CLINICAL STUDY

Sex-Related Differences in the Long-Term Outcomes of Patients with Femoropopliteal Arterial Disease Treated with the IN.PACT Drug-Coated Balloon in the IN.PACT SFA Randomized Controlled Trial: A Post Hoc Analysis

Maureen P. Kohi, MD, Marianne Brodmann, MD, Thomas Zeller, MD, PhD, Antonio Micari, MD, Iris Baumgartner, MD, Hong Wang, MD, MPH, Bridget Wall, PhD, and Mahmood K. Razavi, MD

ABSTRACT

Purpose: To evaluate sex-related disparities in long-term outcomes of patients with peripheral artery disease (PAD) treated with IN.PACT drug-coated balloon (DCB) or percutaneous transluminal angioplasty (PTA).

Materials and Methods: A post hoc analysis of the IN.PACT SFA trial was performed. Participants with Rutherford Clinical Classification 2–4 PAD and femoropopliteal artery lesions up to 18 cm long were randomly assigned to treatment with DCB (n = 220) or PTA (n = 111). Effectiveness outcomes were evaluated, including 36-month primary patency (freedom from binary restenosis and freedom from clinically driven [CD] target lesion revascularization [TLR]).

Results: In the DCB group, women were significantly older (69.4 y ± 9.9) than men (66.4 y ± 9.1; $P = .025$). Mean reference vessel diameter (RVD) was significantly smaller in women (4.4 mm ± 0.68) compared with men (4.8 mm ± 0.89, $P < .001$). Primary patency was 65.4% in women and 71.8% in men ($P = .302$). Freedom from CD-TLR was 81.1% in women and 86.4% in men ($P = .285$). Women treated with PTA were older (70.4 y ± 8.3) than men (66.9 y ± 9.5; $P = .063$). Mean RVD was significantly smaller in women (4.2 mm ± 0.77) compared with men (4.9 mm ± 0.77, $P < .001$). Primary patency was 42.3% in women and 46.7% in men ($P = .551$). Freedom from CD-TLR was 59.4% in women and 75.5% in men ($P = .109$). No significant differences were noted in safety and mortality outcomes.

From the Department of Radiology and Biomedical Imaging (M.P.K.), University of California, San Francisco, 505 Parnassus Avenue, M-361, San Francisco, CA 94143; Division of Angiology (M.B.), Medical University, Graz, Austria; Angiology Department (T.Z.), Universitäts-Herzzentrum Freiburg–Bad Krozingen, Bad Krozingen, Germany; Cardiology Department (A.M.), Humanitas Gavazzeni Hospital, Bergamo, Italy; Division of Angiology (I.B.), University Hospital of Bern Inselspital, University of Bern, Bern, Switzerland; Aortic, Peripheral and Venous Department (H.W.), Medtronic, Santa Rosa, California; Aortic, Peripheral and Venous Department (B.W.), Medtronic, Plymouth, Minnesota; and St. Joseph Heart and Vascular Center (M.K.R.), Orange, California. Received December 16, 2019; final revision received May 4, 2020; accepted May 5, 2020. **Address correspondence to** M.P.K.; E-mail: Maureen.Kohi@ucsf.edu; Twitter handle: #UCSFIR

M.P.K. is a paid consultant for and member of the advisory board for Medtronic (Dublin, Ireland) and Boston Scientific (Marlborough, Massachusetts) and is a paid consultant for Cook Medical (Bloomington, Indiana) and Bard (Murray Hill, New Jersey). M.B. receives honoraria from Biotronik (Berlin, Germany), Medtronic, Philips Spectranetics (Colorado Springs, Colorado), Bard, Bayer HealthCare (Whippany, New Jersey), and Daiichi Sankyo (Tokyo, Japan) and is a paid consultant for Intact Vascular (Wayne, Pennsylvania), Shockwave Medical (Santa Clara, California), Medtronic, Philips Healthcare (Amsterdam, the Netherlands), Philips Spectranetics, Bard, LimFlow (Santa Clara, California), and Avinger (Redwood City, California). T.Z. receives honoraria from Abbott Vascular (Santa Clara, California), Veryan Medical (Horsham, United Kingdom), Biotronik, Boston Scientific, Cook Medical, W.L. Gore & Associates (Flagstaff, Arizona), Medtronic, Philips Spectranetics, TriReme Medical (Pleasanton, California), and Shockwave Medical; is a paid consultant for Boston Scientific, Cook Medical, W.L. Gore & Associates, Medtronic, Philips Spectranetics, Veryan Medical, Intact Vascular, B. Braun (Melsungen, Germany), Shockwave Medical, and Bayer HealthCare; receives research funding from 480 Biomedical (Watertown, Massachusetts), Bard Peripheral Vascular (Tempe, Arizona), Veryan Medical, Biotronik, Cook Medical, W.L. Gore & Associates, Medtronic, Philips Healthcare, Terumo Medical Corporation (Somerset, New Jersey), TriReme Medical, Shockwave Medical, MedAlliance (Nyon, Switzerland), Intact Vascular, and B. Braun; and owns stock in QT Medical (Diamond Bar, California). A.M. is a paid consultant for and member of the advisory board for Medtronic. H.W. and B.W. are paid employees of Medtronic. M.K.R. is a paid consultant for Abbott Vascular, Boston Scientific, Phillips Volcano (San Diego, California), Medtronic, and Terumo Medical Corporation. The other author has not identified a conflict of interest.

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Figure E1 and Tables E1–E7 can be found by accessing the online version of this article on *www.jvir.org* and clicking on the Supplemental Material tab.

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Conclusions: In both groups, women were older and had smaller vessels. Particularly in the PTA group, women had worse clinical outcomes, though not reaching statistical significance. Further evaluation is necessary to understand the disparate nature of disease progression and outcomes following endovascular treatment in women compared with men.

ABBREVIATIONS

CD = clinically driven, DCB = drug-coated balloon, PAD = peripheral artery disease, RVD = reference vessel diameter, TLR = target lesion revascularization, TVR = target vessel revascularization

Peripheral artery disease (PAD) affects > 200 million people worldwide and is now recognized as a cardiovascular pandemic (1). Recent studies have demonstrated that the prevalence of PAD is likely higher in women than in men, and women with PAD are more likely to present at an older age with more advanced disease (2,3). Furthermore, women with PAD have both higher functional impairment and faster functional decline than women without PAD (2). Sex-related differences have also been reported in the outcomes of PAD treatment with standard percutaneous transluminal angioplasty (PTA), where women have demonstrated a higher 12-month reintervention rate compared with men (4). Recent randomized trials have shown superior outcomes with paclitaxel drug-coated balloons (DCBs) over PTA in the treatment of patients with femoropopliteal PAD (5–10). The IN.PACT SFA trial demonstrated superiority of DCB compared with PTA in both men and women (6). The purpose of this post hoc analysis was to examine sex-related disparities in the long-term outcomes of patients with PAD treated with DCB or PTA.

