



## PERIPHERAL VASCULAR DISEASE

## Original Studies

# Drug-coated balloon versus uncoated percutaneous transluminal angioplasty for the treatment of atherosclerotic lesions in the superficial femoral and proximal popliteal artery: 2-year results of the MDT-2113 SFA Japan randomized trial

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## Abstract

**Objectives:** To assess the longer-term safety and efficacy of the IN.PACT Admiral (MDT-2113) drug-coated balloon (DCB) for the treatment of de novo and non-stented restenotic lesions in the superficial femoral and/or proximal popliteal arteries versus uncoated percutaneous transluminal angioplasty (PTA) in a Japanese cohort.

**Background:** Although DCBs are the newest endovascular strategy for patients with peripheral artery disease presenting with femoropopliteal lesions, there remains a paucity of results in non-Caucasian populations.

**Methods:** IN.PACT SFA Japan is an independently-adjudicated, prospective, multicenter, randomized, single-blinded trial. Endpoints through 2 years included primary patency and a composite safety endpoint of freedom from device- and procedure-related death through 30 days, freedom from target limb major amputation and freedom from clinically-driven target vessel revascularization at 24 months.

**Results:** One hundred patients were assigned by 2:1 randomization to treatment with the IN.PACT Admiral DCB (n = 68) or PTA (n = 32). The groups were well-matched at baseline. Mean lesion length for the DCB and PTA groups were  $9.15 \pm 5.85$  and  $8.89 \pm 6.01$  cm ( $P = 0.838$ ), respectively. Patients treated with DCB exhibited superior 24-month primary patency compared to PTA (79.8% vs. 46.9%; log rank  $P < 0.001$ ). The 24-month clinically driven target lesion revascularization rate was 9.1% for DCB versus 20.7% for PTA ( $P = 0.177$ ). There were no device- or procedure-related deaths, major amputations, or thromboses in either group.

**Conclusions:** Two-year results from IN.PACT SFA Japan demonstrated persistently superior patency and low CD-TLR rates through 2 years when compared to uncoated PTA in Japanese patients. These data are consistent with other IN.PACT DCB trials.

## KEYWORDS

balloon angioplasty, drug-coated balloon, peripheral artery disease

## 1 | INTRODUCTION

Femoropopliteal peripheral artery disease (PAD) causes lifestyle-limiting claudication as the most common complication. Endovascular

procedures are now an accepted initial form of treatment, especially when the patient is not a candidate for surgery. However, first generation endovascular interventions including percutaneous transluminal angioplasty (PTA) have demonstrated poor long-term outcomes.<sup>1-4</sup>

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Bare metal stents (BMS) have demonstrated improved short-term outcomes compared to PTA,<sup>5-9</sup> with longer term patency rates of 60–75%.<sup>10-12</sup> However, in-stent restenosis (ISR) and stent fractures remain concerns.<sup>1,2</sup> Drug-eluting stents (DES) were developed to address this concern, and they too show improved outcomes compared to PTA.<sup>13</sup> While it is important to use a metal implant to support vessel scaffolding in the case of a dissection or other procedural complications, the progressive nature of PAD means that it is advantageous to the patient to avoid placing unnecessary stents that may limit future treatment.

Drug-coated balloons (DCBs) were developed to overcome the challenges of uncoated PTA alone and to avoid leaving an indwelling metal implant. Currently, DCBs used in the peripheral space use paclitaxel to prevent restenosis following treatment. Randomized and controlled trials have shown that DCBs are safe and effective to treat patients with femoropopliteal artery disease, and show improved outcomes compared to PTA.<sup>14-21</sup> However, these trials are composed almost entirely of Caucasian patients. There is currently a paucity of longer term outcomes in this patient cohort, though there are several ongoing DCB trials studying in Asian populations (IN.PACT SFA China, NCT02118532; AcoArtI, NCT01850056; LTX DCB China, NCT02720003; Ranger China, NCT02944071; BIOLUX-P4 China, NCT02912715).

However, the clinical applications of these new technologies remain uncertain, and that uncertainty is magnified in non-Caucasian patients due to the lack of longer-term data. Additionally, complex lesions are sometimes a challenge to treat with a standalone device. As such, understanding the appropriate use of DCBs in a landscape that includes DES and newer devices, such as atherectomy, will remain essential moving forward.

Recently, the 1-year results of the IN.PACT SFA Japan study were reported, showing high patency and low rates of clinically driven target lesion revascularization (CD-TLR) in a Japanese population.<sup>22</sup> In this report, longer term data is shared for the IN.PACT SFA Japan trial (MDT-2113) out to 2 years.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

IN.PACT SFA Japan was a Phase III trial conducted in Japan, and the methods are more fully reported in the published 1-year results of this study.<sup>22</sup> This multicenter, prospective, randomized, single-blinded trial evaluated the safety and efficacy of the MDT-2113 device (IN.PACT™ Admiral™ DCB, Medtronic plc., Santa Rosa, CA, USA) compared with standard PTA. Patients in this trial were Japanese and had symptomatic de novo or non-stented restenotic lesions in the superficial femoral artery and/or proximal popliteal artery. The trial was prospectively designed to be part of a series including IN.PACT SFA I (conducted in Europe), IN.PACT SFA II (conducted in the United States), collectively known as the IN.PACT SFA Trial and MDT-2113 SFA Japan (conducted in Japan).

