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TITLE PAGE

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

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ABSTRACT

Objectives: To evaluate the budget impact of progressive replacement of crude polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten®) for below-the-knee (BTK) bypass in patients with critical limb ischemia (CLI).

Design: From a review of the scientific literature we calculated a theoretical BTK primary patency for Propaten® grafts. Using the French hospital expenditure database (PMSI), we retrospectively estimated a rehospitalization rate for crude PTFE grafts. From these data, a model was created to assess the budget impact of a progressive replacement from crude PTFE grafts to Propaten® grafts over a 5-year horizon. We performed a univariate sensitivity analysis to assess the robustness of our results.

Setting: French National Health Insurance (FNHI) perspective.

Participant: Patient with CLI.

Main outcome measures: Budget impact of progressive replacement of crude PTFE grafts by Propaten®.

Results: Data extraction from the PMSI revealed that 656 patients were treated with PTFE grafts in 2011 in French public hospitals for a BTK bypass. Assuming a survival rate of 76.8 %, observed reintervention rate for crude PTFE grafts at 24 months from the PMSI was 35.1%. The mean rehospitalization cost was €10 689. The budget impact analysis based on these data found a net cumulative 5-year payer budget reduction of €112 420, under the assumption of a 75.6 % primary patency for Propaten® grafts for a projected population of 3 215 patients of which 801 received a Propaten® graft.

Conclusions: Based on a literature review and a retrospective nationwide data extraction, we modelled a budget impact analysis that showed a positive impact on the national health insurance budget of the replacement of crude PTFE grafts by Propaten® grafts in below-knee surgical bypasses. This supports the enactment of a reimbursement policy by the FNHI. Our model can be used in other countries with a DRG-based reimbursement system.

Keywords: Critical limb ischemia, Bypass Heparin-bonded graft, Below the knee, Budget impact analysis

Strengths and limitations of this study

- This paper presents a budget impact analysis in real life of a progressive replacement of crude polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten®) for below-the-knee (BTK) bypass in patients with critical limb ischemia (CLI) using the French hospital expenditure (PMSI) database.
- PMSI database allows for studies with exhaustive data on the French population, thus producing results with a high statistical power and negligible sampling fluctuations.
- However, only patients with critical limb ischemia and initially treated by crude PTFE in public hospital could be identified in the PMSI database, underestimating the results of the study.
- Clinical factors potentially influencing patterns of practice, non-hospital consumption of cares, and non-reimbursable items and medicines could not be analyzed.

INTRODUCTION

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

However, to date, the financial impact of Propaten® use on health care spending was not assessed. Using data from the literature and from the French hospital expenditure database (PMSI), we assess the financial impact of a progressive replacement of crude PTFE by Propaten® on a 5-year timeline from the payer perspective, for BTK bypass in patients with CLI.

METHODS

Analytic Overview

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

Source population

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

The population model (Table 1)

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

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®
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)

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

One study was excluded because it focused exclusively on diabetics (11). Another was found to have an outlying rate of renal insufficiency.(12). In total, 5 studies were included in our estimation and the mean 2-year BTK primary patency for Propaten® was 75.6 %.(13–17)

Retrospective cost estimation for crude PTFE grafts

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

Simulated cost estimation for Propaten® grafts

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

Budget impact model:

Our budget impact analysis premised the enactment by the French Health Authorities of a FNHI reimbursement policy, i.e. additional costs from the initial procedure would be charged solely to the FNHI. Our base case for the budget impact model used the estimates from our literature review to simulate a rehospitalization rate for the Propaten® implantation for the 2011 PMSI-extracted population. No analysis was conducted on 2-year secondary patency mainly because of the lack of PMSI data on limb side. Total hospital reimbursement costs for both procedures were calculated by adding the initial intervention costs with subsequent rehospitalizations costs. Each year for 5 years, a new cohort of patients entered the model for duration of 2 years, starting with the 2011 population. The number of patients decrease by a flat 1.0% annually, i.e. the mean decrease rate between 2011 and 2014 for the DRG representing 95% of our population as informed in ATIH online data (8). We hypothesized that the enactment of a reimbursement policy by French Health authorities would result in an initial market penetration rate of 15% for Propaten® grafts, with a subsequent annual increase of 5 percentage points, meaning that after 5 years, 35% of the grafts in this indication would be Propaten® grafts. Numerical values corresponding to the hypotheses we made are presented in Table 1.We based our sensitivity analysis on variation one by one of relevant variables in order to assess the weight of each hypothesis on the overall behavior of the model.(18).

RESULTS

Retrospective database analysis for crude PTFE grafts (Figure 1)

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

Costs of treatment using crude PTFE and Propaten®

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

Postulating treatment with only Propaten® grafts for the 656 patients from 2011, 2-year total hospital reimbursement costs would have been €10 822 598.

