Device Evaluation

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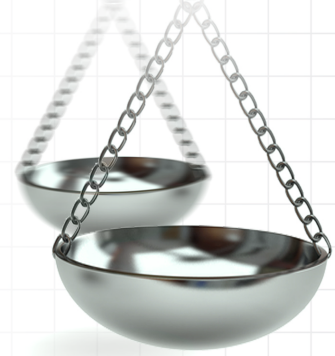

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Are drug-coated balloons cost effective for femoropopliteal occlusive disease? A comparison of bare metal stents and uncoated balloons

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Aim: To perform a cost–effectiveness analysis to help hospital decision-makers with regard to the use of drug-coated balloons compared with bare metal stents and uncoated balloons for femoropopliteal occlusive disease. **Methods:** Clinical outcomes were extracted from the results of meta-analyses already published, and cost units are those used in the Quebec healthcare network. The literature review was limited to the last four years to obtain the most recent data. The cost–effectiveness analysis was based on a 2-year perspective, and risk factors of reintervention were considered. **Results:** The cost–effectiveness analysis indicated that drug-coated balloons were generally more efficient than bare metal stents, particularly for patients with higher risk of reintervention (up to CAD$1686 per patient TASC II C or D). Compared with uncoated balloons, results indicated that drug-coated balloons were more efficient if the reintervention rate associated with uncoated balloons is very high and for patients with higher risk of reintervention (up to CAD$3301 per patient). **Conclusion:** The higher a patient's risk of reintervention, the higher the savings associated with the use of a drug-coated balloon will be. For patients at lower risk, the uncoated balloon strategy is still recommended as a first choice for endovascular intervention.

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Keywords: bare metal stent • cost–effectiveness • drug-coated balloon • femoropopliteal occlusive disease • hospital management • uncoated balloon

Peripheral arterial disease is characterized by a decrease in blood flow and affects up to 29% of higher risk groups (>70 years old or >50 years old with history of smoking or diabetes) [1]. The most common cause of symptomatic peripheral arterial disease is the superficial femoral artery disease which may progress to lifestyle-limiting claudication, critical limb ischemia or limb amputation [2–4]. Given continuous technological advances, endovascular therapy is now the first strategy recommended for the majority of symptomatic patients [5–8]. However, because of their unique anatomy and biomechanics, femoropopliteal arteries have high rates of restenosis following endovascular treatment. As a consequence, patients may need more than one intervention of the target lesion.

Among endovascular techniques, drug-coated balloons are the most recent and perhaps the most promising device [2]. Given this fact, an increase in the use of this technology has been observed in Canada and elsewhere as an alternative to other medical devices, such as bare metal stents and uncoated balloons. With respect to high-quality patient care and better use of available resources, it is necessary to evaluate the cost–effectiveness of these technologies. Note that in several health facilities such as ours, the drug-eluting stent remains restricted to a reintervention of the lesion. The purpose of this study is to evaluate which technology option is the most efficient for the first intervention (*de novo*); the drug-eluting stent is therefore excluded from our analysis.

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Research question

Is the drug-coated balloon cost effective with regard to the rate of target lesion revascularization of the femoropopliteal artery in comparison with the bare metal stent and the uncoated balloon?

