 2011 using the PMSI, we identified  
122 patients who were admitted for a BTK bypass surgery, where a standard PTFE graft was used.  
123 In France, only CLI patients have this surgery, where using a standard PTFE graft is the usual  
124 choice (French medical information agency –ATI– online data)(19). Therefore, no analysis  
125 was conducted on other types of grafts. Propaten® grafts were not available in France in 2011.  
126 Patients under 18 years old were excluded since bypasses in this population are not indicated  
127 to treat an atheromatous disease but to revascularize a lower limb for an inflammatory arterial  
128 disease or an arterial traumatism. Patients having been operated upon for a BTK bypass  
129 surgery in the two years prior were excluded as well as to exclude reinterventions from index  
130 cases. The data included the reference of the diagnosis related groups (DRGs), the type of  
131 bypass grafts used, the duration of stays, the time spent in intensive care unit as well as the  
132 patient's comorbidities. Patients were followed for 24 months.(20)

## 134 **The population model (Table 2)**

135 First of all, the follow up of the source population was determined. Rehospitalization in  
136 relation to the standard PTFE was determined by a retrospective analysis on hospital stays for  
137 our source population during the 24 months following the initial surgery. The follow up of the  
138 source population was adjusted for 2-year mortality and contralateral reintervention.(21,22).  
139 Loss of patency was defined by a hospital stay for a lower limb reintervention hereafter called  
140 the first rehospitalization. These lower limb interventions included angioplasties, major  
141 amputations, thrombectomies, ablations of vascular grafts, stent placements and in situ  
142 fibrinolysis.

143 **Table 2:** Values fed to the model and their sources.

Clinical Data	Values	Sources
First rehospitalization rate due to graft of interest	35.1% (177/504)	French rehospitalization data, adjusted for mortality (22) and contralateral reintervention (21)
Added primary patency for Propaten grafts:	75.6%	Own calculations (Evidence acquisition)
Cost Estimates		
Mean initial intervention cost	€12,290	Own calculations (PMSI-based)
Rehospitalization mean cost (one rehospitalization)	€10,689	Own calculations (PMSI-based)
Propaten initial additional cost	€627	WL Gore®
PTFE reimbursement tariff	€639	FNHI online data (19)
Market Data		
Initial Market Penetration	15%	De Cock (23)
Annual Market Penetration Increase	5%	De Cock (23)
Population growth	-1.0%	ATIH (19)

144 **PMSI: french hospital expenditure database; PTFE: polytetrafluoroethylen; FNHI:**  
 145 **french national health insurance**

#### 147 **Retrospective cost estimation for standard PTFE grafts**

148 As we aimed to estimate the budget impact of an official reimbursement policy, we conducted  
 149 our budget impact analysis from the payer perspective (French National Health Insurance,  
 150 FNHI) and estimated costs only from this perspective. Only direct medical costs, covering in-  
 151 patient treatment, were considered. Costs were estimated by the 2015 official tariffs applied to  
 152 the relevant DRGs, for both initial and further hospitalizations. The tariffs provide the amount  
 153 paid by the FNHI to a hospital with respect to each stay, procedure duration and potential  
 154 additional costs, i.e. hospital costs that are reimbursed in addition to the DRG tariff (e.g.  
 155 intensive care). Variability was estimated for both initial and subsequent interventions using a  
 156 bootstrap technique, with a resampling of 100 random samples of 100 patients.

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**158 Cost estimation for Propaten<sup>®</sup> grafts**

159 We estimated the costs for the initial Propaten<sup>®</sup> procedure using the mean initial intervention  
160 cost (MIIC) for standard PTFE grafts added to the cost difference (€627) between Propaten<sup>®</sup>  
161 graft's market price and the reimbursed tariff for standard PTFE grafts. The mean  
162 rehospitalizations cost (MRC) for standard PTFE was used to estimate the mean cost for  
163 Propaten<sup>®</sup> rehospitalizations. Every bypass graft used during rehospitalization stays was  
164 assumed to be a standard PTFE graft.