MATERIALS AND METHODS

IN.PACT SFA was a prospective, multicenter, multinational, randomized, single-blind trial evaluating safety and effectiveness of a paclitaxel DCB (IN.PACT Admiral; Medtronic, Dublin, Ireland) versus PTA in the treatment of patients with symptomatic superficial femoral artery and/or proximal popliteal artery disease. As this was an investigational device exemption trial, end points and definitions were determined in concert with the US Food and Drug Administration. Clinical sites are listed in **Table E1** (available online on the article's Supplemental Material page at *www.jvir.org*). Methods and results through 5 years have been reported (5–7,11).

IN.PACT SFA I and IN.PACT SFA II were evaluated together for these results. The trials are registered at Clinical Trials.gov: Randomized Trial of IN.PACT Admiral Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease (IN.PACT SFA I); https://clinicaltrials.gov/ct2/show/NCT01175850; ClinicalTrials.gov Identifier: NCT01175850; IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery (SFA) and Proximal Popliteal Artery (PPA) (IN.PACT SFA II); https://clinicaltrials.gov/ct2/show/NCT01566461; ClinicalTrials.gov Identifier: NCT01566461.

Patient Population and Treatment

Eligible patients had moderate to severe intermittent claudication or ischemic rest pain (Rutherford Clinical Classification 2–4); stenosis of 70%–99% with lesion lengths between 4 cm and 18 cm or a complete occlusion with lengths of ≤ 10 cm involving the superficial femoral and/or proximal popliteal arteries; and were required to have successful predilation of the lesion before enrollment (**Table E2** [available online on the article's Supplemental Material page at *www.jvir.org*]). A total of 331 participants were randomly assigned in a 2:1 fashion into a DCB or a PTA group and stratified by site (**Fig 1** and **Fig E1** [available online on the article's Supplemental Material page at *www.jvir.org*]).

Study End Points

Primary patency was defined as freedom from clinically driven (CD) target lesion revascularization (TLR) and freedom from binary restenosis (duplex ultrasonography peak systolic velocity ratio ≤ 2.4) and was analyzed through 36 months. CD-TLR was defined as reintervention at the target lesion because of symptoms or a decrease in ankle-brachial index by ≥ 20% or > 0.15 compared with baseline ankle-brachial index after the procedure. The primary composite safety end point was freedom from device- and procedure-related death through 30 days and freedom from major target limb amputation and CD target vessel revascularization (TVR) through 36 months. A blinded independent Clinical Events Committee reviewed and adjudicated all major adverse events through the 36-month follow-up period. Blinded independent core laboratories (VasCore, Boston, Massachusetts [duplex ultrasonography] and SynvaCor, Springfield, Illinois [angiography]) analyzed all procedural and follow-up images through 36 months.

Statistical Analysis

In this post hoc analysis of the IN.PACT SFA trial, participant demographics, lesion characteristics, procedural details, and rates of primary patency, freedom from CD-TLR, and safety through 3 years were compared based on sex. The DCB arm

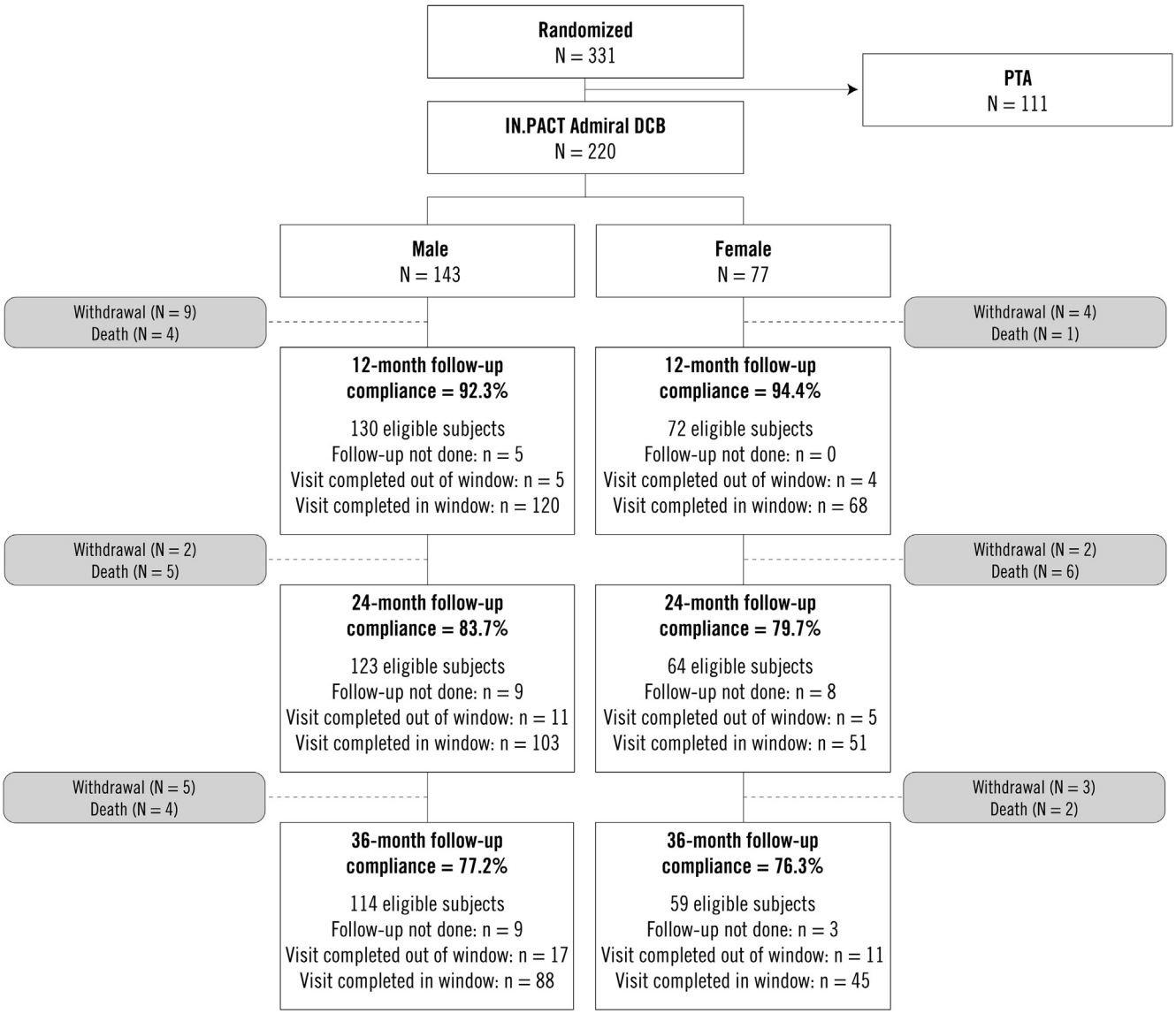

Figure 1. Follow-up of participants treated with a DCB through 3 years.