Methods

Mainly based on the results of published meta-analyses, we performed a cost–effectiveness analysis of drug-coated balloons versus bare metal stents and uncoated balloons. The literature review was divided into two parts. In the first part, we retrieved existing systematic reviews with meta-analyses and health technology assessment (HTA) reports to assess the effectiveness of drug-coated balloons versus bare metal stents and uncoated balloons for the femoropopliteal artery. To obtain the most recent data, our research was limited to the last 4 years (from January 2011 to October 2015). Databases used were MEDLINE (via PubMed), ScienceDirect, Centre for Reviews and Dissemination, the Cochrane Library and the websites of the Canadian Agency for Drugs and Technologies in Health (CADTH; Canada) and the Institut National d'Excellence en Santé et Services Sociaux (INESSS; Canada). The search was performed in English and in French. The keywords used were 'drug coated balloon' and 'femoropopliteal'. In PubMed and ScienceDirect, for example, this gave the following search strategy: drug-coated balloon AND femoropopliteal. Inclusion criteria were: patients treated for *de novo* stenosis and their outcomes at follow-up, including target lesion revascularization (primary outcome), restenosis, limb amputation, mortality and restenosis or reintervention risk factors (secondary outcomes); paclitaxel drug-coated balloons; studies comparing drug-coated balloons to bare metal stents or uncoated balloons. Exclusion criteria were: narrative reviews and systematic reviews that compared drug-coated balloons with only covered stents. In the second part, given that we found no results with regard to risk factors associated with restenosis or reintervention following the first treatment for a femoropopliteal lesion, we performed another literature review. The methodology used was the same as mentioned earlier but included narrative reviews and primary studies as an inclusion criteria. The second literature search was not restricted in terms of publication date, but we retained only the most recent publications. Considering that this literature review was performed to complete the first one as regard to risk factors, this one was conducted up to retrieve a sufficient number of articles to provide enough information on this topic. As a consequence, this second review is not a systematic one, but a narrative one. The keywords used were 'femoropopliteal', 'restenosis', 'occlusion' and synonyms of 'risk factor', such as 'predictors', 'risk stratification', 'association with outcomes' and 'impact on outcomes'. The quality of the systematic reviews retrieved was assessed with the AMSTAR tool (a measurement tool to assess systematic reviews) [9]. The level of scientific evidence associated with each primary study was assessed using the grid developed by Hailey *et al.* [10].

For the cost–effectiveness analysis, we collected all data about the equipment used, the number of health professionals involved and the duration of interventions in angiography during 1 month (June 2014). From the 182 interventions performed, 11 were related to a stenosis of the femoropopliteal artery (conjoint interventions with the iliac artery were excluded). These 11 interventions were considered representative of interventions performed during a regular month by the two surgeons who performed 80% of these interventions in our institution. This allowed us to calculate the cost of an intervention for a *de novo* stenosis and to determine the average number of stents and balloons used in each procedure. Precisely, we calculated the generic cost for a representative patient in our institution (e.g., healthcare professionals, medical furniture), to which we added the specific cost of the device used (i.e., cost of drug-coated balloons, uncoated balloons and bare metal stents). Then, these data were combined with data on clinical effectiveness and restenosis risk factors retrieved in the literature. The perspective of the analysis is that of the Quebec health network. The difference in costs for an intervention and then a reintervention after a failed revascularization between the drug-coated balloons, on the one hand, and the bare metal stents or the uncoated balloons, on the other hand, was calculated on the basis of 100 patients. The primary outcome in this study was the target lesion revascularization rate. This allowed us to calculate the cost per avoided reintervention for failed revascularization. The analysis period was for 2 years. The choice of this period was based on the fact that it is relatively well-documented in comparison to longer follow-up periods but also by the fact that it can cover most of the episodes of restenosis (i.e., more than half of reinterventions occur during the first 2 years) [11,12]. A sensitivity analysis was performed considering an interval of several values regarding the relative efficacy of drug-coated balloons compared with bare metal stents or uncoated balloons. Similarly, several simulations were performed by considering several groups of patients eligible for drug-coated balloons. These patient groups were determined according to the most frequent risk factors of reintervention following the installation of a bare metal stent. Considering that the evaluation period was short, we decided to do not use a discount rate.

Results

Following our research protocol, we found three meta-analyses for clinical effectiveness and ten primary studies for restenosis risk factors. Regarding clinical effectiveness, we found a network meta-analysis including 2532 patients from 16 studies [3], a meta-analysis including 1464 patients from 11 studies [13] and a meta-analysis from the National Institute for Health Research including 290 patients from three studies [2]. These three meta-analyses obtained 11/11 on the AMSTAR tool. Regarding the primary studies on restenosis risk factors, various designs were used and the degree of evidence could be considered as moderate (i.e., mostly retrospective studies and no one was randomized).