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**166 Budget impact model:**

167 Our budget impact analysis premised the enactment by the French Health Authorities of a  
168 FNHI reimbursement policy, i.e. additional costs from the initial procedure would be charged  
169 solely to the FNHI. Our base case for the budget impact model used the estimates from our  
170 literature review to estimate a rehospitalization rate for the Propaten<sup>®</sup> implantation for the  
171 2011 PMSI-extracted population. No analysis was conducted on 2-year secondary patency  
172 mainly because of the lack of PMSI data on limb side. Total hospital reimbursement costs for  
173 both procedures were calculated by adding the initial intervention costs with subsequent  
174 rehospitalizations costs. Each year for 5 years, a new cohort of patients entered the model for  
175 duration of 2 years, starting with the 2011 population. The number of patients decrease by a  
176 flat 1.0% annually, i.e. the mean decrease rate between 2011 and 2014 for the DRG  
177 representing 95% of our population as informed in ATIH online data (19). We hypothesized  
178 that the enactment of a reimbursement policy by French Health authorities would result in an  
179 initial market penetration rate of 15% for Propaten<sup>®</sup> grafts, with a subsequent annual increase  
180 of 5 percentage points, meaning that after 5 years, 35% of the grafts in this indication would

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3 181 be Propaten<sup>®</sup> grafts (23). Numerical values corresponding to the hypotheses we made are  
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5 182 presented in Table 2. We based our sensitivity analysis on variation one by one of relevant  
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7 183 variables in order to assess the weight of each hypothesis on the overall behavior of the  
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9 184 model.(24).

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## 13 14 15 186 **Sensitivity analysis**

### 16 17 18 187 *Univariate analysis*

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21 188 We tested the sensitivity of our results to the main hypotheses used in our model by  
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23 189 estimating the budget impact for a range of values. The tested parameters were the 2-year  
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25 190 BTK primary patencies for Propaten<sup>®</sup> and standard PTFE grafts, the mean cost of  
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27 191 rehospitalization and the additional cost of the initial intervention for Propaten<sup>®</sup> grafts. For  
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29 192 Propaten<sup>®</sup> grafts' patency, we used the 2-year primary patency for standard PTFE grafts  
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31 193 found in our population as low end of the range, and the highest reported primary patency (16)  
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33 194 as high end. For PTFE grafts' patency, we used the 2-year primary patency for standard PTFE  
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35 195 grafts found in our population as the high end of the range, and the value found in the  
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37 196 literature (4) as the low end. For the mean cost of rehospitalizations, we used the low and high  
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39 197 values of our 95% confidence interval as low and high ends of the range. Finally, we used  
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41 198 arbitrary values to test for the sensitivity of our results to the price of the Propaten<sup>®</sup> graft.

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### 47 48 200 *Scenario analysis*

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51 201 We estimated the 5-year budget impact in three additional scenarios, describing one  
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53 202 alternative plausible situation and the two extremes. These extreme scenarios are described in

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3 203 Table 3, and either favored (best case) or disfavored (worst case) Propaten® grafts, based on  
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5 204 2-year BTK primary patency for Propaten® grafts, mean cost of rehospitalizations and 2-year  
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7 205 BTK primary patency for standard PTFE grafts. The alternative plausible scenario assumed  
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9 206 that a maximum patency would decrease the mean cost of rehospitalizations.

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12 207 **Table 3:** Worst and best case of the scenario analysis.

	Base case	Best case	Worst case
PTFE	64,9%	47,0%	64,9%
Propaten	75,6%	85,0%	64,9%

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## 209 RESULTS

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### 212 Retrospective database analysis for standard PTFE grafts

213 The retrospective data from the national expenditure database revealed 656 patients with CLI  
214 treated with standard PTFE grafts for a BTK bypass surgery in 2011. Two years later, 152  
215 patients had died and 504 patients were still alive. Among these 504 patients, 189 patients had  
216 been re-hospitalized at 2-years. From the literature (21,25,26), we estimated that 12 of these  
217 patients had had interventions on the contralateral limb only. Consequently, 177 patients were  
218 hospitalized at 2 years for a BTK surgical intervention on the limb of interest, resulting in a  
219 rehospitalization rate of 35.1%, or a 2-year primary patency of 64.9% for standard PTFE  
220 grafts. In the assumed group (treatment with Propaten<sup>®</sup> grafts) the estimated patency rate was  
221 75.6% at 2 years (Table 1) and we predict 123 rehospitalisations for the Propaten<sup>®</sup> grafts  
222 group.

