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Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and Popliteal Peripheral Artery Disease

12-Month Results From the IN.PACT SFA Randomized Trial

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Background—Drug-coated balloons (DCBs) have shown promise in improving the outcomes for patients with peripheral artery disease. We compared a paclitaxel-coated balloon with percutaneous transluminal angioplasty (PTA) for the treatment of symptomatic superficial femoral and popliteal artery disease.

Methods and Results—The IN.PACT SFA Trial is a prospective, multicenter, single-blinded, randomized trial in which 331 patients with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The primary efficacy end point was primary patency, defined as freedom from restenosis or clinically driven target lesion revascularization at 12 months. Baseline characteristics were similar between the 2 groups. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were 8.94±4.89 and 8.81±5.12 cm (P=0.82) and 25.8% and 19.5% (P=0.22), respectively. DCB resulted in higher primary patency versus PTA (82.2% versus 52.4%; P<0.001). The rate of clinically driven target lesion revascularization was 2.4% in the DCB arm in comparison with 20.6% in the PTA arm (P<0.001). There was a low rate of vessel thrombosis in both arms (1.4% after DCB and 3.7% after PTA [P=0.10]). There were no device- or procedure-related deaths and no major amputations.

Conclusions—In this prospective, multicenter, randomized trial, DCB was superior to PTA and had a favorable safety profile for the treatment of patients with symptomatic femoropopliteal peripheral artery disease.

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Key Words: drug-eluting balloons ■ peripheral arterial disease ■ peripheral vascular diseases

Endovascular treatment of symptomatic atherosclerotic peripheral artery disease (PAD) has gained widespread acceptance and is now recommended as the primary revascularization strategy in many clinical and anatomic scenarios.[1–3] Percutaneous transluminal angioplasty (PTA) of the superficial femoral and popliteal artery has a high initial success rate, but restenosis occurs in up to 60% of cases.[4] Although randomized trials have demonstrated patency rates with bare metal stents and drug-eluting stents superior to those observed with PTA,[5–8] the optimal treatment for superficial femoral and popliteal artery disease remains controversial. Some practice guidelines advise against primary stenting in patients with intermittent claudication,[9] whereas others recommend primary stenting in short- or intermediate-length lesions[3] or

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in the event of acute PTA failure.[1–2] Despite the improved outcomes reported in some trials with stenting, the dynamic stresses applied by the superficial femoral and popliteal artery may result in stent fracture[10–11] or in-stent restenosis.[12] Given the limitations of stenting, there has been considerable interest in identifying the approaches that could improve patency without the need for a permanent metallic implant.

One approach to this challenge has been the development of the drug-coated balloon (DCB), which combines balloon dilatation with local delivery of an antiproliferative drug. Proof-of-concept evidence has demonstrated the utility of different DCB technologies in reducing both restenosis and the need for reintervention in comparison with PTA.[13–17] Promising primary patency and target lesion revascularization rates up to 2 years postimplantation have been reported.[18] However, robust evidence from large randomized, controlled trials is lacking. The IN.PACT SFA Trial was designed to test the safety and efficacy of the IN.PACT Admiral DCB for the treatment of patients with symptomatic PAD in the superficial femoral and proximal popliteal artery.

Methods

Study Design

The IN.PACT SFA Trial is a multicenter, international, single-blinded, randomized, controlled trial to assess the safety and efficacy of the IN.PACT Admiral DCB (Medtronic Inc, Santa Rosa, CA) versus standard PTA balloons in patients with symptomatic superficial femoral and proximal popliteal artery disease. The trial was prospectively designed to be conducted in 2 phases: IN.PACT SFA I (conducted in Europe) and IN.PACT SFA II (conducted in the United States), which are jointly referred to as IN.PACT SFA. The IN.PACT SFA Trial was prospectively analyzed according to a single statistical analysis plan. The 2 phases occurred sequentially in time with enrollment completed in the IN.PACT SFA I phase before the initiation of the IN.PACT SFA II phase. Minor differences between the IN.PACT SFA I phase and the IN.PACT SFA II phase eligibility criteria exist and include subtle variations in concomitant inflow and contralateral limb treatment, along with differences in predilatation requirements. A prespecified poolability test for treatment-by-trial phase interaction was established, with planned data pooling across the 2 phases in the event that there was no significant treatment-by-trial interaction.