Target lesion revascularization

Target lesion revascularization is defined as a repeat revascularization for a lesion located at the site previously treated (within 5 mm borders). The results reported in Table 1 indicate that in all cases, compared with the drug-coated balloon (paclitaxel), the repetition rate of the procedure is higher when the uncoated balloon is used. When the drug-coated balloon is compared with the bare metal stent, only the meta-analysis of Katsanos *et al.* [3] reported a significantly lower reintervention rate. In addition, the reintervention rate at 1 year in Katsanos *et al.* [3] for the drug-coated balloons (8%) are much lower than those reported in Fusaro *et al.* (20%) [13] and Simpson *et al.* (14%) [2]. The reasons for these differences are discussed in the discussion.

Restenosis

Vascular restenosis is defined as a narrowing of the treated area. In the network meta-analysis of Katsanos *et al.* [3], vascular restenosis is defined as a luminal diameter reduction greater than or equal to 50%, while in Fusaro *et al.* [13] and Simpson *et al.* [2], this cut-off is 70%. Vascular restenosis rates from the literature reviewed are presented in Table 2.

As well as for the target lesion revascularization, results for vascular restenosis indicate that the drug-coated balloon (paclitaxel) is a better treatment option in comparison with the uncoated balloon. Moreover, in the two meta-analyses that compared the drug-coated balloon with the bare metal stent, higher rates were observed for the latter technology, but only Katsanos *et al.* [3] found a statistically significant difference.

Amputation & mortality

Amputations are rare events and have been identified in the meta-analyses of Katsanos *et al.* [3] and Fusaro *et al.* (Table 3) [13]. The type of amputation varies from one study to another: it may be the entire leg, the lower leg or the bottom of the ankle. Regarding mortality, only the meta-analysis of Fusaro *et al.* [13] reported these results (Table 4). For a single primary study included in the meta-analysis, the observed mortality must be associated with the procedure or technology, while in the other primary studies, all-cause mortality were considered.

According to the results reported in Table 3, the amputation rates associated with the uncoated balloon or the bare metal stent show no differences compared with the drug-coated balloon. Note that in the meta-analysis of Katsanos *et al.* [3], the authors reported that no statistical test was performed because the number of events was too small to generate scientifically rigorous results. In terms of mortality, no significant difference in comparison with the drug-coated balloon was reported (Table 4).

Risk factors

All studies identified refer to risk factors for restenosis or primary patency [11,12,14–20]. The study of Soga *et al.* [21] also provided results for the risk of target vessel reintervention. Among these studies, the TASC II classification of femoral and popliteal lesions (Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease) was systematically reported as a significant single risk factor. Generally, classes A

Table 1. Target lesion revascularization according to the medical device used.

Study (year)	Drug-coated balloon (paclitaxel)	Uncoated balloon	Bare metal stent	Ref.
Katsanos *et al.* (2014)	8%; 1 year follow-up	22%; 1 year follow-up; **p < 0.001**	16%; 1 year follow-up; **p = 0.01**	[3]
Fusaro *et al.* (2013)	20%; 6–12 months follow-up	45%; 6–12 months follow-up; **p < 0.001**	18%; 6–24 months follow-up; p = 0.29	[13]
Simpson *et al.* (2014)	7%; 6 months follow-up 14%; 1 year follow-up	31%; 6 months follow-up; **p = 0.006** 51%; 1 year follow-up; **p < 0.00001**	NA	[2]

Results for uncoated balloons and bare metal stents were compared with those of drug-coated balloons: a p-value ≤ 0.05 indicates a significant difference (in bold).
NA: Not-available.

Table 2. Vascular restenosis rate according to the medical device used.