Budget Impact Analysis (Figure 2)

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

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

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

Sensitivity analysis (Figure 3)

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

DISCUSSION

Our model-based analysis showed the 5-year budget impact for the diffusion of Propaten® in replacement of crude PTFE to be cost-saving. This is a strong economic incentive in favor of both a widespread use and the enactment of a reimbursement policy for Propaten® grafts.

Our modeling approach was founded on a set of assumptions that deserve mention.

The centralized structure of the French Health Information system allows for low-cost studies with exhaustive data on the French population, thus producing results with a high statistical power and negligible sampling fluctuations.

Few articles on Propaten® grafts presented 2-year primary patency for BTK bypasses in the general population, and the level of their clinical evidence was limited. Furthermore no article presented specific results on BTK bypasses in critically ischemic patients, and two articles had better BTK than above-the-knee results. This usually is not the case in lower limb

bypasses, and could be partially explained by important sampling fluctuations due to their small sample sizes. This very fact gave them a low weight in our estimation of the 2-year primary patency. As there was no other available data, we chose to use reasonably unfavorable hypotheses in our analyses to compensate for these shortcomings and thus strengthen the overall conclusion.

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

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

Finally, even though we based our model on French data and tariffication, it can be used for any DRG-based system to estimate the budget impact of Propaten® reimbursement.

CONCLUSION

At current times of resource allocation rationalization, every innovation in healthcare must pass tests of both clinical and economic value. Propaten® grafts have shown their clinical effectiveness, but had yet to be proven economically attractive.

In this paper, we used existing clinical proof to show that Propaten® grafts in patients with CLI needing a BTK bypass would be financially beneficial for the French NHI in most cases. The decision to specifically reimburse Propaten® at its market price dictates the extent of its use throughout France, as few hospitals can afford it in a DRG-based system, which does not allow them to benefit directly from the increased primary patency. Based on our hypotheses and analysis we conclude that a reimbursement policy would benefit both the French NHI and the patients. Our model allows performing of the same analysis in other countries using local cost and clinical effectiveness data providing they have a similar reimbursement system.

Future research ought to focus on directly comparing crude PTFE and Propaten® grafts in order to confirm its probable cost-effectiveness dominance.

ACKNOWLEDGEMENTS

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

The model was created using Microsoft® Excel®.

COMPETING INTERESTS AND FUNDING

This research was carried out with financial support from GoreTex®.

Pr Gouëffic received consulting fees and travel grant from Cook, Covidien, Medtronic, Pérouse and Terumo.

DATA SHARING STATEMENT

Data sharing: no additional data available.

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FIGURE

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

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

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

CONTRIBUTORSHIP STATEMENT

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

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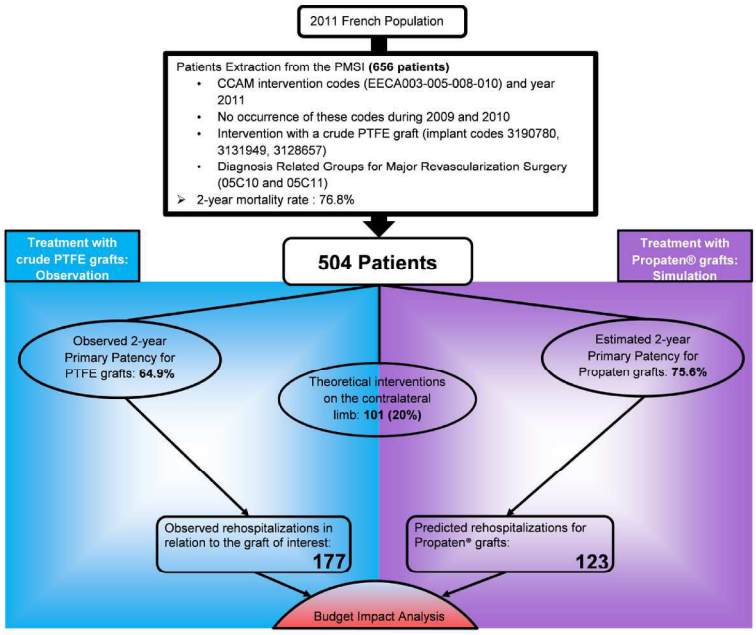
Nicolas Mauduit: Analysis and interpretation, Data collection, Writing the manuscript, Critical revision of the manuscript

Adrien Kaladji: Analysis and interpretation, Writing the manuscript, Critical revision of the manuscript