Both protocols were approved by the institutional review boards or ethics committees at each trial site. All patients provided written informed consent before enrollment. Both trial phases were conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws as specified by all relevant governmental bodies.

An independent clinical events committee adjudicated all major adverse events. Independent core laboratories analyzed all images, including duplex ultrasonography (VasCore, Massachusetts General Hospital, Boston, MA) and angiography (SynvaCor, Springfield, IL).

Patient Population

Patients were eligible for enrollment if they had moderate to severe intermittent claudication or ischemic rest pain (Rutherford 2–4) and stenosis of 70% to 99% with lesion lengths between 4 and 18 cm or occlusion with lengths of ≤10 cm involving the superficial femoral and proximal popliteal arteries, and met all other eligibility criteria.

Randomization and Blinding

Randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and predilatation with a standard PTA balloon 1 mm smaller than the reference vessel diameter in the IN.PACT SFA II phase. A patient was considered enrolled at the time of randomization. Subjects were randomly assigned by an Interactive Voice Response System with the use of a method of permuted blocks to ensure that a 2:1 ratio was maintained across sites (Figure 1).

The patients and the trial sponsor were blinded to the treatment assignments through the completion of all 12-month follow-up evaluations. The independent core laboratories and clinical events committee will remain blinded to the treatment assignments throughout the 60-month follow-up duration. Because of the visual difference between the IN.PACT DCB and standard PTA balloon, treating physicians, research coordinators, and catheterization laboratory staff were not blinded to the treatment assignment. Treating physicians, research coordinators, and catheterization laboratory staff received detailed and specific instructions and training on how to preserve the patients' blinded status.

Treatment and Medical Therapy

Patients randomly assigned to the experimental arm were treated with the IN.PACT Admiral DCB. The IN.PACT DCB has a dual mode of action, comprising mechanical dilatation by the angioplasty balloon plus local drug delivery to the arterial wall intended to inhibit restenosis. The IN.PACT DCB coating includes paclitaxel as the antiproliferative agent at a dose of 3.5 μg/mm^2, with urea as the excipient. Available IN.PACT Admiral DCB sizes included 4-, 5-, 6-, and 7-mm diameters and 20-, 40-, 60-, 80 and 120-mm lengths (the 7-mm diameter device was not available in the 120-mm length). A minimum balloon inflation time of 180 seconds was required for both treatment groups. To avoid geographic miss, DCB length was chosen to exceed the target lesion length by 10 mm at the proximal and distal edges. The IN.PACT DCB is a single-inflation device, and, when treatment required multiple balloons, an overlap of 10 mm was applied for contiguous balloon inflations.

Premedication included a loading dose of aspirin 300 to 325 mg and clopidogrel 300 mg within 24 hours of the index procedure or 2 hours postprocedure. Heparin was administered at the time of the procedure to maintain an activated clotting time ≥250 seconds.