Study (year)	Drug-coated balloon (paclitaxel)	Uncoated balloon	Bare metal stent	Ref.
Katsanos *et al.* (2014)	19%; 1 year follow-up	45%; 1 year follow-up; **p = 0.001**	35%; 1 year follow-up; **p = 0.03**	[3]
Fusaro *et al.* (2013)	21%; 6–12 months follow-up	44%; 6–12 months follow-up; **p < 0.001**	33%; 6–24 months follow-up; p = 0.13	[13]
Simpson *et al.* (2014)	18%; 6 months follow-up	45%; 6 months follow-up; **p = 0.001**	NA	[2]

Results for uncoated balloons and bare metal stents were compared with those of drug-coated balloons: a p-value ≤ 0.05 indicates a significant difference (in bold).
NA: Not-available.

and B are compared with classes C and D. However, in some cases, only class D is compared, either with respect to class C, or to classes A to C. In all cases, it clearly appears that classifications C and D are associated with a higher risk of restenosis or reintervention [11,12,19–21]. Lesions of 15 cm or more or multiple lesions with a sum of more than 15 cm are therefore subject to greater risk with a risk ratio of approximately 2.4. Then, other factors often appear to be significant, such as diabetes mellitus [12,15], chronic total occlusion [12,14], critical limb ischemia [12,14], renal failure [12,21] and female gender [11,12,17]. The risk ratio of these factors usually varies between 1.2 and 1.8. Other factors appear more rarely to be significant: hyperlipidemia [20], poor below-the-knee runoff [12], specific genetic characteristics [15,18], arterial calcification [12], chronic heart failure [12] and patient's age [17].

Given the high prevalence of these risk factors in populations treated for stenosis or occlusion of the femoropopliteal artery in these studies (almost 50% for the TASC II classification C or D, hyperlipidemia, diabetes mellitus, chronic total occlusion and poor below-the-knee runoff; about a third for female gender, renal failure, critical limb ischemia, arterial calcification; nearly one sixth for chronic heart failure and certain genetic characteristics), it is very likely that a person not belonging to class C or D of the TASC II classification has one or more other risk factors for restenosis. Therefore, patients belonging to class C or D and having two or three other risk factors are considered as having a very high level of risk.

Cost–effectiveness analysis

In October 2014, the cost of an intervention with a drug-coated balloon was CAD$7868.98, while it was CAD$7589.49 with a bare metal stent and CAD$6375.60 with an uncoated balloon (Table 5). These costs were calculated from the supplies used to perform a *de novo* revascularization of the femoropopliteal artery, the remuneration of healthcare professionals and medical doctors (payroll taxes and fringe benefits included), antiplatelet therapy for 3 days, hospitalization for 3 days, rehabilitation therapy in 1% of patients, laboratory tests and indirect costs related to the operation of our institution (hereinafter referred support services, corresponding to 16% of clinical expenditures excluding the remuneration of medical doctors).

The initial extra cost associated with the use of a drug-coated balloon compared with a bare metal stent or an uncoated balloon was calculated from the purchase price of these devices and their utilization rates in our angiography department. The extra cost to use a drug-coated balloon is thus of CAD$279.49 compared with a bare metal stent and CAD$1493.38 compared with an uncoated balloon.

Similar calculations were performed to determine the costs of reintervention after a first revascularization failure. These calculations were based on an algorithm of reintervention developed by two interventional radiologists in our institution (see Supplementary Figure). This algorithm of reintervention represents the current practice in our institution. These calculations clearly show that the cost of a reintervention following

Table 3. Amputation rate according to the medical device used.

Study (year)	Drug-coated balloon (paclitaxel)	Uncoated balloon	Bare metal stent	Ref.
Katsanos *et al.* (2014)	1.1%; 1 year follow-up	1.2%; 1 year follow-up	0.5%; 1 year follow-up	[3]
Fusaro *et al.* (2013)	0.5%; 6–12 months follow-up	1.0%; 6–12 months follow-up; p = 0.78	1.5%; 6–24 months follow-up; p = 0.66	[13]

Results for the uncoated balloon and bare metal stent were compared with those of the drug-coated balloon: a p-value ≤ 0.05 indicates a significant difference (in bold).

Table 4. Mortality rate according to the medical device used.

