JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 22, 2016
ISSN 1936-8798
http://dx.doi.org/10.1016/j.jcin.2016.08.036

PERIPHERAL

Cost-Effectiveness of Endovascular Femoropopliteal Intervention Using Drug-Coated Balloons Versus Standard Percutaneous Transluminal Angioplasty

Results From the IN.PACT SFA II Trial

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the cost-effectiveness of drug-coated balloon (DCB) angioplasty versus standard percutaneous transluminal angioplasty (PTA).

BACKGROUND Recent trials have reported lower rates of target lesion revascularization with DCB angioplasty versus standard PTA. However, the cost-effectiveness of DCB angioplasty is unknown.

METHODS A prospective economic study was performed alongside the IN.PACT SFA II (IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA]) trial, which randomized 181 patients with femoropopliteal disease to the IN.PACT DCB versus standard PTA. Resource use data were collected over 2-year follow-up, and costs were assigned using resource-based accounting and billing data. Health utilities were assessed using the EuroQol 5-dimensions questionnaire. Cost-effectiveness was assessed as cost per quality-adjusted life-year (QALY) gained using a decision-analytic model on the basis of empirical data from the trial assuming identical long-term mortality.

RESULTS Initial costs were $1,129 per patient higher with DCB angioplasty than standard PTA, driven by higher costs for the DCB itself. Between discharge and 24 months, target limb-related costs were $1,212 per patient lower with DCB angioplasty such that discounted 2-year costs were similar for the 2 groups ($11,277 vs. $11,359, $p = 0.97$), whereas QALYs tended to be greater among patients treated with DCBs (1.53 ± 0.44 vs. 1.47 ± 0.42, $p = 0.40$). The probability that DCB angioplasty is cost-effective compared with standard PTA was 70% using a threshold of $50,000 per QALY gained and 79% at a threshold of $150,000 per QALY gained.

CONCLUSIONS For patients with femoropopliteal disease, DCB angioplasty is associated with better 2-year outcomes and similar target limb-related costs compared with standard PTA. Formal cost-effectiveness analysis on the basis of these results suggests that use of the DCB angioplasty is likely to be economically attractive. (J Am Coll Cardiol Intv 2016;9:2343–52) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon

ICER = incremental cost-effectiveness ratio

PAD = peripheral artery disease

PTA = percutaneous transluminal angioplasty

QALY = quality-adjusted life-year

Lower extremity peripheral artery disease (PAD) is both common and costly, affecting more than 8 million patients in the United States alone at an annual cost in excess of $21 billion (1–3). In recent years, endovascular intervention has become the dominant mode of revascularization for patients with symptomatic femoropopliteal disease (4), but these procedures are limited by relatively high rates of restenosis (particularly after percutaneous transluminal angioplasty [PTA] alone), leading to costly repeat procedures (5). Although bare-metal and drug-eluting stents improve patency compared with PTA alone, long-term outcomes may be compromised

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by complications such as stent fracture and in-stent restenosis (6,7).

More recently, paclitaxel-coated balloons have been shown to reduce rates of restenosis and repeat revascularization for patients undergoing femoropopliteal intervention without the need for stent implantation (8–10), leading to U.S. Food and Drug Administration approval of 2 such devices. Because drug-coated balloons (DCBs) are significantly more expensive than standard PTA balloons, and given the large number of patients who may be candidates for such treatment, it is important to understand the impact of DCB technology on the costs and cost-effectiveness of revascularization for symptomatic PAD. Although several studies have suggested that DCB angioplasty may be economically attractive (11,12), these studies were based predominantly on short-term mechanistic (rather than clinical) outcomes from early DCB studies. Because the association between mechanistic outcomes and clinical and economic outcomes is not clearly established, questions remain about the validity of these studies and their conclusions. To address these gaps in knowledge, we performed a prospective health economic assessment alongside the IN.PACT SFA II (IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA]) trial, the U.S. phase of the pivotal trial that led to Food and Drug Administration approval of the IN.PACT Admiral DCB (Medtronic, Santa Rosa, California) for femoral and popliteal angioplasty.

METHODS

PATIENT POPULATION. The population for this study was drawn from IN.PACT SFA II trial (NCT01566461), a multicenter randomized trial of the IN.PACT Admiral DCB versus standard PTA in patients undergoing revascularization for symptomatic femoropopliteal PAD. Because our goal was to understand the economics of DCB in the context of the U.S. health care system, the economic analysis was restricted to those patients enrolled at U.S. centers (IN.PACT SFA II trial). The design and outcomes of the overall IN.PACT SFA trial have been described previously (8,9). Briefly, after successful pre-dilation, eligible patients with severe femoral or proximal popliteal stenoses and symptoms of claudication or ischemic rest pain (Rutherford classes II to IV) were randomized in a 2:1 fashion to DCB angioplasty or standard PTA. All patients underwent clinical follow-up, and duplex ultrasound was performed on all patients at 30-day, 6-month, 12-month, and 24-month follow-up.