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### 224 Costs of treatment using standard PTFE and Propaten<sup>®</sup>

225 The MIIC from the payer perspective was €12 290 (95%CI : €11 118 - €13 386) per patient  
226 (Total initial intervention costs: €8 062 382). Most patients (99%) belonged to the DRG for  
227 major revascularization surgeries (DRG 05C10). The MRC from the payer perspective was  
228 €10 689 (95%CI : € 9 464 - € 12 072) . Two-year total hospitalization cost from the national  
229 insurance perspective for the 656 patients with standard PTFE grafts was €9 008 321.  
230 Assuming treatment with only Propaten<sup>®</sup> grafts for the 656 patients from 2011, 2-year total  
231 hospital reimbursement costs would have been €9 130 998. Assuming treatment with only

232 Propaten<sup>®</sup> grafts for the 656 patients from 2011, 2-year total hospital reimbursement costs  
233 would have been 10 822 598 €.

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#### 235 **Budget Impact Analysis (Table 4)**

236 Under the base case assumptions (Table 2), we calculated a difference in MIIC of 502 173 €  
237 in favor of standard PTFE grafts over a 5-year period (Table 4).

238 **Table 4:** Budget impact comparison. A *plus* sign indicates an increase in costs, a *minus* sign  
239 shows savings.

Year	PTFE alone	Propaten + PTFE					Total cost (€)	Cost difference
	Total costs (€)	PTFE grafts	Propaten grafts	Initial additional cost (€)	RH	RH avoided		
1	€9 008 321	558	98	€61 439	85	4	€9 027 006	€18 685
2	€9 857 540	519	130	€81 501	167	9	€9 837 500	€-20 040
3	€9 762 422	482	161	€100 936	162	12	€9 735 095	€-27 327
4	€9 672 648	446	191	€119 744	158	15	€9 637 408	€-35 240
5	€9 570 583	409	221	€138 552	154	17	€9 522 086	€-48 498
Total	€47 871 515	2 414	801	€502 173	726	57	€47 759 095	€-112 420

240 PTFE: polytetrafluoroethylen; RH: Rehospitalization

241 We projected a cumulative population of 3 215 patients over 5 years, of which 801 would  
242 have received a Propaten<sup>®</sup> graft. At 5 years, we would have avoided 57 rehospitalizations,  
243 resulting in a saving costs of €614 593 in favor of Propaten<sup>®</sup> grafts. The amount of savings  
244 due to fewer rehospitalizations offset the difference in MIIC as soon as the 2<sup>nd</sup> year.  
245 Assuming a 15% market penetration during the 1<sup>st</sup> year and then 5% fixed market penetration  
246 (35% over the 5 years), the total difference between the observed standard PTFE and assumed



247 Propaten<sup>®</sup> + PTFE courses was estimated at €112 420 , in favor of Propaten<sup>®</sup> grafts, from the  
 248 FNHI perspective.

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## 250 Sensitivity analysis (Figure 1)

### 251 *Univariate analysis*

252 Primary patency for Propaten<sup>®</sup> had a strong impact on budget results. Using the lower rate of  
 253 primary patency at 2 years (worst case), the additional cost was €486 140. On the contrary,  
 254 using the higher patency rate (best case), the saving was €636 160. For PTFE grafts, a  
 255 primary patency closer to the values found in the literature (47%) increased the savings  
 256 allowed by Propaten<sup>®</sup> grafts (4). The market price for Propaten<sup>®</sup> grafts (initial intervention  
 257 additional cost) had comparatively little impact on the 5-year budget balance and so did MRC  
 258 when including further rehospitalizations. A cheaper graft or a higher MRC led to higher 5-  
 259 year savings.

### 260 *Scenario analysis (Table 5)*

261 Our worst and best case showed the variability of the budget impact of Propaten<sup>®</sup> grafts with  
 262 a difference of more than 2.4 million euros.

263 **Table 5:** Results of the scenario analysis.