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



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

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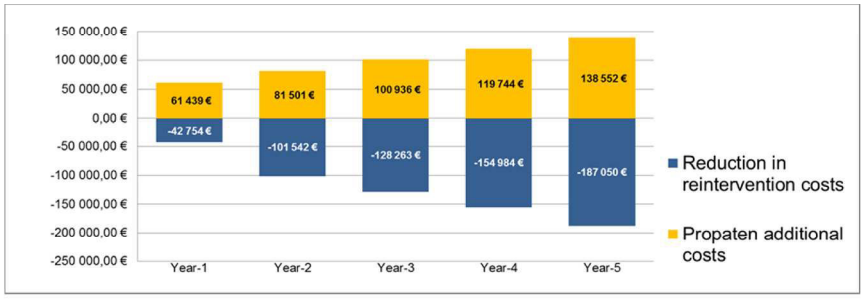

Budget impact comparison. A plus sign indicates an increase in costs, a minus sign shows savings.

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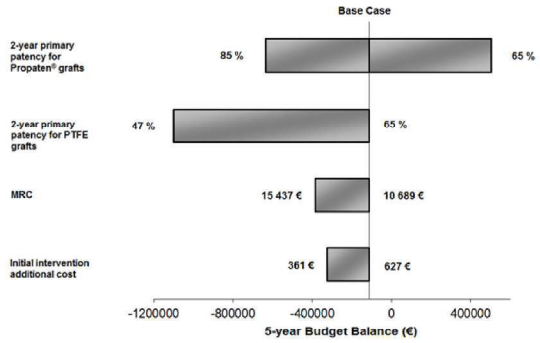

Tornado diagram representing the variation of the 5-year budget balance depending on 4 hypotheses. A negative balance indicates a cost-save.

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

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ABSTRACT

Objectives: To evaluate the budget impact of progressive replacement of standard polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten®) for below-the-knee (BTK) bypass in patients with critical limb ischemia (CLI).

Design: From a review of the scientific literature we calculated a theoretical BTK primary patency for Propaten® grafts. Using the French hospital expenditure database (PMSI), we retrospectively estimated a rehospitalization rate for standard PTFE grafts. From these data, a model was created to assess the budget impact of a progressive replacement from standard PTFE grafts to Propaten® grafts over a 5-year horizon. We performed an univariate sensitivity analysis to assess the robustness of our results.

Setting: French National Health Insurance (FNHI) perspective.

Participant: Patients with CLI.

Main outcome measures: Budget impact analysis

Results: Data extraction from the PMSI revealed that 656 patients were treated with PTFE grafts in 2011 in French public hospitals for a BTK bypass. Assuming a 2-year survival rate of 76.8 %, observed reinterventions rate for standard PTFE grafts at 24 months from the PMSI was 35.1%. The mean rehospitalization cost was €10 689. The budget impact analysis based on these data found a net cumulative 5-year payer budget reduction of €112 420 in favor of Propaten®, under the assumption of a 75.6 % primary patency for Propaten® grafts for a projected population of 3 215 patients of which 801 received a Propaten® graft.

Conclusions: Our budget impact analysis showed a positive impact on the national health insurance budget of the replacement of standard PTFE grafts by Propaten® grafts for below the knee bypass in patients with CLI in France. This supports the enactment of a reimbursement policy by the FNHI.

Strengths and limitations of this study

- The budget impact analysis provides further evidence to adopt and to reimburse the device for decision-makers.
- PMSI database allows for studies with exhaustive data on the French population, thus producing results with a high statistical power and negligible sampling fluctuations.
- However, only patients with critical limb ischemia and initially treated by standard PTFE in public hospital could be identified in the PMSI database, underestimating the results of the study.
- Clinical factors potentially influencing patterns of practice, office-based consumption of cares, and non-reimbursable items and medicines could not be analyzed.

INTRODUCTION

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

However, to date, the financial impact of Propaten® use on health care spending was not assessed. Using data from the literature and from the French hospital expenditure database (PMSI), we assess the financial impact of a progressive replacement of standard PTFE by Propaten® on a 5-year timeline from the payer perspective, for BTK bypass in patients with CLI.

METHODS

Analytic Overview

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

Evidence acquisition

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

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

Table 1: Detailed review of the literature of the Propaten® 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	80.6%
Results with heparin-bonded polytetrafluoroethylene grafts for femorodistal bypasses	2006	Peeters et al.(14)	41	72.6%
Infrainguinal ePTFE vascular graft with bioactive surface heparin bonding	2005	Walluscheck et al. (15)	17	81%
Heparin-bonded expanded polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb ischemia: 2-year results	2008	Dorrucci et al. (16)	20	85%
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%
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%