OVERVIEW OF STUDY DESIGN AND DATA COLLECTION. The economic analysis was conducted from the perspective of the U.S. health care system. We prospectively collected detailed resource use data for the index hospitalization and all subsequent hospitalizations for vascular care; hospital billing data including summary statements (UB-04 forms) as well as itemized bills were also collected. At baseline and at each follow-up visit through 24 months, quality-of-life assessments were performed using the EuroQol 5-dimensions questionnaire (13). All clinical endpoints were adjudicated by a blinded clinical events committee.

DETERMINATION OF MEDICAL CARE COSTS. Medical care costs for the initial hospitalization and through 2-year follow-up were assessed using a combination of "bottom-up" and "top-down" methods as described previously (14). Given the modest sample size of the study, it was important to limit the scope of the economic analysis to focus on those costs that would

equity interest in PQ Bypass and Vascular Therapies; and is on the boards of VIVA Physicians (a 501[c][3] not-for-profit education and research organization) and the Society for Cardiovascular Angiography and Interventions. Dr. Schnieder has received modest royalties for intellectual property from Cook; serves as a noncompensated adviser to Medtronic, Cardinal, Abbott Vascular; and is on the board of VIVA Physicians. Dr. Laird has received research grant support from W.L. Gore and has provided consulting services to Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Cordis and Medtronic. Dr. Cohen has received research grant support from Abbott Vascular, Boston Scientific, and Medtronic; and has provided consulting services to Abbott Vascular, Cardinal Health, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 13, 2016; revised manuscript received August 15, 2016, accepted August 25, 2016.

be expected to be influenced by the treatment strategy. Thus, the primary cost endpoint was total PAD-related costs for the target limb.

PROCEDURAL COSTS. Detailed resource use data was recorded for each index procedure, and the cost of each item was estimated on the basis of the mean hospital acquisition cost for the item in 2014. The acquisition cost of the DCB was set at $1,375, reflecting the average U.S. sales price at the time of the analysis. Costs of additional disposable equipment, overhead, and depreciation for the cardiac catheterization or vascular laboratory were estimated on the basis of the average cost per procedure at Saint Luke's Mid America Heart Institute in 2014 and adjusted for actual procedure duration.

OTHER HOSPITAL COSTS. All other hospital costs were determined using "top-down" accounting methods as described previously (15). Itemized bills were obtained for the initial hospitalization and any subsequent vascular-related hospitalizations during the follow-up period. Hospital costs were determined by multiplying itemized hospital charges by the cost center–specific cost-to-charge ratio obtained from the hospital's Medicare cost report (16). For hospitalizations without billing data (22.1%), nonprocedural costs were estimated using a linear regression model including covariates of intensive care unit length of stay and overall length of stay (model $R^2 = 0.38$). Inclusion of additional covariates did not significantly improve model fit. For follow-up target limb vascular hospitalizations that did not include a revascularization procedure, hospitalization costs were assigned on the basis of the appropriate Medicare severity diagnosis-related group. All costs were converted to 2014 dollars on the basis of the medical care component of the Consumer Price Index.

HEALTH UTILITIES AND QUALITY-ADJUSTED LIFE-YEARS. Quality of life was assessed using the EuroQol 5-dimensions questionnaire, which was administered to all patients at baseline and at 1-, 6-, 12-, and 24-month follow-up. The results of the EuroQol 5-dimensions questionnaire were converted to health utilities using a U.S.-specific algorithm (13), and quality-adjusted life-years (QALYs) were calculated for each patient as time-weighted averages, assuming that transitions between health states occurred at the midpoint of each observation period. Missing utility data were imputed using multiple imputation.

STATISTICAL ANALYSES. Categorical data are reported as frequencies and were compared using the Fisher exact test. Continuous data are reported as mean ± SD and were compared using the Student *t* tests or the Wilcoxon rank sum test as appropriate. Because cost data were not normally distributed, they were compared using nonparametric bootstrapping (1,000 replicates). A p value <0.05 was considered to indicate statistical significance for all comparisons.

COST-EFFECTIVENESS MODEL AND ANALYSES. The original analytic plan was to perform a patient-level cost-effectiveness analysis using the observed 2-year cost and QALY data for each patient. However, as reported previously for the overall IN.PACT SFA trial population (9), a significant imbalance in 2-year mortality was observed between treatment arms in the IN.PACT SFA II trial (10.7% for the DCB angioplasty group vs. 0% for the standard PTA group, $p = 0.005$). However, there were several reasons to believe that this differential mortality was a chance finding. First, the majority of these deaths occurred late in the second year of the follow-up period. Second, after adjudication by an independent, blinded clinical events committee, no relationship was found between any death and either the study device or index revascularization procedure. Finally, the observed mortality rate in the standard PTA group was considerably lower than has been seen in other contemporary PAD studies (9,17,18), suggesting that the low mortality rate in the control group was likely a spurious finding related to the relatively small sample size of the standard PTA group.