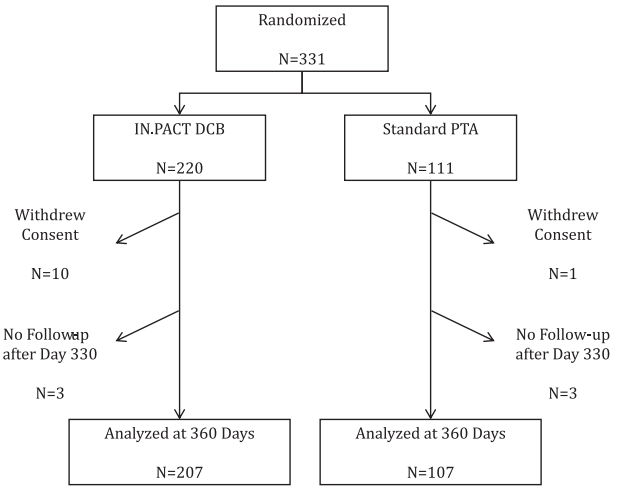

Figure 1. Trial flow diagram. The IN.PACT SFA Trial used a 2:1 randomized, control design, and intent-to-treat (ITT) analysis was conducted at 12 months. Three hundred thirty-one (331) patients with de novo or nonstented restenotic lesions in the superficial femoral and proximal popliteal artery were randomly assigned either to the IN.PACT Admiral drug-coated balloon or standard PTA treatment group. All subjects enrolled in the IN.PACT SFA Trial (n=331) will be followed for up to 5 years. Analysis at 1 year included subjects that provided end point data at the time of data snapshot. A subject was excluded under the following circumstances: (1) consent was withdrawn before the 1-year visit and no event had occurred before withdrawal or (2) there was no contact with the subject permitting a 1-year evaluation and no events had occurred before the 1-year evaluation. DCB indicates drug-coated balloon; PTA, percutaneous transluminal angioplasty; and SFA, superficial femoral artery.

Postdilatation with a standard PTA balloon was allowed at the discretion of the operator. In both treatment groups, provisional stenting was allowed only in the case of PTA failure after repeated and prolonged PTA inflations. PTA failure was defined as a residual stenosis ≥50% or major (≥grade D) flow-limiting dissection confirmed by a peak translesional systolic pressure gradient of >10 mm Hg.

In both arms, postprocedure medical therapy included aspirin 81 to 325 mg daily (for a minimum of 6 months) and clopidogrel 75 mg daily for a minimum duration of 1 month for nonstented patients and 3 months for patients who received stents. Usage of aspirin and antiplatelet drugs did not differ between treatment arms at discharge (97.6%), 30 days (87.6%), or 12 months (51.5%).

Follow-Up

For the primary end point analysis, patients were followed by the treating physician at 30 days, 6 months, and 12 months, including office visits with duplex ultrasonography functional testing and adverse event assessment. Reinterventions, if required within 12 months of the procedure, were performed according to standard practice by using PTA balloons and provisional stenting.

Study End Points

The primary efficacy end point was primary patency at 12 months following the index procedure, defined as freedom from clinically driven target lesion revascularization and restenosis as determined by a duplex ultrasonography–derived peak systolic velocity ratio of ≤2.4.[19] Each component of the primary efficacy end point was independently adjudicated by the blinded Clinical Events Committee (for clinically driven target lesion revascularization) or by the core laboratories (for restenosis). Specifically, the independent Clinical Events Committee determined whether reinterventions at the target lesion were clinically driven on the basis of objective testing (ankle-brachial index decrease ≥20% or >0.15 in comparison with postprocedure ankle-brachial index) or symptoms of exertional limb discomfort.

Safety end points included 30-day device- and procedure-related death, all-cause death, major target limb amputation, and target vessel thrombosis. These events were site reported and Clinical Events Committee adjudicated. Additional efficacy end points included acute procedural success, target vessel revascularization at 12 months, and primary sustained clinical improvement (defined as freedom from target limb amputation, target vessel revascularization, and increase in Rutherford class at 12 months). Functional assessments included general appraisal through administration of a 5-dimension (EQ-5D) health-related quality-of-life questionnaire and specific evaluation of walking capacity by using a Walking Impairment Questionnaire. A Six-Minute Walk Test was additionally conducted in the IN.PACT SFA II phase only.

Statistical Analysis

The planned enrollment of 330 subjects provided a power of 80% to detect a 50% improvement in the primary end point at 12 months (from 40%[4] in the PTA group to 60% in the DCB group) with a 1-sided type I error of 2.5%. From its inception, the trial was intended to have 2 phases under a single statistical analysis plan. Poolability of subjects across trial phases for the primary end point analysis was tested by using Cox proportional hazards regression. For this poolability analysis, model covariates included treatment group, phase, and a treatment-by-phase interaction effect. Because the treatment-by-trial phase interaction value for the primary end point was nonsignificant (P=0.428), the 2 trial phases were pooled for all analyses.