Source population

From a retrospective analysis on hospital stays during 2011 using the PMSI, we identified patients who were admitted for a BTK bypass surgery, where a standard PTFE graft was used. In France, only CLI patients have this surgery, where using a standard PTFE graft is the usual choice (French medical information agency –ATIH– online data)(19). Therefore, no analysis was conducted on other types of grafts. Propaten® grafts were not available in France in 2011. Patients under 18 years old were excluded. Patients having been operated upon for a BTK bypass surgery in the two years prior were excluded as well as to exclude reinterventions from index cases. The data included the reference of the diagnosis related groups (DRGs), the type of bypass grafts used, the duration of stays, the time spent in intensive care unit as well as the patient's comorbidities. Patients were followed for 24 months.(20)

The population model (Table 2)

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

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)

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

Retrospective cost estimation for standard PTFE grafts

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

Cost estimation for Propaten® grafts

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

Budget impact model:

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

be Propaten® grafts (23). Numerical values corresponding to the hypotheses we made are presented in Table 2. We based our sensitivity analysis on variation one by one of relevant variables in order to assess the weight of each hypothesis on the overall behavior of the model.(24).

Sensitivity analysis

Univariate analysis

We tested the sensitivity of our results to the main hypotheses used in our model by estimating the budget impact for a range of values. The tested parameters were the 2-year BTK primary patencies for Propaten® and standard PTFE grafts, the mean cost of rehospitalization and the additional cost of the initial intervention for Propaten® grafts. For Propaten® grafts' patency, we used the 2-year primary patency for standard PTFE grafts found in our population as low end of the range, and the highest reported primary patency (16) as high end. For PTFE grafts' patency, we used the 2-year primary patency for standard PTFE grafts found in our population as the high end of the range, and the value found in the literature (4) as the low end. For the mean cost of rehospitalizations, we used the low and high values of our 95% confidence interval as low and high ends of the range. Finally, we used arbitrary values to test for the sensitivity of our results to the price of the Propaten® graft.

Scenario analysis

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

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

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%

RESULTS

Retrospective database analysis for standard PTFE grafts (Figure 1)

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

Costs of treatment using standard PTFE and Propaten®

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

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

Budget Impact Analysis (Table 4)

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

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

Year	PTFE alone	Propaten + PTFE						Cost difference
	Total costs (€)	PTFE grafts	Propaten grafts	Initial additional cost (€)	RH	RH 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	€502 173	726	57	€47 759 095	€-112 420

PTFE: polytetrafluoroethylen; RH: Rehospitalization

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

Propaten® + PTFE courses was estimated at €112 420 , in favor of Propaten® grafts, from the FNHI perspective.

Sensitivity analysis (Figure 2)

Univariate analysis

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

Scenario analysis (Table 5)

Our worst and best case showed the variability of the budget impact of Propaten® grafts with a difference of more than 2.4 million euros.

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

PTFE: polytetrafluoroethylen; MRC: mean rehospitalizations cost.

DISCUSSION

Our model-based analysis showed the 5-year budget impact for the diffusion of Propaten® in replacement of standard PTFE to be cost-saving. This is a strong economic incentive in favor of both a widespread use and the enactment of a reimbursement policy for Propaten® grafts.

Our modeling approach was founded on a set of assumptions that deserve mention.

The centralized structure of the French Health Information system allows for low-cost studies with exhaustive data on the French population, thus producing results with a high statistical power and negligible sampling fluctuations.

Few articles on Propaten® grafts presented 2-year primary patency for BTK bypasses in the general population, and the level of their clinical evidence was limited. We excluded two articles because of the epidemiological profile (diabetes, renal failure) of their populations, which were associated with higher morbimortality and lower patency rates overall. Usually patients with BTK bypasses represent a homogeneous group of patients with critical limb ischemia in comparison to above the knee bypass, which could be realized for claudicants or CLI patients. Furthermore no article presented specific results on BTK bypasses in critically ischemic patients, and two articles had better outcomes for BTK than above-the-knee revascularization. This usually is not the case in lower limb bypasses, and could be partially explained by important sampling fluctuations due to their small sample sizes. As there was no other available data, we chose to use reasonably unfavorable hypotheses in our analyses to compensate for these shortcomings and thus strengthen the overall conclusion.

As our sensitivity analysis showed, our conclusions are tied to both the effectiveness of Propaten® grafts and the comparative lack of effectiveness of standard PTFE grafts. The observed 2-year primary patency for standard PTFE grafts is about 35% higher than usually described (4). Most clinical studies follow their patients more thoroughly than it is the case in daily care. This is the cause of a follow-up bias in our study, due to the use of reintervention as a measure of loss of patency, which overestimate the patency for standard PTFE grafts. Indeed, in the case of an occluded graft, reintervention and/or amputation are not systematically performed because the patient is asymptomatic or because a palliative treatment is decided. These types of health consumptions are not logged in the PMSI database and as we used intervention-specific codes, we estimated the 2-year primary patency for standard PTFE grafts using only patients with lower limb vascular surgical interventions. The patients lost because of our method of follow-up would only ramp up the costs of the standard PTFE course of action.