Because differential mortality would have led to lower than expected costs as well as QALYs in the DCB angioplasty group (with an unpredictable effect on the cost-effectiveness ratios), it was necessary to use a different analytic approach to compensate for this unexpected result. Therefore, a state-transition Markov model was developed to project 2-year costs and QALYs for the IN.PACT SFA II population. Consistent with the empirical nature of the analysis, all model parameters were on the basis of the observed data from the study population, except that long-term mortality was assumed to be equal for the 2 treatment groups. Full details of the model structure and underlying assumptions are provided in the Online Appendix.

COST-EFFECTIVENESS ANALYSES. The primary cost-effectiveness analysis was performed as a cohort analysis using the Markov model to estimate 2-year QALYs and costs for treatment with either DCB angioplasty or standard PTA for a typical patient from the IN.PACT SFA II trial. The incremental cost-effectiveness ratio (ICER) was calculated for DCB angioplasty versus standard balloon PTA as the difference in 2-year costs divided by the difference in 2-year QALYs. We then performed 1-way sensitivity analyses on each of the model parameters to identify which factors had the greatest impact on the ICERs.

TABLE 1 Baseline Patient Characteristics

	DCB (n = 121)	PTA (n = 60)	p Value
Age (yrs)	68.4 ± 8.8	68.2 ± 9.7	0.891
Male (%)	77 (63.6)	38 (63.3)	0.968
Diabetes (%)	58 (47.9)	24 (40.0)	0.313
Current smoking (%)	39 (32.2)	18 (30.0)	0.761
Rutherford class (%)			0.357
II	50 (41.3)	23 (38.3)	
III	62 (51.2)	34 (56.7)	
IV	9 (7.4)	2 (3.3)	
V	0 (0.0)	1 (1.7)	
Target lesion length (cm)*	8.5 ± 4.9	9.3 ± 5.6	0.322
Total occlusion (%)*	19.7	16.4	0.591
Reference vessel diameter* (mm)	4.8 ± 0.9	4.7 ± 0.8	0.486
Percentage stenosis (%)*	79 ± 16	80 ± 13	0.541

Values are mean ± SD or n (%). *Lesion characteristics analysis: DCB, n = 122; PTA, n = 61.
DCB = drug-coated balloon; PTA = percutaneous transluminal angioplasty.

Finally, to more fully characterize the uncertainty surrounding our results, we performed a probabilistic sensitivity analysis in which all model parameters were sampled from their respective distributions. A total of 1,000 independent analyses were performed, and the results are reported in terms of a cost-effectiveness acceptability curve, which describes the probability that DCB angioplasty will be economically attractive (i.e., cost effective) at any societal cost-effectiveness threshold (19).

TABLE 2 Index Procedure Resource Use and Costs

	DCB (n = 121)	Standard PTA (n = 60)	Difference (95% CI)	p Value
Procedure duration (min)	156 ± 115	171 ± 121	−15 (−52 to 21)	0.42
Guidewires	2.3 ± 1.4	2.6 ± 1.4	−0.2 (−0.7 to 0.2)	0.28
Guiding sheaths/catheters	1.8 ± 1.0	2.0 ± 1.1	−0.1 (−0.4 to 0.2)	0.41
Diagnostic/Glide catheters	0.8 ± 0.9	1.2 ± 1.0	−0.3 (−0.6 to −0.1)	0.02
Backup/support catheters	0.2 ± 0.4	0.2 ± 0.4	0.0 (−0.1 to 0.1)	0.70
Pre-dilation balloons	1.1 ± 0.4	1.1 ± 0.3	0.0 (−0.1 to 0.2)	0.36
IN.PACT Admiral paclitaxel-coated balloons	1.4 ± 0.6	0.0 ± 0.0	1.4 (1.2 to 1.6)	<0.001
Post-dilation balloons	0.2 ± 0.4	0.2 ± 0.4	0.0 (−0.1 to 0.1)	0.91
Provisional stents	0.0 ± 0.2	0.2 ± 0.4	−0.1 (−0.2 to −0.0)	0.003
IVUS catheters	0.0 ± 0.2	0.1 ± 0.3	−0.0 (−0.1 to 0.0)	0.46
Contrast volume (ml)	177 ± 95	192 ± 111	−15 (−47 to 16)	0.34
Closure devices	0.6 ± 0.5	0.6 ± 0.5	0.0 (−0.1 to 0.2)	0.80
Device costs ($)	3,012 ± 1,079	1,444 ± 807	1,568 (1,257 to 1,879)	<0.001
Room/overhead costs ($)	2,276 ± 1,681	2,495 ± 1,759	−219 (−751 to 312)	0.38
Medication costs ($)	33 ± 154	31 ± 178	2 (−49 to 53)	0.86
Nonphysician personnel costs ($)	525 ± 280	562 ± 293	−37 (−125 to 52)	0.38
Additional supply costs ($)	72 ± 0	72 ± 0	0.0 (0.0 to 0.0)	1.00
Total procedure costs ($)	5,953 ± 2,426	4,604 ± 2,331	1,349 (601 to 2,097)	0.002

Values are mean ± SD.
CI = confidence interval; IVUS = intravascular ultrasound; other abbreviations as in Table 1.