	Base case	Best case	Worst case
PTFE	64,9%	47,0%	64,9%
Propaten	75,6%	85,0%	64,9%
MRC	€10 689,00	€12 072,00	€9 464,00
5-year Budget Impact	-€112 419,75	€1 942 406,40	-€502 173,60

264 PTFE: polytetrafluoroethylen; MRC: mean rehospitalizations cost.

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3 265 **DISCUSSION**

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10 268 Our model-based analysis showed the 5-year budget impact for the diffusion of Propaten<sup>®</sup> in  
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12 269 replacement of standard PTFE to be cost-saving. This is a strong economic incentive in favor  
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14 270 of both a widespread use and the enactment of a reimbursement policy for Propaten<sup>®</sup> grafts.  
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18 271 Our modeling approach was founded on a set of assumptions that deserve mention.  
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20 272 The centralized structure of the French Health Information system allows for low-cost studies  
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22 273 with exhaustive data on the French population, thus producing results with a high statistical  
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24 274 power and negligible sampling fluctuations.  
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28 275 Few articles on Propaten<sup>®</sup> grafts presented 2-year primary patency for BTK bypasses in the  
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30 276 general population, and the level of their clinical evidence was limited. We excluded two  
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32 277 articles because of the epidemiological profile (diabetes, renal failure) of their populations,  
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34 278 which were associated with higher morbimortality and lower patency rates overall. Usually  
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36 279 patients with BTK bypasses represent a homogeneous group of patients with critical limb  
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38 280 ischemia in comparison to above the knee bypass, which could be realized for claudicants or  
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40 281 CLI patients. Furthermore no article presented specific results on BTK bypasses in critically  
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42 282 ischemic patients, and two articles had better outcomes for BTK than above-the-knee  
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44 283 revascularization. This usually is not the case in lower limb bypasses, and could be partially  
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46 284 explained by important sampling fluctuations due to their small sample sizes. As there was no  
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48 285 other available data, we chose to use reasonably unfavorable hypotheses in our analyses to  
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50 286 compensate for these shortcomings and thus strengthen the overall conclusion. Nevertheless,  
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52 287 as we excluded those two studies, our results should only be considered valid for unselected  
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3 288 CLI populations. In such populations, diabetes, albeit frequent, rarely has a 100% prevalence  
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5 289 rate, and renal insufficiency rates are about half the rate from the Lösel-Sadée study (31,0%)  
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7 290 (9).  
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10 291 As our sensitivity analysis showed, our conclusions are tied to both the effectiveness of  
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12 292 Propaten<sup>®</sup> grafts and the comparative lack of effectiveness of standard PTFE grafts. The  
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14 293 observed 2-year primary patency for standard PTFE grafts is about 35% higher than usually  
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16 294 described (4). Most clinical studies follow their patients more thoroughly than it is the case in  
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18 295 daily care. This is the cause of a follow-up bias in our study, due to the use of reintervention  
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20 296 as a measure of loss of patency, which overestimate the patency for standard PTFE grafts.  
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22 297 Indeed, in the case of an occluded graft, reintervention and/or amputation are not  
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24 298 systematically performed because the patient is asymptomatic or because a palliative  
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26 299 treatment is decided. These types of health consumptions are not logged in the PMSI database  
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28 300 and as we used intervention-specific codes, we estimated the 2-year primary patency for  
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30 301 standard PTFE grafts using only patients with lower limb vascular surgical interventions. The  
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32 302 patients lost because of our method of follow-up would only ramp up the costs of the standard  
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34 303 PTFE course of action.  
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39 304 We used hospital reimbursement costs only, as they are likely to be cost-drivers in a surgical  
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41 305 course of action. Unavailable costs included those for non-hospital medical consultations and  
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43 306 care, which are likely to decrease with a more effective Propaten<sup>®</sup> graft. Likewise, the  
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45 307 exclusion of readmissions past the first one may only have lessened the difference in costs  
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47 308 between the two types of grafts. It was anyhow not an option to use these readmissions, given  
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49 309 the uncertainty on limb side and the lack of available data.  
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52 310 Our scenario analysis showed the extent of the potential budget impact that would follow the  
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54 311 globalization of Propaten<sup>®</sup> use for BTK bypasses in France. Unfortunately, the uncertainty  
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3 312 around the 2-year primary patency translated to an extensive range for its budget impact. The  
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5 313 worst-case scenario assumed that Propaten<sup>®</sup> grafts were no more effective than standard  
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7 314 PTFE grafts in our population, which is pessimistic, but for which the likelihood does not  
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9 315 seem quantifiable.  
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12 316 Finally, even though we based our model on French data and tariffication, it can be used for  
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14 317 any DRG-based system to estimate the budget impact of Propaten<sup>®</sup> reimbursement.  
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3 318 **CONCLUSION**  
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11 321 At current times of resource allocation rationalization, every innovation in healthcare must  
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13 322 pass tests of both clinical and economic value. Propaten<sup>®</sup> grafts have shown their clinical  
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15 323 effectiveness, but had yet to be proven economically attractive.  
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18 324 In this paper, we used existing clinical proof to show that Propaten<sup>®</sup> grafts in patients with  
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20 325 CLI needing a BTK bypass would be financially beneficial for the French NHI in most cases.  
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23 326 The decision to specifically reimburse Propaten<sup>®</sup> at its market price dictates the extent of its  
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25 327 use throughout France, as few hospitals can afford it in a DRG-based system, which does not  
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27 328 allow them to benefit directly from the increased primary patency. Based on our hypotheses  
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29 329 and analysis we conclude that a reimbursement policy would benefit both the French NHI and  
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31 330 the patients. Our model allows performing of the same analysis in other countries using local  
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33 331 cost and clinical effectiveness data providing they have a similar reimbursement system.  
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36 332 Future research ought to focus on directly comparing standard PTFE and Propaten<sup>®</sup> grafts in  
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38 333 order to confirm its probable cost-effectiveness dominance.  
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3 334 **ACKNOWLEDGEMENTS**