All analyses were based on the intention-to-treat principle. Continuous variables are described as mean±standard deviation and were compared by t tests. Categorical variables are described as proportions and were compared by the Z test owing to the 1-sided testing. The Z test was used to test the hypothesis of equality of proportions in achieving the primary end point. Multiple imputation was performed by using the logistic regression approach for patients with missing primary end point data (29 DCB, 7 PTA). The following variables were included in the imputation model as covariates: age, sex, diabetes mellitus, lesion length, total occlusion, and Rutherford class at baseline. Five data sets were imputed from these covariates that mimic different realizations of the missing data. Within each imputed data set for the end point, the proportion experiencing the end point was statistically compared between treatment groups by using the 2-sample Z test. From these, an overall test statistic for the end point and its associated P value were calculated for the imputed data. The imputed difference (95% confidence interval) and P value are reported along with the as-observed numerator and denominator. A sensitivity analysis of the as-observed rates revealed a similar highly significant P value (P<0.001). As a secondary analysis, clinically driven target lesion revascularization was analyzed by the Kaplan-Meier method during the 12-month follow-up period. The difference in the survival curves between groups was assessed by using log-rank statistics. Statistical analyses were performed using SAS (SAS Institute, Cary, NC) version 9.2 or higher. Additional statistical information is found in Appendix I in the online-only Data Supplement.

Role of the Funding Source

The trial was designed by the principal investigators (G.T., J.L., P.S.) and the sponsor (Medtronic). The data were collected and analyzed by the sponsor. Harvard Clinical Research Institute independently validated the analyses, with funding from the sponsor. The first and last authors prepared the first draft, which was then reviewed and edited by the other coauthors. The sponsor had the right to review but not to approve the final manuscript. The authors had full access to all data and accept full responsibility for the accuracy and completeness of the reported analyses and interpretations of the data, and they vouch for the fidelity of the study to the protocol (available with full text of this article at http://circ.ahajournals.org/).

Results

Baseline and Procedural Characteristics

Between September 2010 and April 2011 (IN.PACT SFA I phase) and between April 2012 and January 2013 (IN.PACT SFA II phase), 331 patients (220 in the DCB group and 111 in the PTA group) were enrolled at 13 sites in Europe and 44 sites in the United States, respectively. Patient flow through the 12-month follow-up is described in Figure 1. Demographics, comorbidities, and lesion characteristics were similar between the DCB and PTA groups (Table 1). The mean lesion length was 8.94±4.89 in the DCB arm and 8.81±5.12 cm in the PTA arm (P=0.82). Occlusions were treated in 25.8% and 19.5% (P=0.22) of patients in the DCB and PTA arms, respectively. No significant differences across the 2 arms were observed, with the exception of a lower number of patent infrapopliteal runoff vessels in the PTA group (P=0.04). Adjustment for differences in runoff between the treatment groups using propensity scores had no impact on the primary efficacy and safety outcomes.

Efficacy Outcomes

Procedural success, defined as a residual diameter stenosis of ≤50% for nonstented patients or ≤30% for stented patients, was achieved in 99.5% of subjects in the DCB arm and 98.2% of subjects in the PTA arm.

In the intention-to-treat population, the 12-month primary patency rate was 82.2% in the DCB arm versus 52.4% in the PTA arm (P<0.001; Table 2). The DCB-treated patients demonstrated lower rates of clinically driven target lesion revascularization versus PTA-treated patients through 12 months (2.4% versus 20.6%; P<0.001; Figure 2). A significantly higher primary sustained clinical improvement (85.2%) was observed in the DCB arm in

Table 1. Baseline and Procedural Characteristics – All Intention-to-Treat Subjects