### 2.2 | Patient population

Patients were between the ages of 20 and 85, with symptoms of claudication and/or ischemic rest pain (Rutherford Clinical Category 2–4) with

a superficial femoral and/or proximal popliteal artery lesion stenosis severity of 70–99%. Total lesion length was between 4 cm and 20 cm for stenotic lesions, or ≤10 cm for those lesions that were fully occluded. Lesions were characterized as TASC A–C, and lesions were required to undergo successful pre-dilatation before inclusion in the trial. Prior to enrollment, written informed consent was obtained from all patients according to the protocols approved by the institutional review boards at each investigational site. Patients were randomly assigned in a 2:1 ratio to treatment with a DCB (n = 68) or PTA (n = 32).

The trial included independent oversight by a Data Safety Monitoring Board. A Clinical Events Committee (CEC) reviewed and adjudicated all major adverse events (MAEs). Independent core laboratories analyzed procedural and follow-up images and included duplex ultrasound (DUS; VasCore, Massachusetts General Hospital, Boston, MA, USA) and angiography (SynvaCor, Springfield, IL, USA). The CEC and independent core laboratories were blinded and will remain blinded to the treatment assignments through the 36-month follow-up duration. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable laws as specified by all relevant governmental authorities.

### 2.3 | Treatment and medical therapy

The MDT-2113 DCB (IN.PACT Admiral DCB) is coated with paclitaxel, an antiproliferative agent, at a dose of 3.5 µg/mm<sup>2</sup> with the excipient urea. Several balloon diameters (4, 5, 6, and 7 mm) and lengths (20, 40, 60, 80, and 120 mm) were available for use in this study. The 7-mm diameter device was not available in the 120 mm length. The balloon inflation time was required to be a minimum of 180 sec for both treatment groups. DCB length was required to exceed the target lesion length by 10 mm at the proximal and distal edges to avoid geographic miss. The MDT-2113 DCB is a single-inflation device, and when treatment required multiple balloons, an overlap of 10 mm was applied for contiguous balloon inflations.

Pre-medication included aspirin (minimum of 81 mg daily for at least five consecutive days prior to the index procedure and the last dose having been taken within 24 hr prior to procedure) and clopidogrel (taken according to the manufacturer's instructions for use [IFU]). Heparin was administered at the time of the procedure to maintain an activated clotting time of 250 sec. Investigators were instructed to follow the IFU. Post-dilatation with a standard uncoated PTA balloon was allowed at the discretion of the operator. In both treatment groups, provisional stenting was allowed following PTA failure. PTA failure was defined as a residual stenosis of 50% or major (≥Grade D) flow-limiting dissection confirmed by a peak translesional gradient >10 mmHg that remained unresolved following repeated and prolonged PTA inflations.

In both arms, post-procedure medical therapy included aspirin at a minimum of 81 mg daily (for a minimum of 6 months) and clopidogrel daily for a minimum duration of 1 month for nonstented patients and 3 months for patients who received stents.

### 2.4 | Follow-up

Patients were followed by the treating physician at 30 days, 6 months, 12 months, and 24 months, including office visits with DUS, functional testing, and adverse event assessment. If a reintervention was required

within 12 months of the procedure, it was performed according to standard practice using PTA balloons and provisional stenting.