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10 337 The data extracted from the PMSI was supplied by the French Medical Information Agency  
11  
12 338 (ATIH) and was used under agreement with the French data protection authority (CNIL) with  
13  
14 339 the authorization numbers DE-2011-066 and 2015-064. Only authorized and discretion-bound  
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17 340 personnel handled this data.

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20 341 The model was created using Microsoft<sup>®</sup> Excel<sup>®</sup>.

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3 342 **CONFLICT OF INTEREST**  
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349 **DATA SHARING STATEMENT**

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352 Data sharing: no additional data available.

For peer review only



353 **REFERENCES**

354

355

- 356 1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-  
357 Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J*  
358 *Vasc Endovasc Surg Off J Eur Soc Vasc Surg*. 2007;33 Suppl 1:S1-75.
- 359 2. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al.  
360 Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011  
361 ACCF/AHA Guideline Recommendations) A Report of the American College of  
362 Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.  
363 *Circulation*. 2013 Apr 2;127(13):1425–43.
- 364 3. Setacci C, de Donato G, Teraa M, Moll FL, Ricco J-B, Becker F, et al. Chapter IV:  
365 Treatment of Critical Limb Ischaemia. *Eur J Vasc Endovasc Surg*. 2011 Dec;42,  
366 Supplement 2:S43–59.
- 367 4. Albers M, Battistella VM, Romiti M, Rodrigues AAE, Pereira CAB. Meta-analysis of  
368 polytetrafluoroethylene bypass grafts to infrapopliteal arteries<sup>1</sup>. *J Vasc Surg*. 2003  
369 Jun;37(6):1263–9.
- 370 5. Jackson MR, Belott TP, Dickason T, Kaiser WJ, Modrall JG, Valentine RJ, et al. The  
371 consequences of a failed femoropopliteal bypass grafting: Comparison of saphenous  
372 vein and PTFE grafts. *J Vasc Surg*. 2000 Sep;32(3):498–505.
- 373 6. Lindholt JS, Gottschalksen B, Johannesen N, Dueholm D, Ravn H, Christensen ED, et  
374 al. The Scandinavian Propaten(®) trial - 1-year patency of PTFE vascular prostheses  
375 with heparin-bonded luminal surfaces compared to ordinary pure PTFE vascular