	DCB (n=220 Subjects n=221 Lesions)	PTA (n=111 Subjects n=113 Lesions)	*P* Value*
Clinical characteristics			
Age, y†	67.5±9.5	68.0±9.2	0.61
Male sex,‡ % (m/n)	65.0 (143/220)	67.6 (75/111)	0.71
Diabetes mellitus, % (m/n)	40.5 (89/220)	48.6 (54/111)	0.16
Hypertension, % (m/n)	91.4 (201/220)	88.3 (98/111)	0.43
Hyperlipidemia, % (m/n)	84.5 (186/220)	82.0 (91/111)	0.64
Current smoker, % (m/n)	38.6 (85/220)	36.0 (40/111)	0.72
Coronary artery disease, % (m/n)	57.0 (122/214)	55.0 (60/109)	0.81
Carotid artery disease, % (m/n)	34.9 (73/209)	31.7 (32/101)	0.61
ABI / TBI§	0.769±0.228	0.744±0.189	0.31
Rutherford class, % (m/n)			0.90
2	37.7 (83/220)	37.8 (42/111)	
3	57.3 (126/220)	55.9 (62/111)	
4	5.0 (11/220)	5.4 (6/111)	
5	0.0 (0/220)	0.9 (1/111)	
Angiographic characteristics			
Lesion type – de novo,‖ % (m/n)	95.0 (209/220)	94.6 (105/111)	0.88
No. of patent runoff vessels, % (m/n)			0.04
0	3.3 (7/212)	4.5 (5/112)	
1	13.7 (29/212)	26.8 (30/112)	
2	41.5 (88/212)	33.0 (37/112)	
3	41.5 (88/212)	35.7 (40/112)	
Proximal popliteal involvement, % (m/n)	6.8 (15/221)	7.1 (8/113)	1.00
Lesion length,¶ cm	8.94±4.89	8.81±5.12	0.82
Total occlusions, % (m/n)	25.8 (57/221)	19.5 (22/113)	0.22
Severe calcification, % (m/n)	8.1 (18/221)	6.2 (7/113)	0.66
Reference vessel diameter, mm	4.647±0.841	4.681±0.828	0.73
Minimum lumen diameter (preprocedure), mm	0.900±0.776	0.933±0.771	0.71
Diameter stenosis (preprocedure), %	81.1±15.5	81.3±13.7	0.95
Procedural characteristics			
Predilatation, % (m/n)	96.4 (212/220)	85.6 (95/111)	<0.001
Postdilatation, % (m/n)	26.8 (59/220)	18.9 (21/111)	0.14
No. of treatment balloons per subject	1.4±0.7	1.1±0.3	<0.001
First treatment balloon maximum pressure, atm	8.3±2.1	8.6±2.1	0.12
Dissections, % (m/n)			0.36
0	36.2 (80/221)	38.9 (44/113)	
A–C	63.8 (141/221)	60.2 (68/113)	
D–F	0.0 (0/221)	0.9 (1/113)	
Provisional stenting, % (m/n)	7.3 (16/220)	12.6 (14/111)	0.11
Minimum lumen diameter (postprocedure), mm	3.903±0.750	3.862±0.732	0.63
Diameter stenosis (postprocedure), %	19.9±10.4	19.1±10.3	0.54
Device success,# % (m/n)	99.0 (308/311)	98.5 (128/130)	0.30
Procedural success,** % (m/n)	99.5 (219/220)	98.2 (109/111)	0.11
Clinical success,‡‡ % (m/n)	99.1 (218/220)	97.3 (108/111)	0.10

ABI indicates ankle-brachial index; DCB, drug-coated balloon; m, numbers in category; n, number of available values; PTA, percutaneous transluminal angioplasty; and TBI, toe-brachial index.

*All *P* values are 2-sided with the exception of success outcomes, which use 1-sided *P* values.

†Values represent mean±SD.

‡Based on number of intention-to-treat subjects with available data.

§TBI allowed / used in cases of incompressible vessels in IN.PACT SFA II Trial phase.

‖Site-reported.

¶Normal-to-normal by Core Laboratory quantitative vascular angiography evaluation.

#Successful delivery, inflation, deflation, and retrieval of the intact trial balloon without burst < rated burst pressure.

**No procedural complications (death, major target limb amputation, thrombosis of target lesion, or target vessel revascularization) before discharge.

‡‡Residual diameter stenosis ≤50% for nonstented subjects or ≤30% for stented subjects.

comparison with the PTA arm (68.9%; *P*<0.001). The ankle-brachial index was significantly higher in the DCB arm at 12 months (Table 2). Implantation of provisional stents was similar in the DCB and PTA arms (7.3% versus 12.6%; *P*=0.11). When stented patients were excluded from the analyses, there were no changes in any of the conclusions. Efficacy outcomes by trial phase are included in Table I in the online-only Data Supplement.