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

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

PTFE grafts in our population, which is pessimistic, but for which the likelihood does not seem quantifiable.

Finally, even though we based our model on French data and tariffication, it can be used for any DRG-based system to estimate the budget impact of Propaten® reimbursement.

CONCLUSION

At current times of resource allocation rationalization, every innovation in healthcare must pass tests of both clinical and economic value. Propaten® grafts have shown their clinical effectiveness, but had yet to be proven economically attractive.

In this paper, we used existing clinical proof to show that Propaten® grafts in patients with CLI needing a BTK bypass would be financially beneficial for the French NHI in most cases. The decision to specifically reimburse Propaten® at its market price dictates the extent of its use throughout France, as few hospitals can afford it in a DRG-based system, which does not allow them to benefit directly from the increased primary patency. Based on our hypotheses and analysis we conclude that a reimbursement policy would benefit both the French NHI and the patients. Our model allows performing of the same analysis in other countries using local cost and clinical effectiveness data providing they have a similar reimbursement system.

Future research ought to focus on directly comparing standard PTFE and Propaten® grafts in order to confirm its probable cost-effectiveness dominance.

ACKNOWLEDGEMENTS

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

The model was created using Microsoft® Excel®.

CONFLICT OF INTEREST

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FIGURE

Figure 1: Patients extraction process using the French expenditure database

PTFE: polytetrafluoroethylen; BTK: below the knee

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

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

AUTHOR'S CONTRIBUTION

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

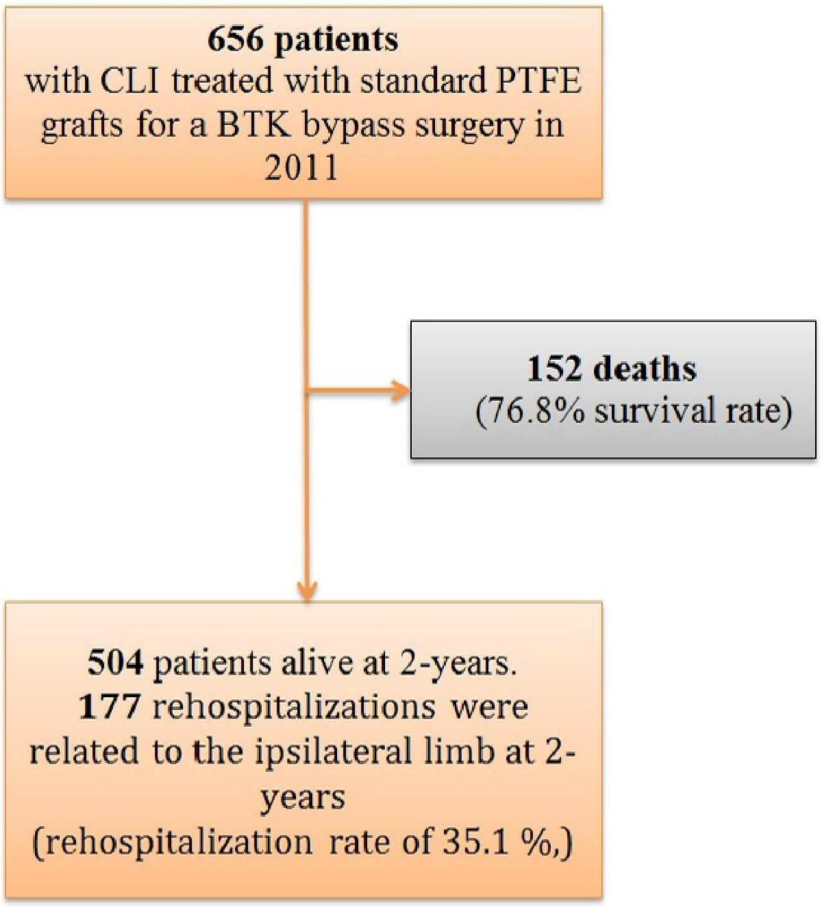
Valéry-Pierre Riche: Conception and Design, Analysis and interpretation, Data collection, Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

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

Nicolas Mauduit: Analysis and interpretation, Data collection, Writing the manuscript, Critical revision of the manuscript