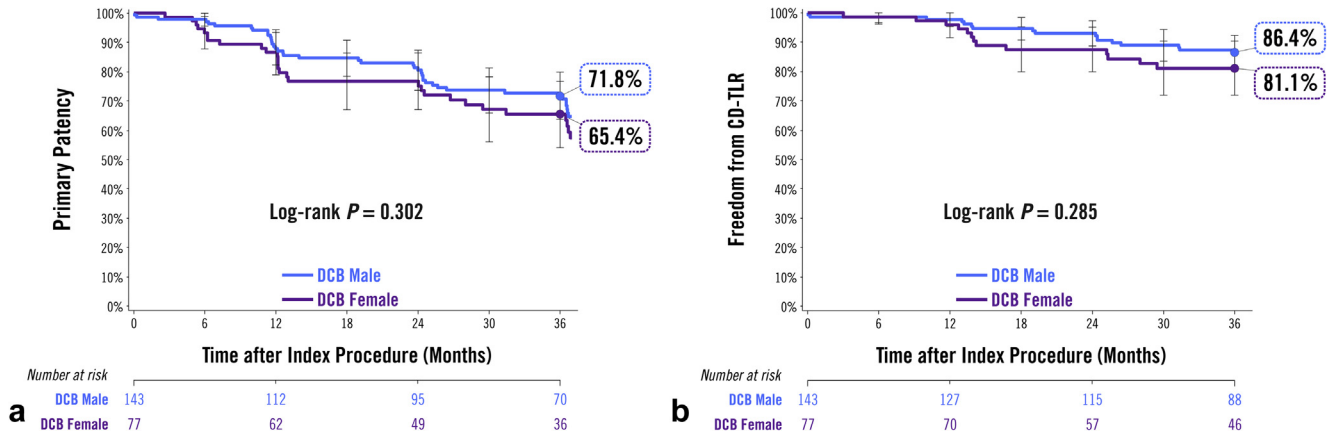

Figure 2. Primary patency and freedom from CD-TLR through 3 years by sex of participants treated with DCB. **(a)** Primary patency by Kaplan-Meier estimate was not statistically significantly different between male and female participants treated with DCB through 36 months (log-rank test, $P = .302$). **(b)** Freedom from CD-TLR by Kaplan-Meier estimate was not statistically significantly different between male and female participants treated with DCB through 36 months (log-rank test, $P = .285$). An independent and blinded Clinical Events Committee adjudicated all TLR events, and independent and blinded core laboratories reviewed all ultrasound and angiographic images.

Table 1. End Points through 3 Years of Participants Treated with DCB

End Points through 3 Years	Male DCB (n = 143 participants)	Female DCB (n = 77 participants)	*P* Value*
Primary safety composite end point† —freedom from:	83.6% (107/128)	76.8% (53/69)	.257
Device- and procedure-related death through 30 days	0.0% (0/143)	0.0% (0/76)	> .999
Major target limb amputation within 1,080 days	0.0% (0/128)	0.0% (0/69)	> .999
CD-TVR within 1,080 days	16.4% (21/128)	23.2% (16/69)	.257
Death (all-cause) within 30 days	0.0% (0/143)	0.0% (0/76)	> .999
Cumulative Complications within 1,080 Days			
MAE composite‡	25.8% (33/128)	31.9% (22/69)	.406
Death (all-cause)	10.2% (13/128)	11.6% (8/69)	.810
CD-TVR	16.4% (21/128)	23.2% (16/69)	.257
Major target limb amputation	0.0% (0/128)	0.0% (0/69)	> .999
Thrombosis at target lesion site§	1.6% (2/128)	2.9% (2/69)	.613
CD-TLR	13.3% (17/128)	18.8% (13/69)	.306
Any TVR	17.2% (22/128)	23.2% (16/69)	.346
Any TLR	14.8% (19/128)	18.8% (13/69)	.544
Other Major Secondary End Points at 36 Months			
Time to first CD-TLR within 1,080 days (d)	575.5 ± 308.5 (17)	500.4 ± 238.0 (13)	.473
Primary sustained clinical improvement‖	72.5% (79/109)	61.4% (35/57)	.161
Secondary sustained clinical improvement¶	87.4% (90/103)	81.1% (43/53)	.343
Change in quality of life from baseline by EQ-5D Index	0.0932 ± 0.2021 (103)	0.0637 ± 0.2757 (53)	.492
Change in walking distance from baseline by 6MWT (m)	13.4 ± 115.1 (38)	−1.4 ± 131.4 (16)	.681
Walking impairment by WIQ (%)	74.8 ± 32.6 (104)	66.2 ± 36.7 (54)	.136
Change in ABI/TBI# from baseline to 36 months (ratio mm Hg)	0.125 ± 0.248 (97)	0.153 ± 0.253 (47)	.527
Nights in hospital due to index lesion	1.2 ± 1.4 (143)	2.3 ± 4.2 (76)	.026

Note—Values are reported as % (n/N) or mean ± SD (N). All events were adjudicated by the independent Clinical Events Committee, and all duplex ultrasound and angiographic measures were made by the independent core laboratories; all other data were site-reported.

6MWT = 6-minute walk test; ABI = ankle-brachial index; CD = clinically driven; DCB = drug-coated balloon; EQ-5D = EuroQoL 5-dimension health-related quality-of-life questionnaire; MAE = major adverse event; PTA = percutaneous transluminal angioplasty; TBI = toe-brachial index; TLR = target lesion revascularization; TVR = target vessel revascularization; WIQ = Walking Impairment Questionnaire.