## 2.5 | Study endpoints through 2 years

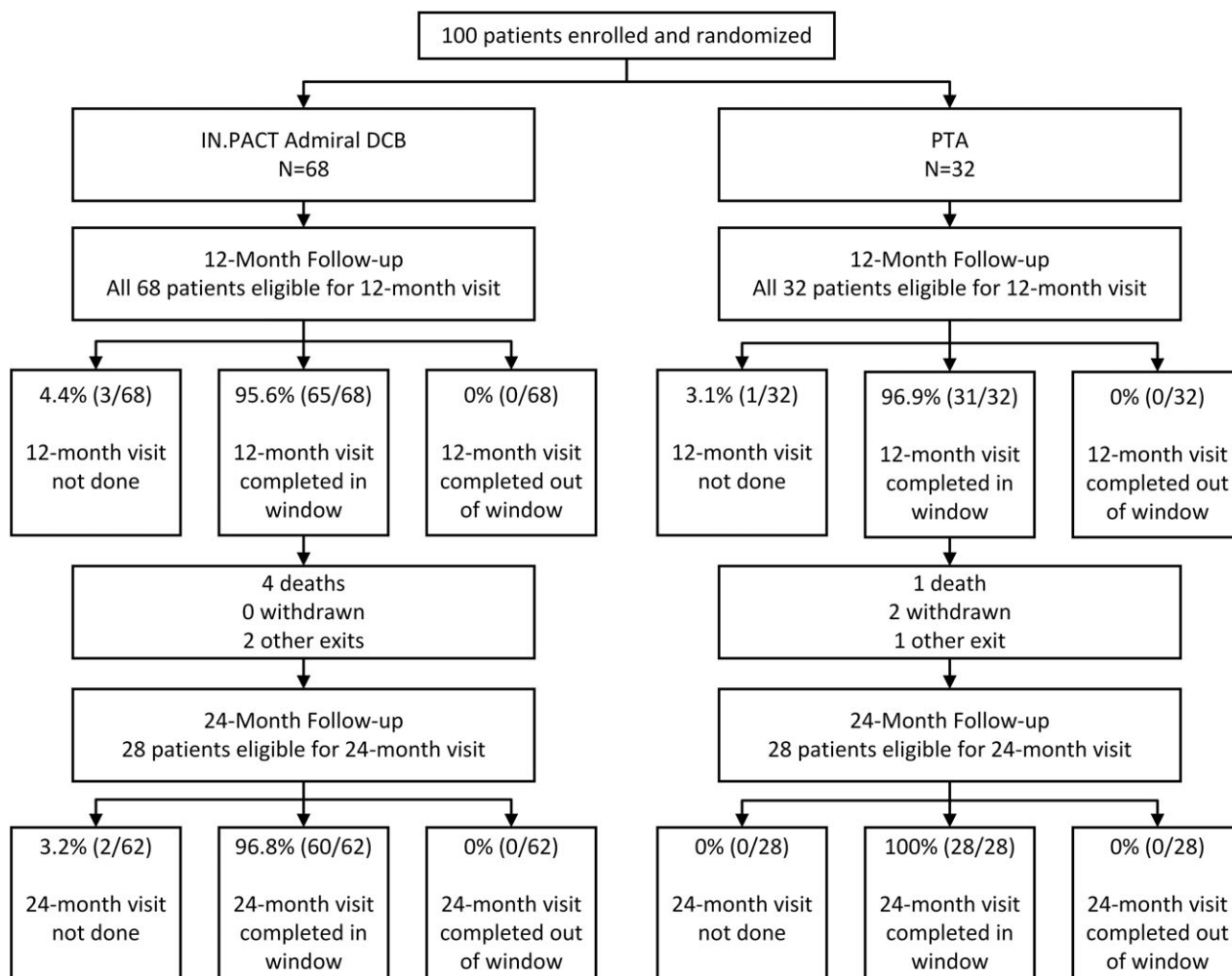
At 24 months, the efficacy endpoint was primary patency at 24 months following the index procedure, defined as freedom from CD-TLR and freedom from restenosis as determined by DUS-derived peak systolic velocity ratio (PSVR)  $\leq 2.4$ . Each component of the endpoint was independently adjudicated by the blinded CEC (for CD-TLR) or by the core laboratories (for restenosis). CD-TLR was defined as re-intervention at the target lesion due to symptoms or decrease in ankle-brachial index (ABI)  $\geq 20\%$  or  $>0.15$ , when compared with post-procedure baseline ABI. At 24 months, the safety composite endpoint was freedom from device- and procedure-related death through 30 days, and freedom from target limb major amputation and clinically driven target vessel revascularization (CD-TVR) through 24 months post index procedure. Severe calcification was adjudicated by the core laboratory, and defined as: "visible calcium along both sides of the arterial wall, covering 2 cm or greater of the target lesion area, encompassing  $>50\%$  of the total target lesion treatment area by visual

estimate and/or the calcium is circumferential ( $360^\circ$ ) in nature (i.e. on both sides of the vessel lumen extending 2 cm or greater on a single AP view), significantly impeding blood flow in the vessel."

Other endpoints included MAEs at 24 months, defined as death from any cause, CD-TVR, major target limb amputation, and thrombosis at the target lesion site. Thrombosis was defined as a total occlusion due to thrombus formation which is rapidly evolving as confirmed by sudden onset of symptoms and documented by DUS and/or angiography. Additional assessments included individual components of the MAE composite, binary restenosis (PSVR  $> 2.4$ ) of the target lesion and primary sustained clinical improvement (defined as freedom from target limb amputation, freedom from TVR, and an improvement shift of one Rutherford class at 12 months). Functional assessments included general appraisal through administration of the EuroQOL (EQ-5D), a 5-dimension generic health status questionnaire, six-minute walk test and evaluation of walking capacity using the Walking Impairment Questionnaire (WIQ).