Safety Outcomes

There were no procedure- or device-related deaths and no major amputations through 12 months in either arm. Site-reported and Clinical Events Committee–adjudicated vessel thrombosis occurred in 1.4% of the subjects in the DCB arm and 3.7% of the subjects in the PTA arm (*P*=0.10). All-cause death through 12 months was 1.9% (n=4) versus 0.0% (n=0) in the DCB and PTA arms, respectively (*P*=0.93). Causes of death included cerebral infarction at 127 days, biliary sepsis at 168 days, sudden death at 287 days, and a perforated colon at 314 days following the index procedure. There were no untoward paclitaxel-related adverse effects as determined by the Clinical Events Committee. Safety outcomes by trial phase are included in Table I in the online-only Data Supplement.

Functional Outcomes

At 12 months, there was no significant difference between treatment groups in the change from baseline in quality-of-life by using the EQ-5D assessment, but the results trended in

Table 2. Key Clinical and Safety Outcomes

Outcome	DCB (n=220)	PTA (n=111)	Difference [95% CI]*	*P* Value †
Primary efficacy – primary patency,‡ % (m/n)	82.2 (157/191)	52.4 (54/103)	26.2% [15.1%–37.3%]	<0.001
12-month efficacy outcomes				
All TLR, % (m/n)	2.9 (6/207)	20.6 (22/107)		<0.001
Clinically driven TLR,§ % (m/n)	2.4 (5/207)	20.6 (22/107)		<0.001
Clinically driven TVR, % (m/n)	4.3 (9/207)	23.4 (25/107)		<0.001
Primary sustained clinical improvement,‖ % (m/n)	85.2 (167/196)	68.9 (73/106)		<0.001
ABI/TBI¶	0.951±0.221#	0.886±0.169		0.002
12-month safety outcomes				
30-day device- and procedure-related death, % (m/n)	0.0 (0/218)	0.0 (0/111)		>0.999
Target limb major amputation, % (m/n)	0.0 (0/207)	0.0 (0/107)		>0.999
All-cause death, % (m/n)	1.9 (4/207)	0.0 (0/107)		0.93
Thrombosis,** % (m/n)	1.4 (3/207)	3.7 (4/107)		0.10
12-month functional outcomes				
Change from baseline by EQ-5D Index	0.1059±0.2089#	0.0730±0.1951		0.095
Walking impairment, %	72.7±31.4#	73.6±29.5		0.590
Change in 6MWT from baseline to 12 mo,‡‡ m	38.7±92.1#	59.1±102.3		0.878

ABI indicates ankle-brachial index; DCB, drug-coated balloon; EQ-5D, 5-dimension health-related quality-of-life questionnaire; m, numbers in category; 6MWT, 6-minute walk test; n, number of available values; PTA, percutaneous transluminal angioplasty; TBI, toe-brachial index; TLR, target lesion revascularization; and TVR, target vessel revascularization

*Based on multiple imputation of missing data.

†One-sided *P* value.

‡Based on number of subjects with available data (ie, as observed).

§Clinically driven TLR adjudicated by an independent Clinical Events Committee that was blinded to the assigned treatment, based on any reintervention at the target lesion attributable to symptoms or drop of ABI of ≥20% or >0.15 in comparison with postprocedure baseline ankle-brachial index.

‖Freedom from target limb amputation, TVR, and increase in Rutherford class at 12 months postprocedure.

¶TBI allowed/used in cases of incompressible vessels in IN.PACT SFA II.

#Values represent mean±SD.

**Defined as an occlusion attributable to thrombus formation that is rapidly evolving as confirmed by the sudden onset of symptoms within 14 days of imaging, and documented by duplex ultrasound and angiography of the index vessel.