**P* values are based on Fisher exact test or *t* test for superiority with significance level of .05.

†Defined as 30-day freedom from device- and procedure-related death and major target limb amputation and 36-month freedom from CD-TVR.

‡Composite of death, CD-TVR, major target limb amputation, and thrombosis at target lesion site.

§Defined as occlusion because of thrombus formation, confirmed by sudden onset of symptoms and documented by duplex ultrasonography and angiography.

‖Defined as sustained upward shift of at least 1 category on Rutherford Clinical Classification scale compared with baseline, freedom from major target limb amputation, and freedom from TVR.

¶Defined as sustained upward shift of at least 1 category on Rutherford Clinical Classification scale compared with baseline, and freedom from major target limb amputation (participants could have had TVR).

#TBI was not measured in IN.PACT SFA I phase.

included 143 men and 77 women (**Fig 1**); the PTA arm included 75 men and 36 women (**Fig E1** [available online on the article's Supplemental Material page at *www.jvir.org*]). Participant-level summaries were used for baseline demographics, clinical characteristics, and outcome analyses; lesion-level summaries were used for lesion characteristics. Continuous variables were displayed as mean ± SD; dichotomous and categorical variables were presented as counts and percentages. For baseline characteristics, continuous variables were compared by Student *t* tests; dichotomous and categorical variables were compared by Fisher exact test and Cochran-Mantel-Haenszel modified ridit scores, respectively. Outcome analyses were performed at the participant level. The Kaplan-Meier method was used to evaluate time-to-event data for primary patency and freedom from CD-TLR over the 36-month follow-up period. The difference in the survival curves between comparison groups was assessed using the log-rank test. For other outcomes, Fisher exact test was used to compare binary outcomes, and the Student *t* test was used for continuous outcomes. For event rates that were expressed as a proportion, the number of participants with an event within 1,080 days was the numerator, and the total number of participants with an

Table 2. Multivariable Analysis of Predictors of Outcomes through 3 Years

Predictors	Hazard Ratio [95% CI]	*P* Value
Predictors of loss of primary patency—women treated with DCB		
Baseline TASC lesion—C/D vs A/B	7.30 [2.77, 19.19]	< .001
Previous limb amputation, yes/no	22.20 [1.80, 273.63]	.016
SFA proximal/mid vs distal	5.87 [0.98, 35.16]	.053
Predictors of loss of primary patency—men treated with DCB		
Lesion length (per cm)*	1.28 [1.09, 1.50]	.002
Total treatment balloon length (per cm)*	0.98 [0.97, 1.00]	.021
SFA proximal/mid vs distal	2.82 [0.98, 8.06]	.054
Age (y)*	0.97 [0.93, 1.01]	.098
Predictors of CD-TLR—women treated with DCB		
Severe calcification, yes/no	4.33 [1.07, 17.48]	.039
Previous ipsilateral revascularization (SFA/PPA), yes/no	5.71 [1.26, 25.81]	.024
Hyperlipidemia, yes/no	0.14 [0.03, 0.66]	.013
Insulin-dependent diabetes mellitus (yes/no)	6.96 [1.65, 29.36]	.008
Reference vessel diameter (per mm)*	0.323 [0.09, 1.19]	.089
Previous limb amputation, yes/no	12.39 [0.99, 155.54]	.051
Predictors of CD-TLR—men treated with DCB		
Reference vessel diameter (per mm)*	0.46 [0.25,0.84]	.012
BMI (per kg/m^2)*	1.12 [1.01, 1.24]	.026

Note–Multiple Cox proportional hazards regression of participants treated with DCB.
BMI = body mass index; CD = clinically driven; CI = confidence interval; DCB = drug-coated balloon; PPA = proximal popliteal artery; SFA = superficial femoral artery; TASC = TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease; TLR = target lesion revascularization.
*For continuous variables, the comparative direction is incremental for these measured characteristics.

event or at least 1,050 days of clinical follow-up was the denominator. The level of statistical significance was set at $P < .05$ with no correction for multiple comparisons. For functional assessment of clinical characteristics at 36 months, participants were required to have data at both baseline and 36 months to assess any changes from baseline. To identify predictive factors for revascularization and loss of patency separately for men and women treated with DCB, a multivariable analysis was performed using a Cox proportional hazard model; identical baseline covariates were used. To identify the predictive factors for primary patency and CD-TLR in each subgroup, univariate analyses followed by a stepwise multivariable Cox regression model were employed. Variables were allowed to enter the model using an entry criterion of 0.2 and stay in the model

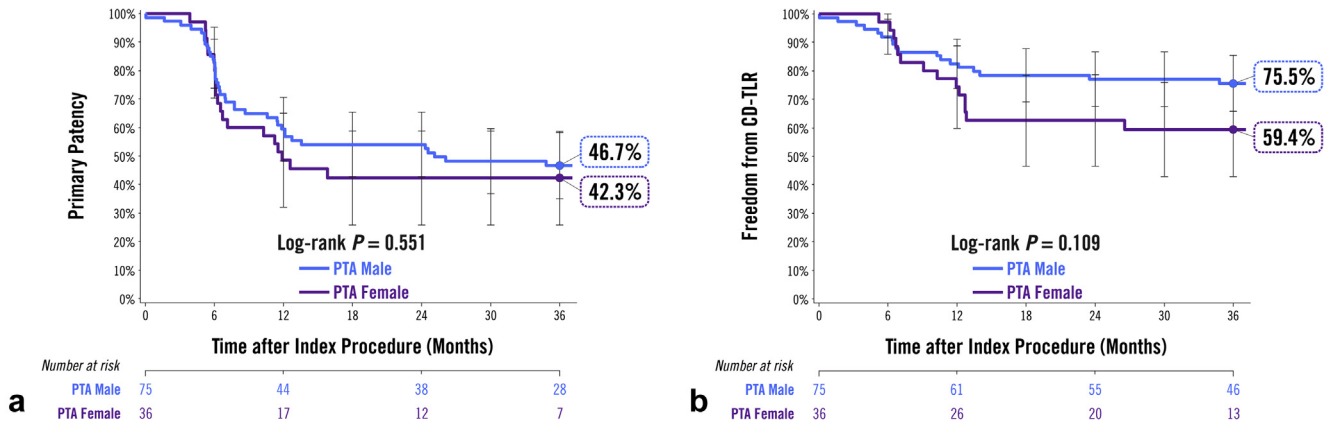

Figure 3. Primary patency and freedom from CD-TLR through 3 years by sex of participants treated with PTA. **(a)** Primary patency by Kaplan-Meier estimate was not statistically significantly different between male and female participants treated with PTA through 36 months (log-rank test, $P = .551$). **(b)** Freedom from CD-TLR by Kaplan-Meier estimate was not statistically significantly different between male and female participants treated with PTA through 36 months (log-rank test, $P = .109$). An independent and blinded Clinical Events Committee adjudicated all TLR events, and independent and blinded core laboratories reviewed all ultrasound and angiographic images.