## 2.6 | Statistical analysis

The planned enrollment of 100 subjects was not independently powered; however, the trial design and endpoint assessments were the same as the



**FIGURE 1** Patient flow. A total of 100 patients enrolled in the MDT-2113 SFA Japan Trial. Patients were randomized in a 2:1 ratio of DCB to PTA. Deaths, lost to follow-up, visit not completed and withdrawals through 2 years are shown. Compliance rates through 24 months were unusually high. DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty

IN.PACT SFA Trial. MDT-2113 SFA Japan Trial was intended to demonstrate consistent effectiveness and safety outcomes for the Japan cohort compared to other measured geographies in the IN.PACT SFA Trial.

All analyses were based on the intent to treat principle. For baseline characteristics, continuous variables were described as mean  $\pm$  standard deviation and were compared by *t*-tests; dichotomous and categorical variables were described as counts and proportions and were compared by Fisher's exact test or Cochran–Mantel–Haenszel (CMH) test, respectively. The Kaplan–Meier method was used to evaluate time-to-event data for primary patency over the 24-month follow-up period. The difference in the survival curves between groups was assessed using the log-rank test. The same analysis was also employed for CD-TLR. For other outcomes, in addition to the descriptive

statistics, Fisher's exact test was employed for binary outcomes and *t*-test for continuous outcomes. In addition, a forest plot was created to explore the treatment effect in primary patency for selected subgroups. For all endpoints, the level of statistical significance was set at  $P < 0.05$  with no correction for multiple comparisons. Statistical analyses were performed using SAS (SAS Institute, North Carolina, USA) version 9.4.

### 3 | RESULTS

#### 3.1 | Baseline and procedural characteristics

One hundred patients (68 in the DCB group and 32 in the PTA group) were enrolled at 11 centers in Japan between September 2013 and

**TABLE 1** Baseline patient and lesion characteristics

Characteristics	MDT-2113 DCB (n = 68 subjects)	PTA (n = 32 subjects)	P-value
<i>Clinical characteristics</i>			
Age (years) <sup>a</sup>	73.3 $\pm$ 7.4 (68)	74.2 $\pm$ 6.1 (32)	0.539
Male (%) (N/n)	73.5% (50/68)	81.3% (26/32)	0.461
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) (N/n)	4.4% (3/68)	0.0% (0/32)	0.549
Diabetes mellitus (%) (N/n)	58.8% (40/68)	56.3% (18/32)	0.831
Insulin dependent diabetes mellitus (%) (N/n)	14.7% (10/68)	18.8% (6/32)	0.771
Current smoker (%) (N/n)	26.5% (18/68)	31.3% (10/32)	0.639
Carotid artery disease (%) (N/n)	18.5% (12/65)	16.1% (5/31)	1.000
Coronary heart disease (%) (N/n)	50.0% (34/68)	50.0% (16/32)	1.000
Renal insufficiency (%) (N/n)	8.8% (6/68)	12.5% (4/32)	0.722
Previous peripheral revascularization (%) (N/n)	57.4% (39/68)	59.4% (19/32)	1.000
BTK vascular disease of target leg (%) (N/n)	33.8% (23/68)	34.4% (11/32)	1.000
Previous limb amputation (%) (N/n)	1.5% (1/68)	0.0% (0/32)	1.000
ABI/TBI <sup>a</sup>	0.764 $\pm$ 0.145 (68)	0.735 $\pm$ 0.166 (32)	0.384
Rutherford category			0.623
2	54.4% (37/68)	59.4% (19/32)	
3	41.2% (28/68)	37.5% (12/32)	
4	4.4% (3/68)	3.1% (1/32)	
<i>Angiographic characteristics</i>			
De novo <sup>b</sup>	91.2% (62/68)	100.0% (32/32)	0.085
Restenotic (non-stented) <sup>b</sup>	8.8% (6/68)	0.0% (0/32)	
Prox. popliteal involvement <sup>c</sup>	1.5% (1/68)	3.1% (1/32)	0.540
Severe calcification <sup>c</sup>	7.4% (5/68)	9.4% (3/32)	0.708
Lesion length (cm) <sup>a,c,d</sup>	9.15 $\pm$ 5.85 (68)	8.89 $\pm$ 6.01 (32)	0.838
Total occlusions (%) <sup>a,c</sup>	16.2% (11/68)	15.6% (5/32)	1.000
TASC II classification <sup>c,e</sup>			0.852
A	57.4% (39/68)	56.3% (18/32)	
B	23.5% (16/68)	21.9% (7/32)	
C	19.1% (13/68)	21.9% (7/32)	
RVD (mm) <sup>a,c</sup>	4.843 $\pm$ 0.751 (68)	4.675 $\pm$ 0.661 (32)	0.280
MLD pre (mm) <sup>a,c</sup>	0.971 $\pm$ 0.731 (68)	0.896 $\pm$ 0.594 (32)	0.610
Diameter stenosis (%) <sup>a,c</sup>	80.2 $\pm$ 14.1 (68)	80.7 $\pm$ 12.5 (32)	0.861

Abbreviations: ABI, ankle-brachial index; DCB, drug-coated balloon; MLD: mean lesion diameter; N, numbers in category; n, number of available values; PTA, percutaneous transluminal angioplasty; RVD, reference vessel diameter; TBI, toe-brachial index.