Study (year)	Drug-coated balloon (paclitaxel)	Uncoated balloon	Bare metal stent	Ref.
Fusaro *et al.* (2013)	5.9%; 6–12 months follow-up	5.9%; 6–12 months follow-up; p = 0.92	4.3%; 6–24 months follow-up; p = 0.55	[13]

Results for uncoated balloons and bare metal stents were compared with those of drug-coated balloons: a p-value ≤ 0.05 indicates a significant difference (in bold).

a *de novo* revascularization with a bare metal stent or an uncoated balloon was higher than for a drug-coated balloon (Table 6). This extra cost was CAD$2626.81 and CAD$522.68, respectively.

The effectiveness of drug-coated balloons compared with bare metal stents and uncoated balloons was given by the hazard ratio (HR) of the target lesion revascularization rate. Regarding the effectiveness of drug-coated balloons compared with bare metal stents, results from the literature were not consistent, with HRs ranging from 0.5 to 1 up to 24 months [3,13]. We thus retain both values and a median scenario with a HR set at 0.8. In terms of effectiveness of drug-coated balloons compared with uncoated balloons, results from the literature indicated a superiority of drug-coated balloons ranging from 0.3 to 0.6 [2,3,13]. These two values and a median scenario at 0.5 were retained.

Regarding the target lesion revascularization on which to apply the HRs, we also faced some variability. That rate would be 16–18% up to 24 months for the bare metal stent [3,13] while 2 years data collected in our institution indicate a rate of 13.6%. Rates of 13.6 and 18% are retained. For uncoated balloons, the available data were highly variable, with rates ranging from 22 to 51% over 1 year. We retained rates of 25 and 50% to perform our cost–effectiveness simulations over 2 years. These simulations were conducted on a deterministic approach in an Excel file.

As stated in the methods section, in each cost–effectiveness simulation, we considered different proportions of patients with different risk factors of reintervention. The main risk factor considered belongs to class C or D of the TASC II classification, with a risk of reintervention set at 2.4. Subsequently, patients in groups A–B or C–D were divided into subgroups according to whether they have more or fewer other risk factors (e.g., diabetes mellitus, renal failure, among others). Given the high prevalence of various risk factors set out in the section on risk factors, it appears that a representative patient should have at least one risk factor statistically significant (apart from class C or D in the TASC II classification). As a consequence, a low-risk patient should show no or only one significant risk factor and a patient at high risk should have a minimum of two significant risk factors. The level of risk for a low-risk patient was considered to be 1.4-times lower than the average patient while it was 1.285-times higher for a high-risk patient. In the end, this categorization of patients provided six groups with different levels of risk of target lesion revascularization after a first intervention. The size of these groups was considered equal. Indeed, most of the studies reviewed in the section on risk factors indicated that approximately 50% of patients were classified C or D in the TASC II classification. Regarding the proportions of patients with one or more risk factors, these data were not available in the literature; we therefore consider by

Table 5. Costs of a *de novo* revascularization for the femoropopliteal artery in 2014 in the Quebec healthcare network.

Device used	Drug-coated balloon (CAD$)	Bare-metal stent (CAD$)	Uncoated balloon (CAD$)
Healthcare professionals	325.79	325.79	325.79
Medical doctors	1014.19	1119.35	1014.19
Furniture	1672.15	1672.15	1672.15
Balloon and/or stent	1879.60	1548.00	592.20
Antiplatelet therapy	4.23	4.23	4.23
Hospitalization	1995.00	1995.00	1995.00
Rehabilitation therapy	15.00	15.00	15.00
Laboratory tests	17.54	17.54	17.54
Support services	945.49	892.43	739.51
Total	**7868.98**	**7589.49**	**6375.60**

Table 6. Costs of a revascularization reintervention for the femoropopliteal artery (second intervention) in 2014 in the Quebec healthcare network.

Device used during the first intervention	Drug-coated balloon (CAD$)	Bare-metal stent (CAD$)	Uncoated balloon (CAD$)
Healthcare professionals	325.79	343.71	325.79
Medical doctors	914.88	1351.38	909.90
Furniture	1672.15	2365.26	1672.15
Balloon and/or stent	1050.23	2 227.40	1505.10
Antiplatelet therapy	4.23	4.23	4.23
Hospitalization	1995.00	1995.00	1995.00
Rehabilitation therapy	15.00	15.00	15.00
Laboratory tests	17.54	17.54	17.54
Support services	812.79	1114.90	885.57
Total	**6807.61**	**9434.42**	**7330.28**

default that they were equivalent. Table 7 indicates the target lesion revascularization rates retained for different groups of patients at risk according to the medical device used (i.e., bare metal stent or uncoated balloon).