‡‡Data collected in IN.PACT SFA II phase only.

favor of IN.PACT DCB (*P*=0.10, 0.1059 versus 0.0730). Both treatment groups also showed improvement from baseline in walking impairment at 12 months. Although the treatment groups showed similar functional outcomes at 12 months, 8.6 times more of the PTA subjects required a clinically driven target lesion revascularization to achieve the same levels of functional outcomes as the IN.PACT Admiral DCB subjects. In the IN.PACT SFA II phase, both treatment groups also showed improvement from baseline to 12 months in the walking distance assessed by the 6-Minute Walk Test, with no statistically significant difference between treatment groups. Functional outcomes by trial phase are included in Table I in the online-only Data Supplement.

Discussion

In this trial, the IN.PACT Admiral drug-coated balloon resulted in superior efficacy in comparison with a plain angioplasty balloon for the treatment of patients with symptomatic superficial femoral and proximal popliteal PAD. There was significantly better primary patency and a marked reduction in the need for target lesion revascularization at 12 months following treatment with the DCB.

The efficacy of paclitaxel in reducing restenosis in the femoropopliteal artery has been previously reported by the use of different DCB technologies in various trials.[13–18] Although paclitaxel was the most commonly used antiproliferative drug in these preceding trials, each DCB was unique with respect to the paclitaxel dose (varying from 2 to 3.5 μg/mm^2), the carrier molecule (excipient), the balloon material, and the balloon and coating technology used. The findings from the present trial are consistent with these previous DCB proof-of-concept trials[13–16] that, although smaller because they were powered on a 6-month angiographic end point, enrolled a similar patient population with symptomatic femoropopliteal disease. All of these trials demonstrated significant reductions in late lumen loss at 6 months and lower rates of target lesion revascularization at 1 year for DCB versus PTA.[13–16] Moreover, the IN.PACT SFA Trial results are concordant with the 83.7% primary patency at 1 year reported by Micari et al[20] from a multicenter registry of IN.PACT DCB use in a similar patient population.

Numerous modalities are available for the treatment of superficial femoral and popliteal artery disease, including implant-based technologies such as bare metal stents,[5–7,20,21]

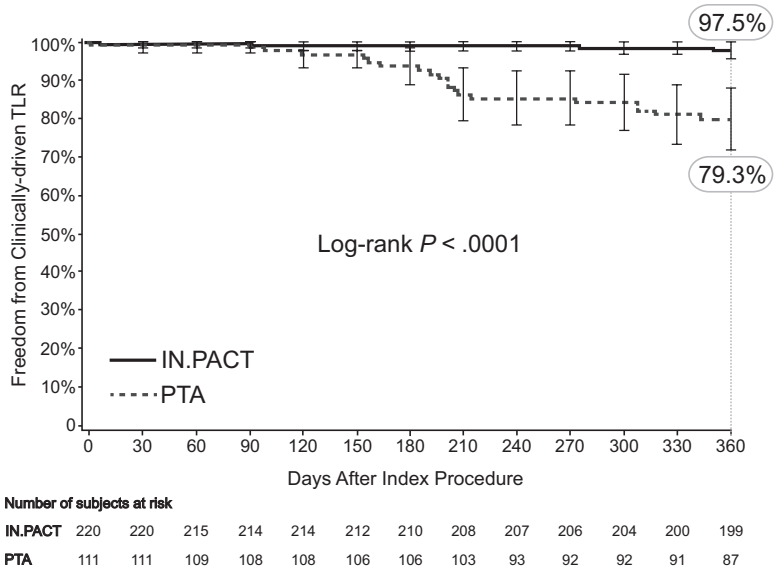

Figure 2. Twelve-month freedom from target lesion revascularization. Freedom from target lesion revascularization in 331 patients with superficial femoral and popliteal peripheral artery disease were randomly assigned to receive drug-coated balloons or standard angioplasty. The rate of freedom from clinically driven TLR was significantly higher in the group receiving drug-coated balloons than in the standard PTA group. PTA indicates percutaneous transluminal angioplasty; and TLR, target lesion revascularization.