<sup>a</sup> Value represents mean  $\pm$  SD (sample size).

<sup>b</sup> Site-reported.

<sup>c</sup> Per lesion assessment reported by the core lab.

<sup>d</sup> Normal-to-normal by Core Lab QVA evaluation.

<sup>e</sup> TASC II classification is a lesion classification according to the Inter-Society Consensus for the Management of Peripheral Artery Disease.

**TABLE 2** Procedural characteristics

Procedural characteristics	MDT-2113 DCB (n = 68 subjects)	PTA (n = 32 subjects)	P-value
Pre-dilatation <sup>a,b</sup>	100.0% (68/68)	100.0% (32/32)	> 0.999
Post-dilatation <sup>a,b</sup>	23.5% (16/68)	18.8% (6/32)	0.796
Provisional stenting <sup>b</sup>	4.4% (3/68)	3.1% (1/32)	0.759
Index procedural IVUS use	39.7% (27/68)	25.0% (8/32)	0.181
#Treatment balloons per subject <sup>a,b</sup>	1.4 ± 0.5 (68)	1.1 ± 0.2 (32)	<0.001
Dissection			0.235
None	26.5% (18/68)	28.1% (9/32)	
A-C	73.5% (50/68)	71.9% (23/32)	
D-F	0.0% (0/68)	0.0% (0/32)	
Days of hospitalization <sup>a,b</sup>	2.0 ± 1.0 (68)	2.1 ± 1.2 (32)	0.778
Target lesion length treated(cm) <sup>a,c</sup>	13.43 ± 5.05 (68)	13.72 ± 5.60 (32)	0.800
Device success	100.0% (97/97)	97.1% (33/34)	0.260
Procedural success	97.1% (66/68)	100.0% (32/32)	1.000
Clinical success	97.1% (66/68)	100.0% (32/32)	1.000

Abbreviations: DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty.

<sup>a</sup> Value represents mean ± SD (sample size).

<sup>b</sup> Site-reported.

<sup>c</sup> Per lesion assessment reported by the core lab.

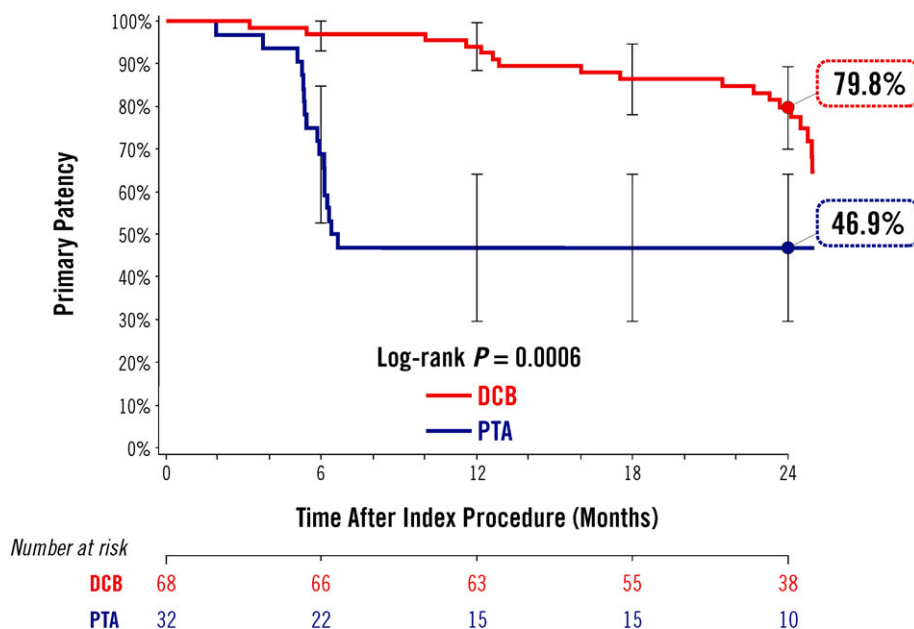
February 2015. Patient flow through 24-month follow-up is shown in Figure 1.