Table 8 shows the simulation results for the drug-coated balloon versus the alternative depending on the target lesion revascularization rate (i.e., target lesion revascularization [TLR] with a bare metal stent or an uncoated balloon), the HR (i.e., effectiveness of the drug-coated balloon compared with the alternative) and the group of patients at risk. For each of the comparators, we gave priority in our analysis to the two median scenarios (HR: 0.8 for the bare metal stent and HR: 0.5 for the uncoated balloon).

Three main findings spring from Table 8. First, the median scenario always shows that the use of a drug-coated balloon is more cost effective than the use of a bare metal stent when the analysis involves all categories of patients. However, greater savings are observed for patients at highest risk (TASC II C or D), particularly due to the high difference in reintervention costs. Cost savings for the most at-risk patients derive from this important difference even when the retained HR is equal to 1. Second, the median scenario is cost effective for the drug-coated balloon compared with the uncoated balloon only if the target lesion revascularization rate with the uncoated balloon is very high (i.e., 50%). Third, the more the population targeted to use the drug-coated balloon is at risk of a subsequent reintervention, the greater the cost savings will be.

Discussion

The methodology used in this study restricted the literature search on the effectiveness of drug-coated balloons to the last 4 years and limited the search to

Table 7. Target lesion revascularization according to the categories of patients at risk of reintervention and the type of *de novo* intervention.

Risk of reintervention	TLR in TASC II A or B (%)			TLR in TASC II C or D (%)		
	Low risk	Average risk	High risk	Low risk	Average risk	High risk
***De novo* intervention with a bare metal stent**						
Simulation 1 with average TLR of 13.6%	5.7	8	10.3	13.7	19.2	24.7
Simulation 2 with average TLR of 18%	7.6	10.6	13.6	18.1	25.4	32.6
***De novo* intervention with an uncoated balloon**						
Simulation 3 with average TLR of 25%	10.5	14.7	18.9	25.2	35.3	45.3
Simulation 4 with average TLR of 50%	21.0	29.4	37.8	50.4	70.6	90.7

TLR: Target lesion revascularization.

Table 8. Cost–effectiveness simulations over 2 years for 100 patients in the Quebec healthcare network (extra cost in Canadian Dollars).

Effectiveness of DCB vs the alternative (HR)	All patients (CAD$)	TASC II A or B (CAD$)	TASC II C or D (CAD$)	TASC II C or D with high risks (CAD$)
DCB vs BMS with TLR at 13.6% (local data)				
HR: 1.0 DCB (13.6%) vs BMS (13.6%)	-7767 (0.00)	6922 (0.00)	-22,457 (0.00)	-36,933 (0.00)
HR: 0.8 DCB (10.9%) vs BMS (13.6%)	-26,280 (2.72)	-3976 (1.60)	-48,583 (3.84)	-70,563 (4.94)
HR: 0.5 DCB (6.8%) vs BMS (13.6%)	-54,048 (6.80)	-20,324 (4.00)	-87,772 (9.59)	-121,007 (12.35)
DCB vs BMS with TLR at 18% (literature data)				
HR: 1.0 DCB (18%) vs BMS (18%)	-19,279 (0.00)	89 (0.00)	-38,646 (0.00)	-57,685 (0.00)
HR: 0.8 DCB (14.4%) vs BMS (18%)	-43,758 (3.60)	-14,351 (2.12)	-73,163 (5.07)	-102,071 (6.52)
HR: 0.5 DCB (9%) vs BMS (18%)	-80,476 (8.99)	-36,012 (5.30)	-124,940 (12.68)	-168,649 (16.30)
DCB vs UB with TLR at 25% (literature data)				
HR: 0.6 DCB (15%) vs UB (25%)	68,268 (9.99)	101,599 (5.88)	34,937 (14.10)	2307 (18.12)
HR: 0.5 DCB (12.5%) vs UB (25%)	51,264 (12.49)	91,586 (7.35)	10,943 (17.62)	-28,532 (22.65)
HR: 0.3 DCB (7.5%) vs UB (25%)	17,257 (17.48)	71,560 (10.30)	-37,046 (24.67)	-90,209 (31.71)
DCB vs UB with TLR at 50% (literature data)				
HR: 0.6 DCB (30%) vs UB (50%)	-12,807 (19.98)	53,882 (11.76)	-79,495 (28.20)	-144,950 (36.27)
HR: 0.5 DCB (25%) vs UB (50%)	-46,815 (24.98)	33,861 (14.70)	-127,491 (35.25)	-206,675 (45.33)
HR: 0.3 DCB (15%) vs UB (50%)	-114,832 (34.97)	-6181 (20.59)	-223,482 (49.35)	-330,123 (63.47)