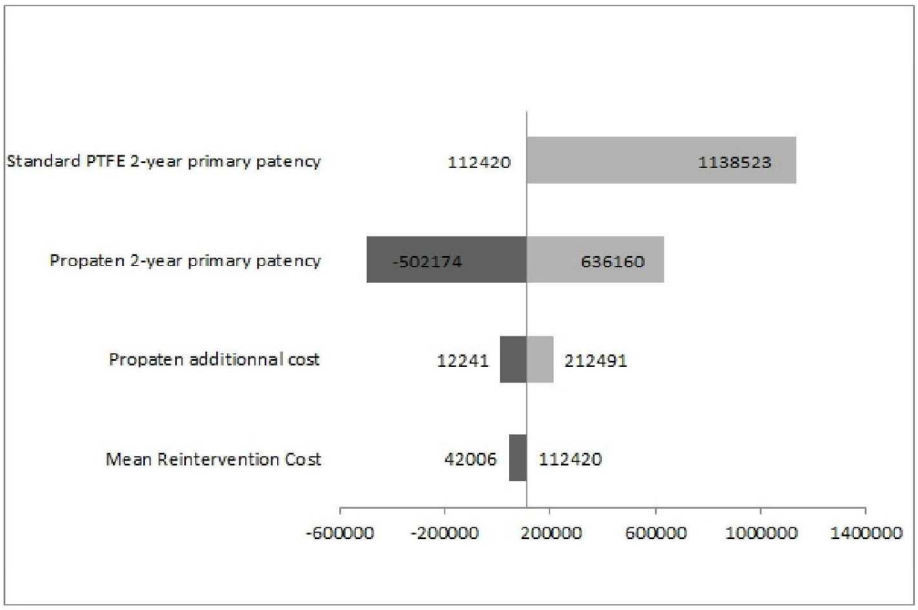
Adrien Kaladji: Analysis and interpretation, Writing the manuscript, Critical revision of the manuscript

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



Patients extraction process using the French expenditure database

209x297mm (150 x 150 DPI)



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

297x209mm (150 x 150 DPI)

			Line		Checklist-Criteria
Study design				**Study question**	
	1				
		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			**Selection of alternatives**	
		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
	3				
		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
Data collection	4			**Effectiveness data**	
		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			**Benefit measurement and valuation**	
		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			**Costing**	
		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			**Modelling**	
		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
Analysis and interpretation of Results					
	8			**Adjustments for timing of costs and benefits**	
		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			**Allowance for uncertainty**	
		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			**Presentation of results and discussion**	
		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)

BMJ Open

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

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TITLE PAGE

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

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ABSTRACT

Objectives: To evaluate the budget impact of progressive replacement of standard polytetrafluoroethylen (PTFE) grafts by heparin-bound PTFE (Propaten®) for below-the-knee (BTK) bypass in patients with critical limb ischemia (CLI).

Design: From a review of the scientific literature we calculated a theoretical BTK primary patency for Propaten® grafts. Using the French hospital expenditure database (PMSI), we retrospectively estimated a rehospitalization rate for standard PTFE grafts. From these data, a model was created to assess the budget impact of a progressive replacement from standard PTFE grafts to Propaten® grafts over a 5-year horizon. We performed an univariate sensitivity analysis to assess the robustness of our results.

Setting: French National Health Insurance (FNHI) perspective.

Participant: Patients with CLI.

Main outcome measures: Budget impact analysis

Results: Data extraction from the PMSI revealed that 656 patients were treated with PTFE grafts in 2011 in French public hospitals for a BTK bypass. Assuming a 2-year survival rate of 76.8 %, observed reinterventions rate for standard PTFE grafts at 24 months from the PMSI was 35.1%. The mean rehospitalization cost was €10 689. The budget impact analysis based on these data found a net cumulative 5-year payer budget reduction of €112 420 in favor of Propaten®, under the assumption of a 75.6 % primary patency for Propaten® grafts for a projected population of 3 215 patients of which 801 received a Propaten® graft.

Conclusions: Our budget impact analysis showed a positive impact on the national health insurance budget of the replacement of standard PTFE grafts by Propaten® grafts for below the knee bypass in patients with CLI in France. This supports the enactment of a reimbursement policy by the FNHI.

Strengths and limitations of this study

- The budget impact analysis provides further evidence to adopt and to reimburse the device for decision-makers.
- PMSI database allows for studies with exhaustive data on the French population, thus producing results with a high statistical power and negligible sampling fluctuations.
- However, only patients with critical limb ischemia and initially treated by standard PTFE in public hospital could be identified in the PMSI database, underestimating the results of the study.
- Clinical factors potentially influencing patterns of practice, office-based consumption of cares, and non-reimbursable items and medicines could not be analyzed.

INTRODUCTION

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

However, to date, the financial impact of Propaten® use on health care spending was not assessed. Using data from the literature and from the French hospital expenditure database (PMSI), we assess the financial impact of a progressive replacement of standard PTFE by Propaten® on a 5-year timeline from the payer perspective, for BTK bypass in patients with CLI.