Table 3. End Points through 3 Years of Participants Treated with PTA

End Points through 3 Years	Male PTA (n = 75 participants)	Female PTA (n = 36 participants)	*P* Value*
Primary safety composite end point† —freedom from:	70.0% (49/70)	51.5% (17/33)	.081
Device- and procedure-related death through 30 days	0.0% (0/75)	0.0% (0/36)	> .999
Major target limb amputation within 1,080 days	0.0% (0/70)	0.0% (0/33)	> .999
CD-TVR within 1,080 days	30.0% (21/70)	48.5% (16/33)	.081
Death (all-cause) within 30 days	0.0% (0/75)	0.0% (0/36)	> .999
Cumulative Complications within 1,080 Days			
MAE composite‡	31.4% (22/70)	51.5% (17/33)	.081
Death (all-cause)	1.4% (1/70)	3.0% (1/33)	.540
CD-TVR	30.0% (21/70)	48.5% (16/33)	.081
Major target limb amputation	0.0% (0/70)	0.0% (0/33)	> .999
Thrombosis at target lesion site§	7.1% (5/70)	0.0% (0/33)	.174
CD-TLR	25.7% (18/70)	42.4% (14/33)	.111
Any TVR	30.0% (21/70)	51.5% (17/33)	.049
Any TLR	27.1% (19/70)	48.5% (16/33)	.045
Other Major Secondary End Points at 36 Months			
Time to first CD-TLR within 1,080 days (d)	293.6 ± 249.5 (18)	314.9 ± 162.7 (14)	.783
Primary sustained clinical improvement‖	58.5% (38/65)	40.6% (13/32)	.131
Secondary sustained clinical improvement¶	88.5% (54/61)	86.2% (25/29)	.741
Change in quality of life from baseline by EQ-5D Index	0.0630 ± 0.2040 (62)	0.0731 ± 0.1864 (28)	.825
Change in walking distance from baseline by 6MWT (m)	48.9 ± 115.5 (19)	69.5 ± 70.7 (10)	.611
Walking impairment by WIQ (%)	71.4 ± 30.0 (62)	81.9 ± 26.6 (29)	.110
Change in ABI/TBI# from baseline to 36 months (ratio mm Hg)	0.163 ± 0.231 (59)	0.141 ± 0.352 (26)	.770
Nights in hospital due to index lesion	2.0 ± 3.0 (75)	1.9 ± 2.0 (36)	.769

Note–Values are reported as % (n/N) or mean ± SD (N). All events were adjudicated by the independent Clinical Events Committee and all duplex ultrasound and angiographic measures were made by the independent core laboratories; all other data were site-reported. 6MWT = 6-minute walk test; ABI, ankle-brachial index; CD = clinically driven; EQ-5D = EuroQoL 5-dimension health-related quality-of-life questionnaire; MAE = major adverse event; PTA = percutaneous transluminal angioplasty; TBI = toe-brachial index; TLR = target lesion revascularization; TVR = target vessel revascularization; WIQ = Walking Impairment Questionnaire.

**P* values are based on Fisher exact test or *t* test for superiority with significance level of .05.

†Defined as 30-day freedom from device- and procedure-related death and major target limb amputation and 36-month freedom from CD-TVR.

‡Composite of death, CD-TVR, major target limb amputation, and thrombosis at target lesion site.

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#TBI was not measured in IN.PACT SFA I phase.

using an exit criterion of 0.1. Variables that remained in the multivariable analysis were reported as hazard ratios with confidence intervals. For continuous variables, the comparative direction was incremental for these measured characteristics. A multivariable analysis for participants treated with PTA could not be performed owing to small participant numbers. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Among participants treated with DCB, women were significantly older (69.4 y ± 9.9) than men (66.4 y ± 9.1, $P = .025$) (**Table E3** [available online on the article's Supplemental Material page at *www.jvir.org*]). Women had lower rates of coronary heart disease (47.3% vs 62.1%, $P = .043$) and renal insufficiency (2.6% vs 11.4%, $P = .037$). The mean reference vessel diameter (RVD) was significantly smaller in women (4.4 mm ± 0.68) compared with men (4.8 mm ± 0.89, $P < .001$). The remaining baseline characteristics, including outflow impairment, were not significantly different between the 2 groups. Percent diameter stenosis before the procedure was similar between groups, though directionally smaller in women (79.8% ± 16.2%) compared with men (81.8% ± 15.2%, $P = .356$). Diameter stenosis after the procedure was statistically significantly smaller in

women (17.8% ± 9.9%) compared with men (21.0% ± 10.5%, $P = .028$).

The 3-year primary patency rate by Kaplan-Meier estimate following treatment with DCB was 65.4% in women compared with 71.8% in men (log-rank $P = .302$) (Fig 2a). The 3-year freedom from CD-TLR rate by Kaplan-Meier estimate following DCB was 81.1% in women compared with 86.4% in men (log-rank $P = .285$) (Fig 2b).

The primary safety composite of freedom from device- and procedure-related death through 30 days and freedom from major target limb amputation and CD-TVR through 36 months was 76.8% in women and 83.6% in men ($P = .257$) (Table 1). The rate of major adverse events was 31.9% in women and 25.8% in men ($P = .406$). Both groups had a thrombosis rate of < 3% and no amputations. Women had a longer length of stay in the hospital compared with men (2.3 d ± 4.2 vs 1.2 d ± 1.4; $P = .026$). All-cause mortality through 3 years was 11.6% in women and 10.2% in men ($P = .810$); causes of death are listed in Table E4 (available online on the article's Supplemental Material page at *www.jvir.org*) (12).

Among participants treated with DCB, predictors of loss of primary patency through 3 years in women were TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) C/D lesions and previous limb amputation; predictors of loss of primary patency through 3 years in men were longer lesions and shorter total balloon treatment length (Table 2). Predictors of CD-TLR in women were previous ipsilateral revascularization, absence of hyperlipidemia, insulin-dependent diabetes, and severely calcified lesions; predictors of CD-TLR in men included higher body mass index and smaller RVDs.