For each group of patients, the number of avoided reinterventions is given in parentheses. A negative value indicates a saving.
BMS: Bare metal stent; DCB: Drug-coated balloon; HR: Hazard ratio; TLR: Target lesion revascularization; UB: Uncoated balloon.

meta-analyses and health technology assessment agencies reports. As a consequence, some recent data from primary studies may not have been considered in this analysis. Indeed, the three meta-analyses identified, those of Katsanos *et al.* [3], Fusaro *et al.* [13] and Simpson *et al.* [2], reported that their last literature search was conducted in January 2013, November 2012 and May 2011, respectively. However, recent primary studies on this topic do not show very different results from these meta-analyses. Tepe *et al.* [22] and Rosenfield *et al.* [23], for example, indicate no difference as regard to amputation and mortality at 12 months between drug-coated balloon and uncoated balloon. The IN.PACT study by Tepe *et al.* [22] indicates a significant reduction in TLR (2.4 vs 20.6%), whereas the LEVANT 2 study by Rosenfield *et al.* [23] indicates a nonsignificant reduction in TLR (12.3 vs 16.8%), which they explain by the very low TLR rate in the uncoated balloon group as compared with previous studies. As for these recent primary studies, studies included in the three meta-analyses were randomized. A limit of the included studies is their short-term follow-up (less than 2 years) and the small number of subjects did not allow for subgroup analysis. In this regard, it would have been appropriate to perform subanalyses for certain classes of technologies and even patients. Indeed, because the search for primary studies conducted by Katsanos *et al.* [3], Fusaro *et al.* [13] and Simpson *et al.* [2] was spread over several years, the results generated by these authors did not take into account improvements to the technology. Katsanos *et al.* [3] indicate, for example, the presence of differences in the design and geometry of the stents used in the various studies reviewed. However, we believe that we have limited this type of bias using a literature research methodology that was limited to the last 4 years. In this way, this evaluation took into account more recent data by eliminating systematic reviews that may put too much emphasis on outdated technologies. For example, some less efficient technologies that are no longer used for revascularization of the femoropopliteal artery, such as stent 'tantalum' and 'balloon-expendable stainless steel stent' were not included in the meta-analyses of Katsanos *et al.* [3], Fusaro *et al.* [13] and Simpson *et al.* [2]. The data for these technologies, however, were included in some less recent meta-analyses published in 2008 and 2009 [4,24,25]. As regard to a longer follow-up with drug-coated balloon, a very recent study by Laird *et al.* [26] indicates that the efficacy of the drug-coated balloon is maintained at 2 years as compared with the uncoated balloon (TLR of 9.1 vs 28.3%).