METHODS

Analytic Overview

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

Evidence acquisition

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

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

Table 1: Detailed review of the literature of the Propaten® 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	80.6%
Results with heparin-bonded polytetrafluoroethylene grafts for femorodistal bypasses	2006	Peeters et al.(14)	41	72.6%
Infrainguinal ePTFE vascular graft with bioactive surface heparin bonding	2005	Walluscheck et al. (15)	17	81%
Heparin-bonded expanded polytetrafluoroethylene grafts for infragenicular bypass in patients with critical limb ischemia: 2-year results	2008	Dorrucci et al. (16)	20	85%
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%
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%

Source population

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

The population model (Table 2)

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

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)

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

Retrospective cost estimation for standard PTFE grafts

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

Cost estimation for Propaten® grafts

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

Budget impact model:

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

be Propaten® grafts (23). Numerical values corresponding to the hypotheses we made are presented in Table 2. We based our sensitivity analysis on variation one by one of relevant variables in order to assess the weight of each hypothesis on the overall behavior of the model.(24).

Sensitivity analysis

Univariate analysis

We tested the sensitivity of our results to the main hypotheses used in our model by estimating the budget impact for a range of values. The tested parameters were the 2-year BTK primary patencies for Propaten® and standard PTFE grafts, the mean cost of rehospitalization and the additional cost of the initial intervention for Propaten® grafts. For Propaten® grafts' patency, we used the 2-year primary patency for standard PTFE grafts found in our population as low end of the range, and the highest reported primary patency (16) as high end. For PTFE grafts' patency, we used the 2-year primary patency for standard PTFE grafts found in our population as the high end of the range, and the value found in the literature (4) as the low end. For the mean cost of rehospitalizations, we used the low and high values of our 95% confidence interval as low and high ends of the range. Finally, we used arbitrary values to test for the sensitivity of our results to the price of the Propaten® graft.

Scenario analysis

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

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

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%

RESULTS

Retrospective database analysis for standard PTFE grafts

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

Costs of treatment using standard PTFE and Propaten®

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

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

Budget Impact Analysis (Table 4)

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

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

Year	PTFE alone	Propaten + PTFE						Cost difference
	Total costs (€)	PTFE grafts	Propaten grafts	Initial additional cost (€)	RH	RH 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	€502 173	726	57	€47 759 095	€-112 420

PTFE: polytetrafluoroethylen; RH: Rehospitalization

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

Propaten® + PTFE courses was estimated at €112 420 , in favor of Propaten® grafts, from the FNHI perspective.

Sensitivity analysis (Figure 1)

Univariate analysis

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

Scenario analysis (Table 5)

Our worst and best case showed the variability of the budget impact of Propaten® grafts with a difference of more than 2.4 million euros.

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

PTFE: polytetrafluoroethylen; MRC: mean rehospitalizations cost.

DISCUSSION

Our model-based analysis showed the 5-year budget impact for the diffusion of Propaten® in replacement of standard PTFE to be cost-saving. This is a strong economic incentive in favor of both a widespread use and the enactment of a reimbursement policy for Propaten® grafts.

Our modeling approach was founded on a set of assumptions that deserve mention.

The centralized structure of the French Health Information system allows for low-cost studies with exhaustive data on the French population, thus producing results with a high statistical power and negligible sampling fluctuations.

Few articles on Propaten® grafts presented 2-year primary patency for BTK bypasses in the general population, and the level of their clinical evidence was limited. We excluded two articles because of the epidemiological profile (diabetes, renal failure) of their populations, which were associated with higher morbimortality and lower patency rates overall. Usually patients with BTK bypasses represent a homogeneous group of patients with critical limb ischemia in comparison to above the knee bypass, which could be realized for claudicants or CLI patients. Furthermore no article presented specific results on BTK bypasses in critically ischemic patients, and two articles had better outcomes for BTK than above-the-knee revascularization. This usually is not the case in lower limb bypasses, and could be partially explained by important sampling fluctuations due to their small sample sizes. As there was no other available data, we chose to use reasonably unfavorable hypotheses in our analyses to compensate for these shortcomings and thus strengthen the overall conclusion. Nevertheless, as we excluded those two studies, our results should only be considered valid for unselected

CLI populations. In such populations, diabetes, albeit frequent, rarely has a 100% prevalence rate, and renal insufficiency rates are about half the rate from the Lösel-Sadée study (31,0%) (9).

As our sensitivity analysis showed, our conclusions are tied to both the effectiveness of Propaten® grafts and the comparative lack of effectiveness of standard PTFE grafts. The observed 2-year primary patency for standard PTFE grafts is about 35% higher than usually described (4). Most clinical studies follow their patients more thoroughly than it is the case in daily care. This is the cause of a follow-up bias in our study, due to the use of reintervention as a measure of loss of patency, which overestimate the patency for standard PTFE grafts. Indeed, in the case of an occluded graft, reintervention and/or amputation are not systematically performed because the patient is asymptomatic or because a palliative treatment is decided. These types of health consumptions are not logged in the PMSI database and as we used intervention-specific codes, we estimated the 2-year primary patency for standard PTFE grafts using only patients with lower limb vascular surgical interventions. The patients lost because of our method of follow-up would only ramp up the costs of the standard PTFE course of action.