In this trial, 111 participants were treated with PTA (75 men and 36 women); demographic characteristics are reported in Table E5 (available online on the article's Supplemental Material page at *www.jvir.org*). Among participants treated with PTA, women were older (70.4 y ± 8.3) than men (66.9 y ± 9.5, $P = .063$). Women had a lower body mass index (25.9 ± 5.4 vs 27.9 ± 4.4; $P = .036$) and a higher rate of restenotic lesions (13.9% vs 1.3%; $P = .006$). More women had less severe TASC lesions (80.6% of lesions were TASC A lesions in women vs 54.5% in men) yet higher Rutherford classes overall (11.1% of participants were Rutherford Clinical Classification 4 and 5 in women vs 4.0% in men). The mean RVD was significantly smaller in women (4.2 mm ± 0.77) compared with men (4.9 mm ± 0.77, $P < .001$). The remaining baseline characteristics, including outflow impairment, were not significantly different between the 2 groups. Percent diameter stenosis before the procedure was similar between groups, though directionally smaller in women (80.1% ± 13.2%) compared with men (81.8% ± 13.9%, $P = .535$). Diameter stenosis after the procedure was statistically smaller in women (15.5% ± 8.3%) compared with men (20.8% ± 10.8%, $P = .011$).

The 3-year primary patency rate by Kaplan-Meier estimate following treatment with PTA was 42.3% in women and 46.7% in men (log-rank $P = .551$) (Fig 3a). The 3-year freedom from CD-TLR rate by Kaplan-Meier estimate following PTA was 59.4% in women and 75.5% in men (log-rank $P = .109$) (Fig 3b).

The primary safety composite through 36 months was 51.5% in women and 70.0% in men ($P = .081$) (Table 3). The rate of major adverse events was 51.5% in women and 31.4% in men ($P = .081$). Women spent a similar amount of time in the hospital owing to the index lesion as men (1.9 d ± 2.0 compared with 2.0 d ± 3.0; $P = .769$). All-cause mortality through 3 years was 3.0% in women compared with 1.4% in men ($P = .540$); causes of death are listed in Table E6 (available online on the article's Supplemental Material page at *www.jvir.org*) (12).

DISCUSSION

The reported efficacy and safety of DCBs in women has been inconsistent, and long-term outcomes have yet to be reported (Table E7 [available online on the article's Supplemental Material page at *www.jvir.org*]) (13–19). In the LEVANT 2 trial, superior 1-year patency of a DCB over PTA was observed in men (70.6% DCB, 48.4% PTA) (16). However, women appeared to have consistently poorer efficacy outcomes in both the experimental and the control arms of LEVANT 2 (56.4% DCB, 61.4% PTA). Interestingly, a subgroup analysis of LEVANT 2 showed contradictory results in the German population: men and women had similar outcomes. Primary patency at 1 year was 68.0% in women treated with DCB compared with 42.9% in women treated with PTA and 76.2% in men treated with DCB compared with 54.4% in men treated with PTA (17). In the ILLUMENATE US study of a different DCB platform, men and women benefited equally through 1 year (men DCB 75.2%, women DCB 77.6%) (9). However, there were sex-related differences in the ILLUMENATE Global Registry; women had lower primary patency and freedom from CD-TLR rates compared with men (male patency 84.5%, female patency 72.8%; male freedom from CD-TLR 96.2%, female freedom from CD-TLR 90.7%) (20). In this post hoc analysis of the IN.PACT SFA trial, while women were older and had smaller RVDs, there were no statistically significant sex-related differences in outcomes observed through 3 years following treatment with this DCB.

This lack of consistency in efficacy of DCBs in women suggests that there is no sex-related class effect and that each DCB platform should be evaluated for effectiveness and safety by sex. Performance characteristics of the balloon platforms, variations in the populations in these studies, and procedural techniques employed in different studies may contribute to disparate outcomes between men and women.

In the current analysis, women treated with DCB had a smaller baseline RVD than men treated with DCB, but there was no statistically significant difference in the 3-year CD-TLR rates between men and women. Women treated with DCB spent more time in the hospital than men treated with DCB; however, reasons for increased hospital stay were not captured as part of this study. Interestingly, women and men

had different risk factors for PAD and different predictors of primary patency and CD-TLR. While the outcomes may not have been different, there appears to be a sex-related difference in PAD comorbidities and predictors of success following DCB intervention. Whether this DCB platform nullifies the negative impact of older age and smaller RVD on outcomes is unclear at this time.

Women treated with PTA also had smaller RVDs, and also tended to have worse outcomes. In contrast to women treated with DCB, women treated with PTA had higher rates of TLR and TVR compared with men treated with PTA. However, similar to women treated with DCB, Kaplan-Meier analyses of both patency and freedom from CD-TLR showed clinically worse, yet not statistically significantly worse, outcomes in women.

While all groups had comparable percent diameter stenosis before the procedure, women in both the DCB group and the PTA group had a statistically significantly smaller percent diameter stenosis after the procedure compared with their male counterparts. While this could signal that women received a better angioplasty during the procedure and this may have improved their outcomes overall, it is important to note that percent diameter stenosis is an imperfect way to extrapolate the increased blood flow that could potentially affect longer-term results. In this study, men and women had similar levels of stenosis, but women had smaller vessels; the volume of blood flowing through women's vessels was smaller. After the procedure, even though the percent diameter stenosis was smaller in women, the minimal lumen diameter was also smaller: directionally in the PTA group and reaching statistical significance in the DCB group. As such, these differences in percent diameter stenosis could be related more to the generally smaller vessel sizes of women rather than preferentially better angioplasty. More research is necessary to understand the interplay of vessel size, procedural details, and long-term outcomes.

A recent meta-analysis reported a higher risk of mortality in patients treated with paclitaxel (21); this analysis showed no difference in mortality between men and women through 3 years. Following this meta-analysis, the Food and Drug Administration put forth recommendations for interventionalists as they consider use of DCBs encompassing patient informed consent and the risk-benefit ratio of all available PAD treatment options (22). As reported in this article, women treated with PTA had a higher rate of TLR and TVR compared with men treated with PTA, and this higher risk of restenosis should be taken into consideration when treating women with PAD.