Some differences between the meta-analyses reviewed could explain the differences in the target

lesion revascularization rates observed in Table 1. Specifically, in the meta-analysis of Katsanos *et al.* [3], they observed a rate of 8% for the drug-coated balloon, while this percentage was 20 and 14% in the meta-analyses of Fusaro *et al.* [13] and Simpson *et al.* [2], respectively. The meta-analysis of Katsanos *et al.* [3] is the most recent and therefore it is the only one to have included the 'DEBELLUM' study [27]. However, the work of Fanelli *et al.* [27] has generated very low target lesion revascularization rates (i.e., 6%), which could have pulled down the estimate generated in the meta-analysis of Katsanos *et al.* [3] For their part, the work of Fusaro *et al.* [13] also identified a study that was not present in the meta-analysis of Katsanos *et al.* [3]; the BIOLUX P-1 study, which has not yet been published but was presented as part of a conference [28]. Although it was not possible to obtain the data from this study for the target lesion revascularization rates, these data could also have influenced the final estimate generated in the meta-analysis of Fusaro *et al.* [13]

Regarding the methodology used in the cost–effectiveness analysis, we note two limitations in the calculation of the costs per intervention. First, it should be noted that the revascularization of the femoropopliteal artery requires a number of medical devices that varies greatly from one patient to another. Thus, for each category of intervention, we calculated the mean number of devices. For example, one intervention with the drug-coated balloon requires on average 1.25 drug-coated balloons, together with 1.5 uncoated balloons. However, these means were obtained from a limited number of interventions (11 cases analyzed), which limits the accuracy of the results. The second limitation about the costs per intervention concerns the risk factors of reintervention. In our model, we calculated an average cost per procedure, depending on the technology used, regardless of the TASC II classification. However, classes C and D are associated with longer lesions that may require longer devices. According to the price differences associated with the length of the devices, the calculated intervention costs may thus be different for one or the other technology. However, after examination of these various prices in our institution, we believe that these differences may only have a marginal impact on our results.

Conclusion

This study assessed whether the use of drug-coated balloons for revascularization of the femoropopliteal artery was cost effective compared with bare metal stents and uncoated balloons. First, our literature search indicated that the use of drug-coated balloons was associated with lower rates of target lesion revascularization compared with uncoated balloons. The results of two meta-analyses also indicated that target lesion revascularization rates for drug-coated balloons were lower or equivalent to those with bare metal stents. However, our study also indicates a substantial heterogeneity in clinical results. In a cost–effectiveness analysis this turns to uncertainty that we dealt with a sensitivity analysis. The cost–effectiveness analysis indicated that the use of drug-coated balloons was generally cost effective compared with bare metal stents, particularly for patients at high risk of recurrence. In addition, drug-coated balloons are cost effective in comparison with uncoated balloons if the target lesion revascularization rate associated with uncoated balloons is very high and for the most at-risk patients (TASC II C or D). In short, in a Canadian context where the use of drug-coated balloons are three-times more expensive than uncoated balloons and slightly more expensive than bare metal stents, our analysis indicated that the use of drug-coated balloons in a context of high risk of restenosis and reintervention was associated with greater savings. For patients at low risk of restenosis and reintervention, uncoated balloons remained the optimal choice.

Supplementary Data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2015-0016

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Cost of the drug-coated balloon is higher in comparison to commonly used medical devices.
- A cost–effectiveness analysis was conducted to compare drug-coated balloon to uncoated balloon and bare-metal stent with regard to target lesion revascularization for femoropopliteal occlusive disease.
- The analysis considered patients for *de novo* intervention and calculated costs associated with this intervention and subsequent costs if the intervention was unsuccessful.
- Sensitivity analyses were performed regarding the initial levels of reintervention and the effectiveness of drug-coated balloons versus bare metal stents and uncoated balloons (i.e., hazard ratio).
- Meta-analyses indicate that target lesion revascularization rate (repeated intervention) was lower for drug-coated balloons compared with uncoated balloons. When compared with bare metal stents, the results were comparable to or in favor of the drug-coated balloons. The same tendency was observed for the restenosis rate. For the mortality rate or limb amputation, no significant difference was found.
- The cost–effectiveness analysis showed that drug-coated balloon were more efficient than uncoated balloon and bare metal stent when used with patients with high risks of reintervention.
- The reintervention cost is much higher for bare metal stent than drug-coated balloon.

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