- 1  
2  
3 376 prostheses - a randomised clinical controlled multi-centre trial. *Eur J Vasc Endovasc*  
4  
5 377 *Surg Off J Eur Soc Vasc Surg*. 2011 May;41(5):668–73.  
6  
7  
8 378 7. Lindholt JS, Houlind K, Gottschalksen B, Pedersen CN, Ravn H, Viddal B, et al. Five-  
9  
10 379 year outcomes following a randomized trial of femorofemoral and femoropopliteal  
11  
12 380 bypass grafting with heparin-bonded or standard polytetrafluoroethylene grafts. *Br J*  
13  
14 381 *Surg*. 2016 Sep;103(10):1300–5.  
15  
16 382 8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting  
17  
18 383 Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*.  
19  
20 384 2009 Jul 21;6(7):e1000097.  
21  
22  
23 385 9. Dorigo W, Pulli R, Castelli P, Dorrucchi V, Ferilli F, De Blasis G, et al. A multicenter  
24  
25 386 comparison between autologous saphenous vein and heparin-bonded expanded  
26  
27 387 polytetrafluoroethylene (ePTFE) graft in the treatment of critical limb ischemia in  
28  
29 388 diabetics. *J Vasc Surg*. 2011 Nov;54(5):1332–8.  
30  
31  
32 389 10. Lösel-Sadée H, Alefelder C. Heparin-bonded expanded polytetrafluoroethylene graft for  
33  
34 390 infragenicular bypass: five-year results. *J Cardiovasc Surg (Torino)*. 2009  
35  
36 391 Jun;50(3):339–43.  
37  
38  
39 392 11. Diehm N, Shang A, Silvestro A, Do D-D, Dick F, Schmidli J, et al. Association of  
40  
41 393 Cardiovascular Risk Factors with Pattern of Lower Limb Atherosclerosis in 2659  
42  
43 394 Patients Undergoing Angioplasty. *Eur J Vasc Endovasc Surg*. 2006 Jan;31(1):59–63.  
44  
45  
46 395 12. Wasmuth S, Baumgartner I, Do D-D, Willenberg T, Saguner A, Zwahlen M, et al. Renal  
47  
48 396 Insufficiency is Independently Associated with a Distal Distribution Pattern of  
49  
50 397 Symptomatic Lower-limb Atherosclerosis. *Eur J Vasc Endovasc Surg*. 2010  
51  
52 398 May;39(5):591–6.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 399 13. Dorigo W, Di Carlo F, Troisi N, Pratesi G, Innocenti AA, Pulli R, et al. Lower limb  
4 400 revascularization with a new bioactive prosthetic graft: early and late results. *Ann Vasc*  
5 401 *Surg.* 2008 Jan;22(1):79–87.
- 6  
7  
8  
9 402 14. Peeters P, Verbist J, Deloose K, Bosiers M. Results with heparin bonded  
10 403 polytetrafluoroethylene grafts for femorodistal bypasses. *J Cardiovasc Surg Torino.*  
11 404 2006 Aug;47(4):407–13.
- 12  
13  
14  
15  
16 405 15. Walluscheck KP, Bierkandt S, Brandt M, Cremer J. Infrainguinal ePTFE vascular graft  
17 406 with bioactive surface heparin bonding. First clinical results. *J Cardiovasc Surg Torino.*  
18 407 2005 Aug;46(4):425–30.
- 19  
20  
21  
22  
23 408 16. Dorrucchi V, Griselli F, Petralia G, Spinamano L, Adornetto R. Heparin-bonded expanded  
24 409 polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb  
25 410 ischemia: 2-year results. 2008 Apr;49–2.
- 26  
27  
28  
29  
30 411 17. Daenens K, Schepers S, Fourneau I, Houthoofd S, Nevelsteen A. Heparin-bonded  
31 412 ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses:  
32 413 1- and 2-year results. *J Vasc Surg.* 2009 May;49(5):1210–6.
- 33  
34  
35  
36  
37 414 18. Samson RH, Morales R, Showalter DP, Lepore MR, Nair DG. Heparin-bonded  
38 415 expanded polytetrafluoroethylene femoropopliteal bypass grafts outperform expanded  
39 416 polytetrafluoroethylene grafts without heparin in a long-term comparison. *J Vasc Surg.*  
40 417 2016 Sep;64(3):638–47.
- 41  
42  
43  
44  
45  
46 418 19. Statistics from the French Medical Information Agency (ATIH [Internet]. ScanSanté.  
47 419 [cited 2016 Jan 8]. Available from: <http://www.scansante.fr/>
- 48  
49  
50  
51 420 20. Conte MS. Understanding Objective Performance Goals for Critical Limb Ischemia  
52 421 *Trials. Semin Vasc Surg.* 2010 Sep;23(3):129–37.
- 53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 422 21. de Vries SO, Donaldson MC, Hunink MGM. Contralateral symptoms after unilateral  
4 423 intervention for peripheral occlusive disease. *J Vasc Surg.* 1998 Mar;27(3):414–21.  
5  
6  
7 424 22. Martini R, Andreozzi GM, Deri A, Cordova R, Zulian P, Scarpazza O, et al. Amputation  
8 425 rate and mortality in elderly patients with critical limb ischemia not suitable for  
9 426 revascularization. *Aging Clin Exp Res.* 2012 Jun;24(3 Suppl):24–7.  
10  
11  
12  
13  
14 427 23. De Cock E, Sapoval M, Julia P, de Lissovoy G, Lopes S. A Budget Impact Model for  
15 428 Paclitaxel-eluting Stent in Femoropopliteal Disease in France. *Cardiovasc Intervent*  
16 429 *Radiol.* 2013 Apr;36(2):362–70.  
17  
18  
19  
20  
21 430 24. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al.  
22 431 Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012  
23 432 Budget Impact Analysis Good Practice II Task Force. *Value Health.* 2014 Jan;17(1):5–  
24 433 14.  
25  
26  
27  
28  
29  
30 434 25. Shah AP, Klein AJ, Sterrett A, Messenger JC, Albert S, Nehler MR, et al. Clinical  
31 435 outcomes using aggressive approach to anatomic screening and endovascular  
32 436 revascularization in a veterans affairs population with critical limb ischemia. *Catheter*  
33 437 *Cardiovasc Interv.* 2009 Jul;74(1):11–9.  
34  
35  
36  
37  
38  
39 438 26. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-Eluting Balloon in  
40 439 Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) A  
41 440 Randomized Trial in Diabetic Patients With Critical Limb Ischemia. *Circulation.* 2013  
42 441 Aug 6;128(6):615–21.  
43  
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3 442 **FIGURE**  
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10 445 Figure 1: Tornado diagram representing the variation of the 5-year budget balance depending