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

Our scenario analysis showed the extent of the potential budget impact that would follow the globalization of Propaten® use for BTK bypasses in France. Unfortunately, the uncertainty

around the 2-year primary patency translated to an extensive range for its budget impact. The worst-case scenario assumed that Propaten® grafts were no more effective than standard PTFE grafts in our population, which is pessimistic, but for which the likelihood does not seem quantifiable.

Finally, even though we based our model on French data and tariffication, it can be used for any DRG-based system to estimate the budget impact of Propaten® reimbursement.

CONCLUSION

At current times of resource allocation rationalization, every innovation in healthcare must pass tests of both clinical and economic value. Propaten® grafts have shown their clinical effectiveness, but had yet to be proven economically attractive.

In this paper, we used existing clinical proof to show that Propaten® grafts in patients with CLI needing a BTK bypass would be financially beneficial for the French NHI in most cases. The decision to specifically reimburse Propaten® at its market price dictates the extent of its use throughout France, as few hospitals can afford it in a DRG-based system, which does not allow them to benefit directly from the increased primary patency. Based on our hypotheses and analysis we conclude that a reimbursement policy would benefit both the French NHI and the patients. Our model allows performing of the same analysis in other countries using local cost and clinical effectiveness data providing they have a similar reimbursement system.

Future research ought to focus on directly comparing standard PTFE and Propaten® grafts in order to confirm its probable cost-effectiveness dominance.

ACKNOWLEDGEMENTS

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

The model was created using Microsoft® Excel®.

CONFLICT OF INTEREST

This research was carried out with financial support from WL Gore®.

Pr Gouëffic received consulting fees and travel grant from Abbott, Bard, Biotronik, Boston Sc, Cook, Medtronic, Perouse, Spectranetics, Terumo and WL Gore.

DATA SHARING STATEMENT

Data sharing: no additional data available.

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FIGURE

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

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

AUTHOR'S CONTRIBUTION

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

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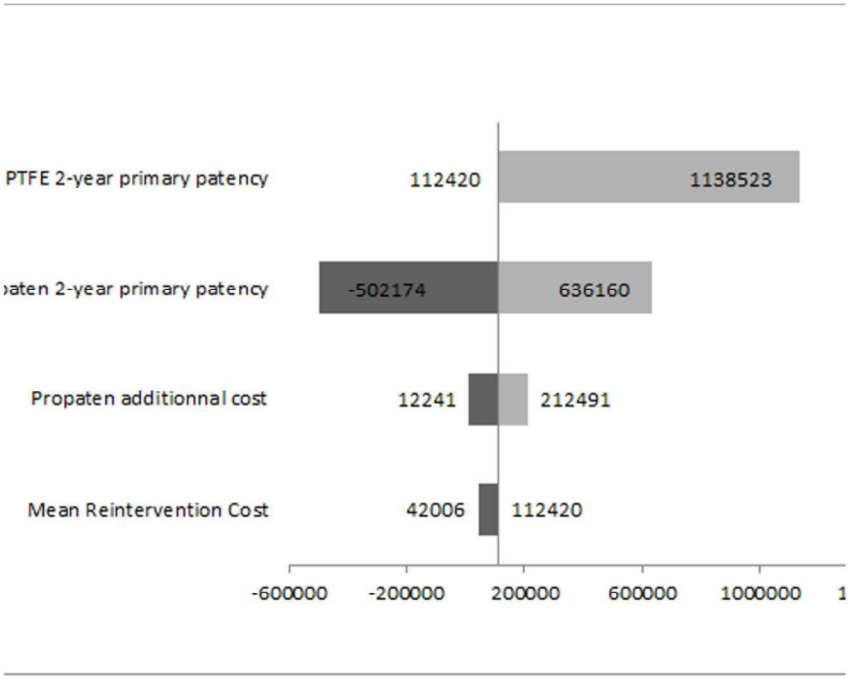
Philippe Tessier: Conception and Design, Analysis and interpretation, Data collection, Writing the manuscript, Critical revision of the manuscript, Statistical Analysis

Nicolas Mauduit: Analysis and interpretation, Data collection, Writing the manuscript, Critical revision of the manuscript

Adrien Kaladji: Analysis and interpretation, Writing the manuscript, Critical revision of the manuscript

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



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209x148mm (300 x 300 DPI)