RESULTS

PATIENT POPULATION. Between April 2012 and January 2013, a total of 181 U.S. patients were enrolled in the IN.PACT SFA II trial and randomized to either initial DCB treatment with the IN.PACT Admiral balloon (n = 121) or standard PTA (n = 60). Baseline characteristics were well balanced between the 2 groups with respect to key demographic, clinical, and angiographic characteristics (Table 1).

INDEX HOSPITALIZATION RESOURCE USE AND COSTS. Resource use and costs for the index revascularization procedure and the associated hospitalization are summarized in Tables 2 and 3. On average, 1.4 ± 0.6 DCBs were used to treat each patient in the DCB arm. Provisional stenting was performed more frequently in patients treated with standard PTA (13.3% vs. 2.5%; p = 0.007). Index procedural costs were approximately $1,300 per patient higher for the DCB angioplasty group compared with standard PTA ($5,953 vs. $4,604; p = 0.002), driven by the cost of the DCB itself. During the initial hospitalization, there were no significant differences in clinical events or length of stay; total index hospitalization costs were $1,129 higher for patients treated with DCB angioplasty compared with standard PTA ($8,293 vs. $7,164; p = 0.03).

2-YEAR OUTCOMES AND COSTS. Clinical outcomes, resource use, and costs through 2-year follow-up are summarized in Table 4. Target limb revascularization procedures were less frequent in patients treated with DCB angioplasty versus standard PTA (9.9% vs. 30.0%; p < 0.001). When analyzed in terms of the total number of repeat revascularization procedures, the difference was slightly larger, reflecting the more frequent need for second and third target limb revascularization procedures in a small number of patients in the standard PTA group.

Overall, this reduction in repeat revascularization procedures was associated with approximately $1,200 per patient lower follow-up target limb-related costs with DCB angioplasty versus standard PTA; however, this difference was not statistically significant. After including the cost of the index revascularization procedures, total target limb-related costs through 2 years were similar in patients treated with DCB angioplasty versus standard PTA ($11,277 ± $14,224 vs. $11,359 ± $8,874; 95% confidence interval for difference: −$4,043 to $3,878; p = 0.95). Mean costs

within the DCB angioplasty group were strongly influenced by a single high-cost outlier who required a total of 6 vascular-related hospitalizations and 7 target limb revascularization procedures over the 2-year follow-up period. In an analysis in which that patient's follow-up costs were trimmed to those of the next highest cost patient, mean total 2-year costs were about $700 per patient lower with DCB angioplasty versus standard PTA ($10,656 ± $8,776 vs. $11,359 ± $8,874; p = 0.61).

UTILITY WEIGHTS AND QUALITY-ADJUSTED LIFE EXPECTANCY. At baseline and 1-month follow-up, mean utility weights were virtually identical between the DCB angioplasty and standard PTA groups (Table 5). Although there were trends toward higher utilities with DCB at 12- and 24-month follow-up, none of these differences were statistically significant. Quality-adjusted life expectancy over the 2-year follow-up period was also similar for the DCB angioplasty and standard PTA groups (1.53 ± 0.44 vs. 1.47 ± 0.42; p = 0.40). For patients surviving through 2-year follow-up, those who required at least 1 repeat revascularization had numerically fewer 2-year QALYs than patients who did not require repeat revascularization (1.47 vs. 1.52; p = 0.59). After adjusting for age, sex, and 1-month utility, the reduction in QALYs associated with repeat revascularization (i.e., the disutility of repeat revascularization) was 0.059 ± 0.034.

COST-EFFECTIVENESS ANALYSIS. Under our base-case assumptions, including the assumption of identical mortality for the 2 groups, the trial-based Markov model projected that index DCB angioplasty treatment would be an economically dominant strategy, with lower 2-year costs (by $576) and a small gain in QALYs of 0.01. The results of 1-way sensitivity analyses to examine the impact of variation of key model inputs on the ICER for DCB angioplasty versus standard PTA are displayed in Figure 1. The ICER for DCB versus standard PTA exceeded $50,000 per QALY gained only if the cost of repeat revascularization after PTA was <$8,647 (vs. base-case assumption of $12,772) or if the relative risk for target limb revascularization during the first year of follow-up exceeded 0.57 (vs. base-case assumption 0.30).

Probabilistic sensitivity analysis demonstrated moderate uncertainty in these results, mainly because of considerable variability in the 2-year cost difference between the 2 treatments (Figure 2). As shown in the cost-effectiveness acceptability curve (Figure 3), the probability that the DCB angioplasty strategy was economically attractive at a societal willingness-to-pay threshold of $50,000 per QALY gained was 69.7%. At a more liberal willingness-to-pay threshold of $150,000 per QALY gained, the probability that the DCB strategy was economically attractive was 79.3%. When we used the full population of the IN.PACT SFA trial (pooled data from IN.PACT SFA I and IN.PACT SFA II) to estimate the relative risk for target limb revascularization, the probability that the DCB strategy was economically attractive at thresholds of $50,000 per QALY gained and $150,000 per QALY gained was similar at 65.1% and 75.5%, respectively.