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12 446 on 5 hypotheses. A negative balance indicates a cost-save.

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3 448 **AUTHOR'S CONTRIBUTION**  
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8 450 Simon Vergnaud: Conception and Design, Analysis and interpretation, Data collection,  
9 451 Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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13 453 Valéry-Pierre Riche: Conception and Design, Analysis and interpretation, Data collection,  
14 454 Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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19 457 the manuscript, Critical revision of the manuscript, Statistical Analysis

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23 459 Nicolas Mauduit: Analysis and interpretation, Data collection, Writing the manuscript, Critical  
24 460 revision of the manuscript

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34 466 Critical revision of the manuscript, Obtaining funding

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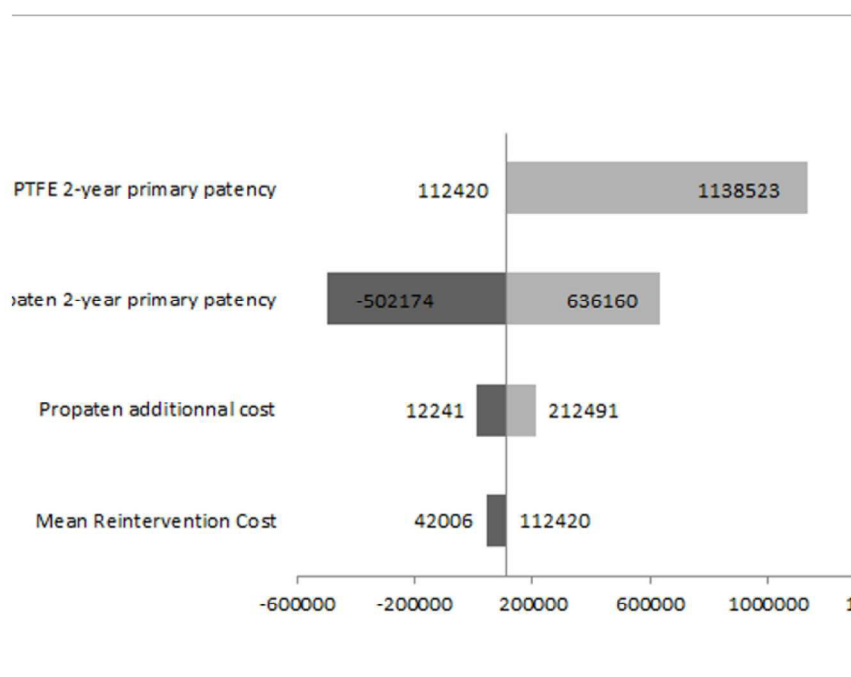


Figure 1: Tornado diagram representing the variation of the 5-year budget balance depending on 5 hypotheses. A negative balance indicates a cost-save.

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