Patients were well-matched at baseline with similar demographics, comorbidities, and lesion characteristics regardless of treatment with DCB or PTA (Table 1). Complete total occlusions were present in 16.2% of patients treated with a DCB and 15.6% of patients treated with PTA ( $P = 1.000$ ). Mean lesion length was  $9.15 \pm 5.85$  cm in the DCB group versus  $8.89 \pm 6.01$  cm in the PTA group ( $P = 0.838$ ). TASC C lesions were present in 19.1% patients treated with a DCB and 21.9% treated with PTA. Procedural success was achieved in 97.1% of

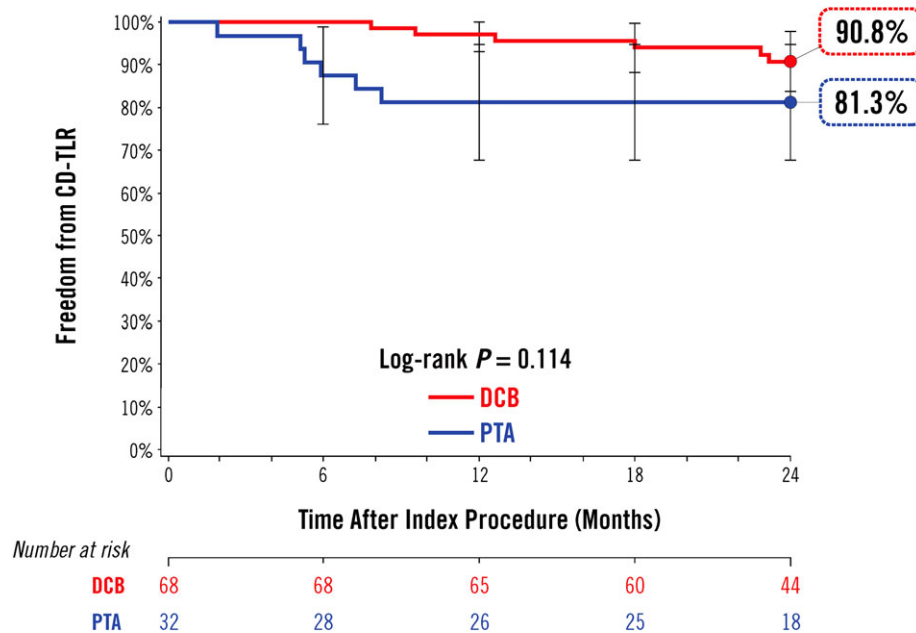
patients treated with DCB and 100.0% of subjects treated with PTA ( $P = 1.000$ ; Table 2).

### 3.2 | Efficacy outcomes

Primary patency through 24 months was 79.8% in the DCB arm and 46.9% in the PTA arm (log-rank  $P < 0.001$ , Figure 2). Freedom from CD-TLR as determined by the Kaplan–Meier analysis was 90.8% in the DCB arm through 2 years compared to a value of 81.3% in the PTA arm (log-rank  $P = 0.114$ ; Figure 3). The proportion rate of CD-



**FIGURE 2** The Kaplan–Meier estimate of primary patency through 24 months. Primary patency by the Kaplan–Meier estimate was significantly higher in the DCB group compared with PTA group ( $P < 0.001$ ). Bars represent 95% confidence intervals. All TLR events were adjudicated by the independent and blinded CEC and all ultrasound and angiographic images were analyzed by independent and blinded core laboratories. DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; CEC, Clinical Events Committee



**FIGURE 3** Freedom from clinically driven target lesion revascularization through 24 months. Freedom from clinically driven target lesion revascularization were not statistically different between the DCB group and the PTA group ( $P = 0.114$ ). Bars represent 95% confidence intervals. All TLR events were adjudicated by the independent and blinded CEC. DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; CEC, Clinical Events Committee

TLR at 2 years was 9.1% in the DCB arm (6/66 patients) and 20.7% in the PTA arm (6/29 patients;  $P = 0.117$ ; see Table 3). The mean time to first CD-TLR was  $470.2 \pm 199.8$  days in the DCB arm and  $168.2 \pm 65.4$  days in the PTA arm ( $P = 0.012$ ). Similar primary sustained clinical improvement, defined as freedom from target limb amputation, TVR, and an increase in at least one Rutherford class, was seen in both arms ( $P = 0.795$ ; see Table 3). Males appear to respond

better to treatment with a DCB, with a primary patency rate of 84.8% through 24 months compared to 66.7% in women.

### 3.3 | Safety outcomes

Safety outcomes through 24 months are reported in Table 3. The primary safety composite endpoint of freedom from 30-day device and