Beyond the endovascular treatment modalities of DCB and PTA, analysis of the lower extremity arterial revascularization literature reveals that women have increased risks of 30-day mortality, stroke, early graft thrombosis, amputation, cardiopulmonary events, embolization, incisional site complications, and repeat revascularization procedures (4,23). The evident sex-related disparity in outcomes suggests that additional studies are required to refine and update understanding of not only how PAD is different in women and men, but also how to define the differences in responses to individual treatment modalities. To do so, it is critical to recruit and retain more women in clinical trials, report outcomes by sex as standard practice in clinical studies, and perform meaningful meta-analyses investigating the effects of sex on outcomes.

This study has several limitations. The relatively small number of participants followed through 3 years and the low rate of women included in the trial limit the strength of the study conclusions; trends and insignificant numerical differences observed here may reach significance or become conclusively nonsignificant in larger patient populations. As women typically have smaller vessels, device characteristics, such as device diameters, may have influenced participant selection and the smaller number of women enrolled in the study. Stringent inclusion and exclusion criteria of randomized trials may reduce the generalizability of observations to the population at large.

In conclusion, in the IN.PACT SFA clinical trial, women with PAD were older and had smaller vessels and trended toward worse, yet not statistically significantly different, outcomes following treatment with DCB compared with men. Women treated with PTA had higher reintervention rates. Further studies are needed to characterize the differences in disease progression and outcomes following endovascular treatment in men compared with women.

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CME TEST QUESTIONS: SEPTEMBER 2020

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The CME questions in this issue are derived from the article "Sex-Related Differences in the Long-Term Outcomes of Patients with Femoropopliteal Arterial Disease Treated with the IN.PACT Drug-Coated Balloon in the IN.PACT SFA Randomized Controlled Trial: A Post Hoc Analysis" by Kohi et al.

This is a post-hoc analysis on the influence of gender as observed in the IN.PACT SFA randomized controlled trial that compared the use of percutaneous transluminal angioplasty (PTA) to the use of drug-coated balloon (DCB) technology. This study evaluated primary patency after treatment in Rutherford Clinical Category 2–4 with femoropopliteal arterial disease.

1. Among those treated with DCB, which of the following was NOT significantly different?
   a. Age
   b. Mean reference vessel diameter (RVD)
   c. Percent diameter stenosis, pre-procedure
   d. Rate of coronary heart disease

2. What was the 3-year primary patency in women treated with DCB?
   a. 65.4%
   b. 71.8%
   c. 81.1%
   d. 86.4%

3. True or False: Women treated with DCB had a significant difference in clinically-driven target lesions revascularization (CD-TLR) compared to men.
   a. True
   b. False

4. In women treated with DCB, which of the following were predictors of primary patency loss through 3 years?
   a. TASC C/D lesions
   b. Previous limb amputation
   c. Longer lesions
   d. A and B
   e. A, B, and C

APPENDIX

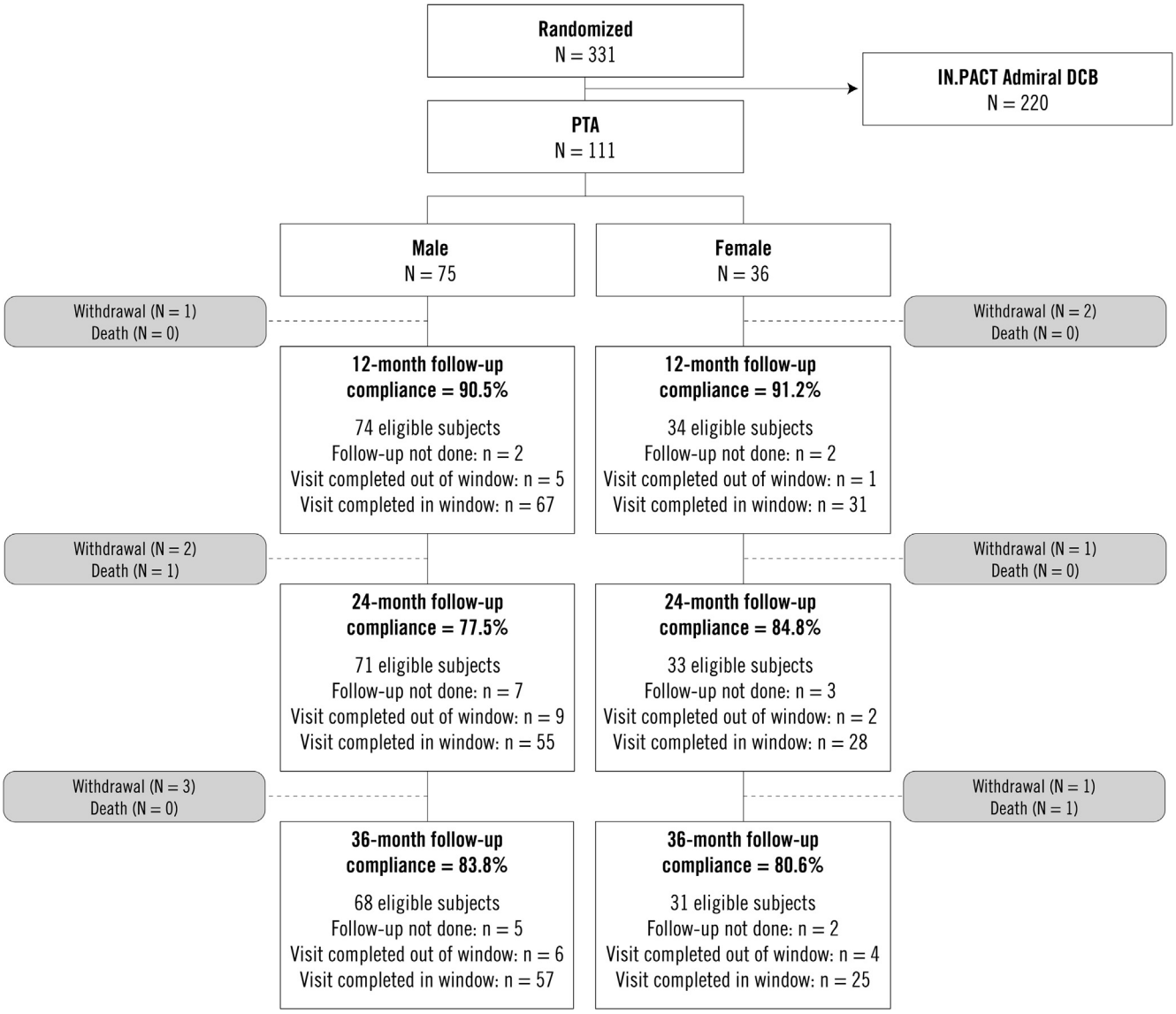

Figure E1. Follow-up of participants treated with PTA through 3 years.