TABLE 3 Index Hospitalization Resource Use and Costs

	DCB (n = 121)	Standard PTA (n = 60)	Difference (95% CI)	p Value
Length of stay (days)	0.65 ± 0.63	0.73 ± 1.21	−0.08 (−0.35 to 0.19)	0.56
ICU length of stay (days)	0.04 ± 0.30	0.10 ± 0.44	−0.06 (−0.17 to 0.05)	0.29
Non-ICU length of stay (days)	0.61 ± 0.60	0.63 ± 0.88	−0.02 (−0.24 to 0.20)	0.85
Nonprocedural hospitalization costs ($)*	1,774 ± 1,619	1,966 ± 2,041	−192 (−743 to 360)	0.53
Inpatient physician fees ($)	566 ± 110	594 ± 193	−28 (−73 to 16)	0.30
Total hospitalization cost ($)	8,293 ± 3,230	7,164 ± 3,325	1,129 (113 to 2,146)	0.03

Values are mean ± SD. *Nonprocedural hospitalization costs include the room, nursing, and ancillary costs. ICU = intensive care unit; other abbreviations as in Tables 1 and 2.

DISCUSSION

This study is the first prospective economic analysis of DCB angioplasty versus standard PTA for treatment of intermittent claudication secondary to severe femoropopliteal PAD. On the basis of results obtained alongside the IN.PACT SFA II trial, we found that the initial costs of PTA using the DCB were approximately $1,100 per patient higher than with PTA alone. However, reductions in the need for repeat target limb revascularization over 2-year follow-up led to substantial cost offsets such that total 2-year target limb-related costs were virtually identical for the 2 strategies. When we performed a formal cost-effectiveness analysis using a decision-analytic model that was on the basis of the empirical trial data (and assuming equal long-term mortality), we found that the initial DCB angioplasty strategy was economically dominant, with projected 2-year cost savings of $576 per patient and a gain in quality-adjusted life expectancy of 0.01 years. Although there was uncertainty in these projections (particularly the difference in costs), the overall results were relatively robust in sensitivity analyses. Specifically, in a probabilistic sensitivity analysis in which all model parameters were varied simultaneously, the probabilities that the DCB angioplasty strategy would be cost-effective at thresholds of $50,000 and $150,000 per QALY gained—thresholds that are

TABLE 4 2-Year Follow-Up Events and Costs

	DCB (n = 121)	Standard PTA (n = 60)	Difference (95% CI)	p Value
Clinical events (%)				
Death	10.7	0.0	10.7 (5.2 to 16.3)	0.005
Limb-related death	0	0	0	1.00
Target limb revascularization	9.9	30.0	−20.1 (−32.8 to 7.3)	<0.001
PTA	9.9	30.0	−20.1 (−32.8 to 7.3)	<0.001
Surgical bypass	0.8	0	0.8 (−0.8 to 2.4)	1.00
Target vessel revascularization	9.1	26.7	−17.6 (−29.9 to −0.3)	0.002
PTA	9.1	26.7	−17.6 (−29.9 to −5.3)	0.002
Surgical bypass	0.8	0.0	0.8 (−0.8 to 2.4)	1.00
Amputation	1.7	1.7	−0 (−4.0 to 4.0)	1.00
Resources (count per 100 patients)				
Target limb revascularization	20.7 ± 99.9	41.7 ± 78.7	−21.0 (−50.1 to 8.1)	0.16
PTA	20.7 ± 99.9	41.7 ± 78.7	−21.0 (−50.1 to 8.1)	0.16
Surgical bypass	1.7 ± 18.2	0.0 ± 0.0	1.7 (−3.0 to 6.3)	0.48
Target vessel revascularization	19.8 ± 99.7	38.3 ± 78.3	−18.5 (−47.5 to 10.5)	0.21
PTA	18.2 ± 83.7	38.3 ± 78.3	−20.2 (−45.7 to 5.4)	0.12
Surgical bypass	1.7 ± 18.2	0.0 ± 0.0	1.7 (−3.0 to 6.3)	0.48
Amputation	1.7 ± 12.8	5.0 ± 38.7	−3.4 (−11.0 to 4.3)	0.39
Vascular hospitalization for the target limb	19.0 ± 84.0	45.0 ± 96.0	−26.0 (−53.0 to 2.0)	0.06
Costs ($)				
Target limb vascular hospitalizations	2,171 ± 12,208	3,158 ± 7,143	−987 (−4,354 to 2,379)	0.48
Inpatient physician fees	208 ± 1,029	368 ± 933	−159 (−470 to 152)	0.30
Follow-up medications	605 ± 757	670 ± 776	−65 (−303 to 173)	0.54
2-year follow-up	2,984 ± 13,247	4,196 ± 8,251	−1,212 (−4,899 to 2,476)	0.44

Values are % or mean ± SD.
Abbreviations as in Tables 1 and 2.

currently considered to represent high and intermediate economic value within the U.S. health care system (20)—were estimated at 69.7% and 79.3%, respectively. These findings suggest that for patients undergoing femoropopliteal revascularization who are similar to those enrolled in the IN.PACT SFA II trial, a strategy of initial DCB angioplasty treatment is likely to be reasonably cost effective (if not economically dominant) compared with standard PTA within the context of the U.S. health care system.