covered stents,[22,23] and drug-eluting stents,[8,24] and implant-free technology, as well, such as atherectomy devices.[25] DCB is an attractive alternative because it offers the promise of improved patency in comparison with PTA and a reduction in the need for stents. This is particularly important in the dynamic environment of the superficial femoral and popliteal arteries, where mechanical fatigue may lead to stent fracture and increased risk of in-stent restenosis.[10–11] Restenosis following superficial femoral and popliteal artery stenting has been reported to occur in recent trials with a frequency of ≈20% at 12 months with higher rates of ≤50% following stenting of long-segment disease.[12,20,21,26] Diffuse in-stent restenosis or in-stent occlusion is a very difficult problem to treat,[12,26,27] with recurrent restenosis rates of >70% at 1 to 2 years, although recent results have suggested improved outcomes with peripheral drug-eluting stents[28] and DCB.[29,30] Use of a DCB (and avoidance of stent implantation) does not limit future treatment options, an important consideration given the chronic and progressive nature of PAD.

These findings compare favorably with other randomized clinical trials in this patient population. Despite the inclusion of longer lesion lengths that are at a higher risk of treatment failure, the 2.4% target lesion revascularization rate experienced in this trial is the lowest reported for an SFA device trial at 12 months. Clinically driven target lesion revascularization rates of 12.7% and 9.5% were reported in 2 recent randomized trials of bare metal and drug-eluting stents, despite their inclusion of shorter lesions (average lesion lengths of 7.0 and 5.4 cm, respectively).[7,8] IN.PACT DCB was associated with a low complication rate, including the absence of major amputations and a low rate of vessel thrombosis.

Study Limitations

The trial was deliberately and prospectively conducted in 2 sequential phases. The blinding of phase I was rigorously maintained until the completion of phase II. When the data were analyzed, there were no statistical differences between the 2 phases.

Although improvements in the functional assessments of quality of life, walking impairment, and walking distance were observed in both treatment groups, the interpretation of these measures is complicated by the subjective nature of patient questionnaires and the influence of comorbidities, including progressive disease in nontreated vessels.

The results of this trial cannot be generalized to patients not included in this trial. Future studies should encompass longer lesions and consider comparison with bare metal stents, drug-eluting stents, and bypass, and optimal medical therapy and exercise, as well. Longer-term follow-up is needed to confirm the durability of the benefit.

Conclusions

In conclusion, in this large, prospective, multicenter, international, randomized trial, DCB was superior to PTA and had a favorable safety profile for the treatment of patients with symptomatic superficial femoral and proximal popliteal artery PAD. The IN.PACT DCB demonstrated impressive patency rates with low repeat revascularization rates in comparison with other modern endovascular therapies. DCB stands to become an important treatment option for patients with superficial femoral and popliteal artery disease.

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CLINICAL PERSPECTIVE

The clinical data from the IN.PACT SFA Trial, which was designed as a 2-phase, global, multicenter, single-blind, randomized trial, provide valid scientific evidence to conclusively demonstrate the effectiveness and safety of the IN.PACT Admiral Drug-Coated Balloon (DCB) in the treatment of patients with peripheral artery disease in the superficial femoral and proximal popliteal artery. The IN.PACT Admiral DCB achieved the primary effectiveness and safety end points of the trial, demonstrating superiority of IN.PACT Admiral DCB to percutaneous transluminal angioplasty. Despite the inclusion of longer lesion lengths that are at a higher risk of treatment failure, the 2.4% target lesion revascularization rate is the lowest reported for a superficial femoral artery device trial at 12 months. The significant sustained clinical improvement, the low rate of clinically driven target lesion revascularization, the absence of amputation, and the minimal incidence of thrombosis observed in the IN.PACT Admiral DCB group further underscore the clinical benefits of IN.PACT Admiral DCB and validate the favorable results generated by previous clinical trials. The IN.PACT SFA Trial data demonstrate an important therapeutic advantage over the existing alternative treatments for peripheral artery disease. DCB is an attractive alternative, because it offers the promise of improved patency in comparison with percutaneous transluminal angioplasty and a reduction in the need for stents. This is particularly important in the dynamic environment of the superficial femoral and popliteal arteries, where mechanical fatigue may lead to stent fracture and the increased risk of in-stent restenosis. The results of this trial support DCB as an important treatment option for patients with superficial femoral and popliteal artery disease.