**TABLE 3** Key efficacy and safety outcomes at 24-months

	MDT-2113 DCB	PTA	P-value
<i>24-month efficacy outcomes</i>			
Clinically driven TLR <sup>a</sup>	9.1% (6/66)	20.7% (6/29)	0.117
All TLR <sup>b</sup> % (N/n)	9.1% (6/66)	20.7% (6/29)	0.117
Time to 1st CD-TLR	$470.2 \pm 199.8$	$168.2 \pm 65.4$	0.012
Primary sustained clinical improvement <sup>c</sup>	75.8% (47/62)	71.4% (20/28)	0.795
<i>24-month safety outcomes</i>			
Primary safety composite <sup>d</sup>	89.4% (59/66)	79.3% (23/29)	0.207
30-day device- and proc.-related death	0.0% (0/68)	0.0% (0/32)	> 0.999
Major adverse event <sup>e</sup>	15.2% (10/66)	24.1% (7/29)	0.384
Target limb major amputation	0.0% (0/66)	0.0% (0/29)	> 0.999
Clinically-driven TVR	10.6% (4/66)	20.7% (6/29)	0.207
All-cause death	6.1% (4/66)	3.4% (1/29)	1.000
Thrombosis	0.0% (0/66)	0.0% (0/29)	> 0.999

Abbreviations: TLR, target lesion revascularization; TVR, target lesion revascularization; DCB, drug-coated balloon; N, numbers in category; n, number of available values; PTA, percutaneous transluminal angioplasty; CD-TLR, clinically-driven TLR.

<sup>a</sup> Clinically driven TLR is defined as any re-intervention within the target vessel due to symptoms or drop of ABI/TBI of  $\geq 20\%$  or  $>0.15$  when compared to post-procedure baseline ABI/TBI.

<sup>b</sup> All TLR includes clinically driven and incidental or duplex-driven TLR.

<sup>c</sup> Primary sustained clinical improvement defined as freedom from target limb amputation, TVR, and increase in Rutherford class at 12 months post-procedure.

<sup>d</sup> Primary safety composite is defined as freedom from device and procedure-related 30-day death and freedom from target limb major amputation and clinically-driven TVR through 24 months.

<sup>e</sup> MAE is defined as a composite of target limb major amputation, clinically-driven TVR, all-cause death, and thrombosis within 24 months.



**TABLE 4** 24-Month functional outcomes

24-month functional outcomes	MDT-2113 DCB	PTA	Difference [95%CI]	P-value
ABI/TBI	0.883 ± 0.144 (n = 60)	0.945 ± 0.110 (n = 28)	-0.062 [-0.123, -0.001]	0.047
Change in ABI/TBI from baseline to 24 months	0.121 ± 0.185	0.207 ± 0.188	-0.087 [-0.171, -0.002]	0.045
6MWT (meters)	365.9 ± 126.9 (n = 54)	371.4 ± 61.4 (n = 22)	-5.6 [-48.8, 37.6]	0.798
Change in 6MWT from baseline to 24 months	10.9 ± 120.0	9.7 ± 48.9	1.2 [-37.6, 40.1]	0.950
Walking impairment (%)	73.8 ± 30.0 (n = 60)	75.0 ± 31.9 (n = 28)		0.859
EQ-5D index	0.8213 ± 0.1585 (n = 60)	0.7976 ± 0.2094 (n = 28)		0.559
Change from baseline to 24 months EQ-5D index	0.0264 ± 0.1629	0.0149 ± 0.2606		0.831

Abbreviations: 6MWT, six-month walking test; ABI, ankle-brachial index; DCB, drug-coated balloon; EQ-5D, EuroQOL Five Dimensional measure; N, numbers in category; n, number of available values; PTA, percutaneous transluminal angioplasty; TBI, toe-brachial index.

procedure-related death and target limb major amputation and CD-TVR within 24 months was 89.4% in the DCB group versus 79.3% in the PTA group ( $P = 0.207$ ). There were no major target limb amputations or thromboses through 24 months in either group. The four deaths in the DCB group were due to oropharyngeal cancer, pneumonia, lung adenocarcinoma, and small cell lung cancer. The one death in the PTA group was due to pneumonia. All deaths were adjudicated as not procedure- or device-related by the CEC.

### 3.4 | Functional outcomes

At 24 months, both treatment groups showed improvement in all measured functional outcomes (Table 4). Changes in the six-month walking test, WIQ, and EQ-5D index were similar between cohorts. However, ABI/TBI values were statistically significantly higher in the PTA arm at 24 months (0.945) compared to the DCB arm (0.883;  $P = 0.047$ ).

## 4 | DISCUSSION

Randomized trials have demonstrated the superiority of DCB compared to PTA in patients with femoropopliteal PAD.<sup>14,15,17-21</sup> Though important as a starting place to determine the safety and efficacy of a given device, the subjects studied in these trials are overwhelmingly of Caucasian race. These results are the first longer term RCT data describing the safety and efficacy of a DCB in a Japanese population. This study increases the evidence supporting use of a DCB to prevent restenosis and avoid leaving a metal implant behind.

Results of endovascular treatment in Japanese patients have been reported previously, and mainly focus on stent deployment, whether treatment devices are BMS or DES.<sup>23-26</sup> Not surprisingly, femoropopliteal lesions in Japanese patients are treated primarily with PTA and stents. Part of this paradigm is due to availability; only BMS, DES, and stent grafts are available for use in Japan as of 2018. However, there are clinical treatment concerns with all of these devices, including long-term rates of restenosis and stent fractures.