COMPARISON WITH PREVIOUS STUDIES. Several previous studies have used decision-analytic modeling to evaluate the cost-effectiveness of alternative approaches to percutaneous revascularization for femoropopliteal PAD. To date, Pietzsch et al. (12) have performed the only study to examine this issue from the perspective of the U.S. health care system. They used a decision-analytic model to estimate the 2-year costs of standard balloon angioplasty, bare-metal stenting, DCB angioplasty, and drug-eluting stents from both a payer's perspective (Medicare) as well as the perspective of hospitals providing vascular care. With the exception of 1 trial comparing drug-eluting stenting versus PTA, clinical outcomes data for their model were derived predominantly from small trials examining predominantly mechanistic endpoints across a heterogeneous patient population. Costs were on the basis of estimated sales prices for the various devices and published Medicare reimbursement rates. On the basis of these model inputs, they concluded that from a Medicare perspective, DCB was the lowest cost strategy, followed by DES, standard PTA, and finally bare-metal stent implantation.

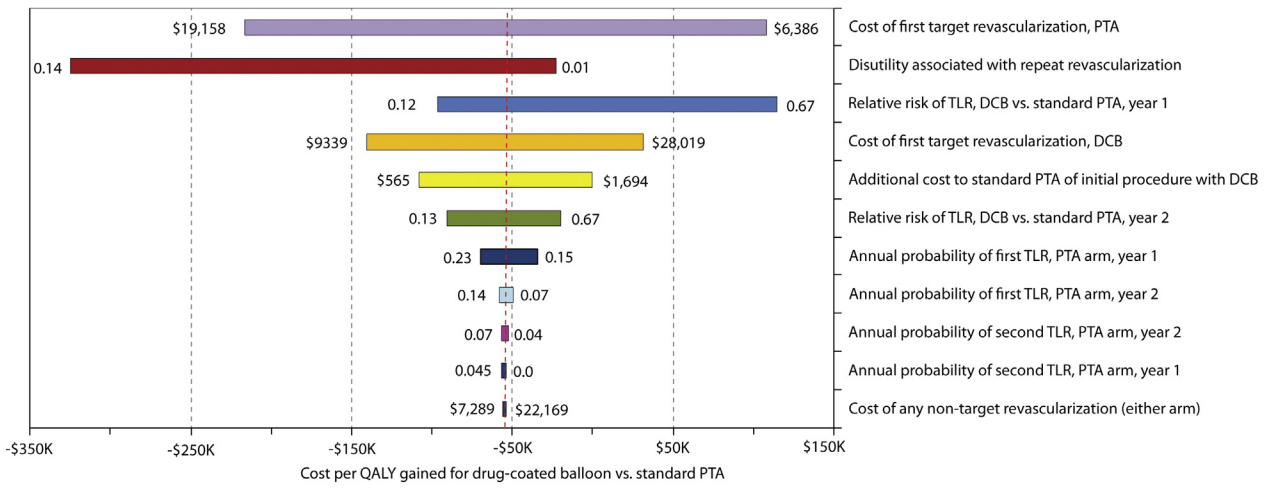
Although the results reported by Pietzsch et al. (12) were robust over a range of sensitivity analyses, the study was limited by the need to derive key parameter inputs from small studies including patient

TABLE 5 Utility Weights by Treatment Group

	DCB (n = 121)	Standard PTA (n = 60)	p Value
Baseline	0.74 ± 0.02	0.75 ± 0.02	0.71
1 month	0.85 ± 0.01	0.85 ± 0.02	0.84
6 months	0.81 ± 0.01	0.82 ± 0.02	0.69
12 months	0.83 ± 0.02	0.78 ± 0.02	0.10
24 months	0.82 ± 0.02	0.77 ± 0.03	0.12

Values are mean ± SE.
Abbreviations as in Table 1.

FIGURE 1 1-Way Sensitivity Analysis

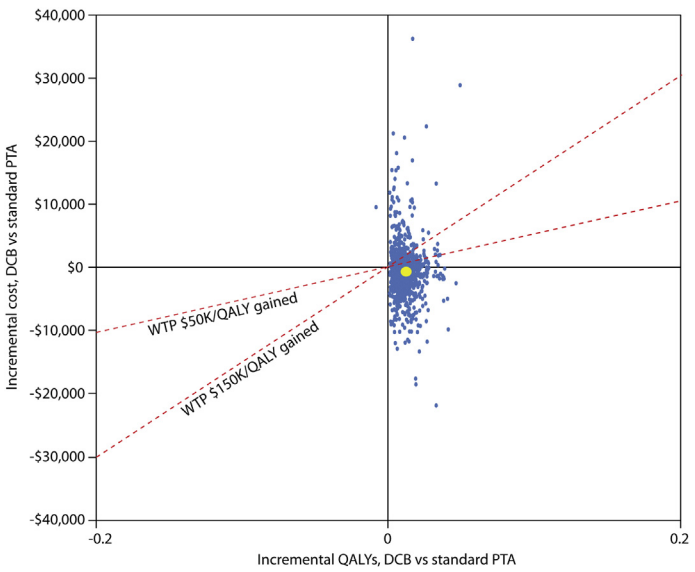


Univariate sensitivity analyses presented as a tornado diagram. The x-axis represents the incremental cost-effectiveness ratio (ICER) for drug-coated balloon (DCB) versus standard balloon percutaneous transluminal angioplasty (PTA). The diagram is stacked in order of decreasing width, whereby variations in inputs near the top have the greatest impact on the ICER. The **dotted red line** reflects a base case of −$54,849. QALY = quality-adjusted life-year; TLR = target lesion revascularization.

populations that often differed substantially with respect to key variables such as lesion length. Our study extends these findings by using prospectively collected clinical event rates, resource use, and cost data obtained alongside an adequately powered randomized clinical trial to inform the decision-analytic model. In addition, ours is the first U.S.-based analysis to evaluate not only costs but also cost-effectiveness. The fact that our cost-effectiveness results were on the basis of prospectively collected health status data further strengthens our findings.

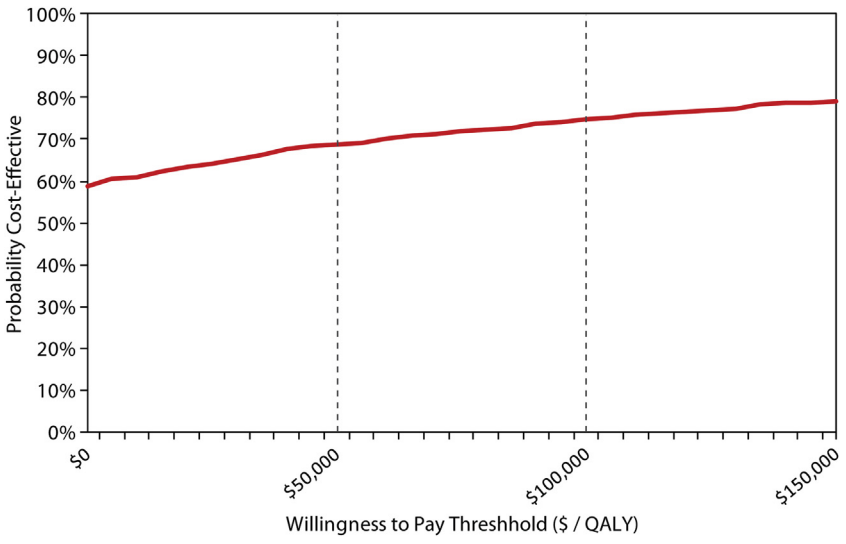
Our study reached similar conclusions to those of Kearns et al. (11), who used a decision-analytic model to examine the cost-effectiveness of several alternative approaches to lower extremity revascularization for the treatment of both intermittent claudication and critical limb ischemia from the perspective of the United Kingdom National Health Service. Similar to Pietzsch et al. (12), they relied on inputs from disparate studies to inform their model. In a lifetime cost-effectiveness analysis, they found that PTA with a DCB was a dominant strategy compared with each of the competing revascularization strategies, including standard balloon angioplasty, drug-eluting stent or bare-metal stent use (either as a primary approach or a bailout strategy), stent graft implantation, vascular brachytherapy, or cryotherapy. On the basis of probabilistic sensitivity analyses, the probability that DCB angioplasty would be cost-effective ranged from 58.3% to 63.2% across

FIGURE 2 Incremental Cost-Effectiveness of Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty



Scatterplot of the joint distribution of cost and quality-adjusted life-year (QALY) differences between drug-coated balloon (DCB) angioplasty and standard balloon percutaneous transluminal angioplasty (PTA) for a population of patients similar to IN.PACT SFA II (IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA]) on the basis of probabilistic sensitivity analysis. Each **dot** represents a model-based simulation. The **diagonal lines** represent willingness-to-pay (WTP) thresholds of $50,000 per QALY gained and $150,000 per QALY gained.

FIGURE 3 Probability That Drug-Coated Balloon Angioplasty Is Cost Effective Across Willingness-to-Pay Thresholds



The proportion of incremental cost-effectiveness ratio replicates from probabilistic sensitivity analyses that demonstrate economically attractive results across a range of willingness-to-pay thresholds. QALY = quality-adjusted life-year.

willingness-to-pay thresholds ranging from £0 per QALY to £100,000 per QALY.