Notably, the largest trial investigating treatment with a drug-eluting device is a post-market registry of the Zilver PTX DES.<sup>23</sup> Patients in this trial and the registry had similar baseline demographic characteristics, though the registry enrolled patients that had any Rutherford class or ABI compared to this trial, where only RCC 2-4

were enrolled. The one-year outcomes in the registry of 907 patients showed patency of 86.4% using the Kaplan-Meier analysis, a number calculated from approximately 65% of the patients in the trial. In the registry, the thrombosis rate was estimated by the Kaplan-Meier analysis to be 3.0%. There were no thromboses reported in IN.PACT SFA Japan out to 2 years, emphasizing one of the potential clinical benefits of DCBs. In addition to higher thrombosis rates, another potential complication of stenting is fractures, and the registry reported a fracture rate of 1.5%. While quite low, the clinical implications of fracture were not reported in this analysis.

IN.PACT SFA Japan was structured similar to the IN.PACT SFA trial, and compares favorably to the results seen in the DCB arm of IN.PACT SFA. Primary patency using Kaplan-Meier analysis at day 720 was 79.8% in IN.PACT Japan, and 78.9% in IN.PACT SFA. Notably, the 77 women in IN.PACT SFA had higher patency through day 720 than the 18 women enrolled in IN.PACT Japan (76.7% vs 66.7%).<sup>15</sup> As such, the question of outcomes by sex merits further investigation in a Japanese population. The CD-TLR rate in both studies was the same: 9.1%. When comparing patients in this trial to other IDE trials, Japanese patients are older and more likely to be diabetic.<sup>15,17,20,21</sup> The mean lesion length in the DCB arm of  $9.15 \pm 5.85$  cm in this trial was also longer than in the other IDE trials ( $8.94 \pm 4.89$  cm for IN.PACT SFA,  $6.27 \pm 4.14$  cm for LEVANT 2, and  $8.0 \pm 4.5$  cm for ILLUMENATE US).<sup>15,17,21</sup> Longer term data for these IDE trials, as well as the forthcoming Ranger study will allow for further comparisons between the IN.PACT Admiral DCB and other DCBs currently on the market.

Drug-coated balloons were designed to reduce stenosis, but clinical outcomes vary depending on patient characteristics, treated limbs, and the severity of the lesions. In this analysis, there were still failures with opportunities to improve the reliability of outcomes after conventional therapies. In particular, lesions that are severely calcified or occluded may result in insufficient drug transfer into the vessel wall, hampering long-term anti-restenotic effects of the DCB.<sup>27</sup> Recently, more endovascular devices have been approved and available for use outside of Japan, and investigated as potential options to further improve DCB outcomes. Atherectomy and specialty balloons have been designed to specifically remove plaque or alter vessel compliance, and their use prior to inflation of a DCB is hypothesized to increase uptake of the anti-restenotic drug. This could be particularly important in complex lesions to maximize the effectiveness of DCB therapy.

When comparing trials both in Japan and across the globe, it is clear that both DCBs and DES will play a role in future treatment of Japanese patients. However, appropriate use of these drug-based solutions and other vessel preparation modalities remains an open question. The few trials that have been reported in Japan are difficult to compare given intrinsic differences in the baseline demographic and lesion characteristics of patient cohorts, balloon usage characteristics, varying choices for outcome measurements, and differing time scales. In addition, as of 2018, PTA is the only vessel preparation device available on the market in Japan. Given the outcomes seen in other patient groups and complex lesion types, investigating the use of lesion preparation tools like atherectomy and specialty balloons is of interest. Fortunately, several medical device studies are ongoing in Japan studying different devices, and will also contribute to the development of an optimal treatment algorithm for Japanese patients, and include bio-mimetic stents, atherectomy, covered stents, and other DCBs (MIMICS-2, NCT02400905; J-Supreme, NCT02733653; Gore VJH 11-01, NCT01575808; and RANGER II SFA, NCT03064126).

## 5 | LIMITATIONS

This study was smaller than other studies in the IN.PACT DCB clinical program and was not independently powered, yet adds an important data point in the generalizability of results across patient populations and lesion types. No economic data were gathered during this study, and no specific guidelines for other treatments were provided other than following standard of care. Finally, patients will only be followed out to 3 years.

## 6 | CONCLUSION

Results from the IN.PACT SFA Japan Trial showed significantly higher patency rates and lower CD-TLR rates out to 2 years following treatment with an IN.PACT Admiral DCB. There was a favorable treatment effect comparing DCB to treatment with PTA. These results demonstrate the safety and efficacy of this DCB in an Asian population.

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## CONFLICT OF INTEREST

OI, YS, KU, SS, and HY have no relevant conflicts to report.

HW and HO are full-time employees of Medtronic.

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