Our study provides several important advantages over these previous studies. First, by prospectively collecting resource use and cost data alongside a randomized clinical trial, our study required few assumptions regarding the actual cost of the alternative revascularization procedures. In contrast, for each of the previous studies, costs for the various interventions were on the basis of a variety of simplifying assumptions. For example, Pietzsch et al. (12) assumed that only 1 DCB was used for both index and repeat revascularization procedures, but we observed that use of more than 1 device was frequent among patients treated with DCB (mean 1.4 ± 0.6 DCBs per procedure), a key driver of procedural cost. Similarly, in the absence of empirical data, Pietzch et al. (12) assumed that patients would undergo a maximum of 1 repeat intervention during the 2-year follow-up interval. In contrast, we noted that many patients required >1 repeat revascularization procedure, and we modeled both the cost and quality of life impact of multiple events explicitly. Finally, previous studies also assumed similar costs for follow-up angioplasty regardless of whether the patient was treated with DCB or standard balloon angioplasty at the index procedure. However, in IN.PACT SFA II, we found that repeat revascularization treatment patterns (and the associated costs) differed substantially following restenosis with standard PTA or DCB (higher after initial DCB) and accounted for these differential costs in our decision-analytic model as well.

STUDY LIMITATIONS. The results of our study should be considered in light of several limitations. First, only patients from the United States were included in the primary economic analysis, and these results may not be generalizable to patients in other health care systems that have different patterns of care and cost structures. Moreover, given the size of the U.S. phase of the IN.PACT trial, a relatively small number of patients were included in the analysis, and it is possible that outliers more strongly influenced costs and clinical outcomes compared with a larger study. Nonetheless, the results of several sensitivity analyses support the robustness of our findings.

Second, we did not examine the cost-effectiveness of other approaches to femoropopliteal angioplasty, such as primary stenting with bare-metal stents or drug-eluting stents or the use of atherectomy devices. In the absence of head-to-head comparative data between the IN.PACT Admiral DCB and these alternative approaches, however, such comparisons would be speculative at best. Further studies are thus needed to examine the relative costs and cost-effectiveness of these approaches. The results of this study should also not be extrapolated to other DCBs that differ from the

DCB examined in this study with respect to the balloon platform, drug dose, excipient, and other factors.

Third, as noted earlier, the IN.PACT SFA trial demonstrated differential 2-year mortality between the DCB angioplasty arm and the standard PTA arm (9). Because the most likely explanation for this excess mortality was chance, we chose to ignore this finding with respect to our cost-effectiveness analysis and to assume equivalent long-term mortality for the 2 treatment strategies. If long-term mortality were truly higher with DCB use, however, in light of the small gain in QALYs associated with avoidance of repeat revascularization, it is likely that we would have found standard PTA to be the preferred strategy on clinical grounds, even in the absence of economic factors.

Fourth, providers evaluating patients at follow-up were not blinded to treatment assignment in IN.PACT SFA, and it is possible that this knowledge could have influenced repeat revascularization rates.

Finally, our study used a 2-year time horizon. This approach offers the advantage of using only directly observed cost and outcome data but does not account for potential differences in the longer term outcomes of DCB versus standard balloon angioplasty. Although existing data indicate a sustained reduction in repeat revascularization in patients treated with other DCB platforms (21), longer term clinical and cost outcomes with the IN.PACT Admiral DCB are currently unknown.

CONCLUSIONS

In this randomized trial of the IN.PACT Admiral DCB versus standard PTA for patients with intermittent claudication due to severe femoropopliteal PAD, we found that the initial DCB angioplasty strategy was both less costly and more effective with respect to repeat revascularization than standard balloon angioplasty over 2 years of follow-up. Assuming that there is no true difference in long-term mortality between the 2 strategies, formal cost-effectiveness analysis on the basis of the IN.PACT SFA II trial results demonstrates that there is a high probability that use of the DCB is economically attractive (ICER <$150,000 per QALY) and a reasonable probability that DCB angioplasty is highly attractive (ICER <$50,000 per QALY) for such patients. Further studies are needed to better understand the cost-effectiveness of DCB PTA compared with other contemporary strategies such as primary stenting with bare-metal or drug-eluting stents or use of atherectomy devices.

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PERSPECTIVES

WHAT IS KNOWN? DCBs have been shown to improve long-term patency and reduce clinically-driven target vessel revascularization rates compared to standard balloon angioplasty alone for severe, symptomatic femoral and popliteal PAD. However, these devices are more expensive than standard balloons, and their costs and cost-effectiveness compared with PTA have not been previously studied in a prospective economic analysis.

WHAT IS NEW? We found that higher initial costs of DCB angioplasty were offset by lower follow-up costs secondary to fewer target limb revascularizations over 2-year follow-up. Formal cost-effectiveness based upon the IN.PACT SFA II results demonstrated a high probability that DCB are cost-effective compared with standard PTA using established wiliness-to-pay thresholds.

WHAT IS NEXT? Further studies are needed to compare the costs and cost-effectiveness of DCBs with other contemporary strategies for femoropopliteal PTA, such primary stenting with bare metal or drug-eluting stents.

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KEY WORDS angioplasty, cost-effectiveness, drug-coated balloon, femoropopliteal artery, peripheral arterial disease

APPENDIX For full details of the state-transition Markov model structure and underlying assumptions, please see the online version of this article.