Table E1. List of Clinical Sites That Enrolled Participants in the IN.PACT SFA Trial

US Clinical Site	Location	Principal Investigator
Landeskrankenhaus–Universitätsklinikum Graz	Graz, Austria	Marianne Brodmann
Inselspital Universitätsspital Bern	Bern, Switzerland	Iris Baumgartner
Ospedale Regionale di Lugano	Lugano/TI, Switzerland	Jos Van den Berg
Imeldaziekenhuis	Bonheiden, Belgium	Patrick Peeters
AZ Sint-Blasius	Dendermonde, Belgium	Marc Bosiers
Universitair Ziekenhuis Gent	Gent, Belgium	Frank Vermassen
Universitäts-Herzzentrum Freiburg–Bad Krozingen GmbH	Bad Krozingen, Germany	Thomas Zeller
RoMed Klinikum Rosenheim	Rosenheim, Germany	Gunnar Tepe
MVZ Prof. Mathey, Prof. Schofer GmbH	Hamburg, Germany	Sebastian Sixt
Universitätsklinikum Leipzig AöR	Leipzig, Germany	Dierk Scheinert
Università Cattolica del Sacro Cuore Policlinico Gemelli	Roma, Italy	Carlo Trani
Clinical Montevergine	Mercogliano (AV), Italy	Giovanni Sorropago
Maria Eleanora Hospital	Palermo, Italy	Antonio Micari
US Clinical Site		
Cleveland Clinic	Cleveland, Ohio	Mehdi Shishehbor
Saint Luke's Episcopal Hospital–Texas Medical Center	Houston, Texas	Neil Strickman
Hospital of the University of Pennsylvania	Philadelphia, Pennsylvania	Ronald Fairman
University of Virginia Medical Center	Charlottesville, Virginia	John Angle
Mount Sinai Medical Center	New York, New York	Prakash Krishnan
EMH Elyria Medical Center	Elyria, Ohio	Naim Farhat
Saint Luke's Hospital	Kansas City, Missouri	Steven Laster
New York Presbyterian Hospital/Columbia University Medical	New York, New York	William Gray
Sentara Norfolk General Hospital	Norfolk, Virginia	Marc Glickman
Washington Hospital	Fremont, California	Ash Jain
Munroe Regional Medical Center	Ocala, Florida	Robert Feldman
Mercy Medical Center	Des Moines, Iowa	David Chew
Arizona Heart Institute	Phoenix, Arizona	Venkatesh Ramaiah
Abbott Northwestern Hospital	Minneapolis, Minnesota	Peter Alden
Scripps Green Hospital/Scripps Clinic Torrey Pines	La Jolla, California	Curtiss Stinis
Banner Good Samaritan Medical Center	Phoenix, Arizona	Ashish Pershad
Holy Spirit Hospital	Camp Hill, Pennsylvania	Rajesh Dave
Washington Hospital Center	Washington, DC	Robert Gallino
Wellmont Holston Valley Medical Center	Kingsport, Tennessee	Christopher Metzger
Riverside Methodist Hospital	Columbus, Ohio	Gary Ansel
Deborah Heart and Lung Center	Browns Mills, New Jersey	Richard Kovach
Saint Vincent Heart Center of Indiana	Indianapolis, Indiana	Brian Bigelow
University of Kansas Hospital	Kansas City, Kansas	Kamal Gupta
Mercy Hospital and Medical Center	Chicago, Illinois	Paul Jones
Beth Israel Deaconess Medical Center	Boston, Massachusetts	Marc Schermerhorn
The Christ Hospital	Cincinnati, Ohio	Monica Hunter
The Miriam Hospital	Providence, Rhode Island	Peter Soukas
Stanford Hospital and Clinics	Stanford, California	Michael Dake
Saint Francis Hospital	Roslyn, New York	George Petrossian
Saint Elizabeth's Medical Center	Boston, Massachusetts	Lawrence Garcia
WakeMed Health and Hospitals	Raleigh, North Carolina	Ravish Sachar
Christiana Hospital	Newark, Delaware	Mark Garcia
Baptist Hospital of Miami	Miami, Florida	James Benenati
Aurora Saint Luke's Medical Center	Milwaukee, Wisconsin	Mark Mewissen
Providence Health Center	Waco, Texas	Rodney Brown
Arrowhead Hospital	Glendale, Arizona	Rahul Malhotra
Rex Hospital	Raleigh, North Carolina	James Zidar
Edward Hospital	Naperville, Illinois	Mark Goodwin
Terrebonne General Medical Center	Houma, Louisiana	Craig Walker

continued

Table E1. List of Clinical Sites That Enrolled Participants in the IN.PACT SFA Trial *(continued)*

US Clinical Site	Location	Principal Investigator
Kaiser Permanente—Moanalua Medical Center and Clinic	Honolulu, Hawaii	Peter Schneider
Pomerado Hospital	Poway, California	Rod Serry
Longview Regional Medical Center	Longview, Texas	Samir Germanwala
Advanced Vascular Associated	Morristown, New Jersey	Amit Patel
University of Pittsburgh Medical Center Passavant	Pittsburgh, Pennsylvania	Luke Marone

Table E2. Inclusion and Exclusion Criteria

Key Inclusion Criteria
Documented ischemia with Rutherford Clinical Classification 2, 3, or 4
Life expectancy, in the investigator's opinion, of at least 12 months
Target lesion is in SFA and/or PPA above the knee, located in the arterial segment starting at least 1 cm beyond CFA bifurcation between superficial and profunda femoris arteries (proximal anatomic landmark) to distal P1 segment of the popliteal artery at the level of the proximal edge of the patella (distal anatomic landmark)
Angiographic evidence that target lesion consists of single de novo or restenotic lesion without stent (or tandem lesions or a combination lesion as defined) that is: • 70%–99% occluded with total lesion length $\geq$ 40 mm and $\leq$ 180 mm (by visual estimate); or • 100% occluded with total lesion length $\leq$ 100 mm (by visual estimate)
Key Exclusion Criteria
Contralateral SFA/PPA disease requiring treatment in the same setting as index procedure
Any major (eg, cardiac, peripheral, abdominal) intervention (including in contralateral SFA/PPA) performed within 30 days before enrollment or planned within 30 days after index procedure
Presence of a second lesion in target vessel that requires treatment but does not meet the definition of tandem lesions
Failure to successfully cross target lesion with guide wire (successful crossing means tip of the crossing device is distal to target lesion in the absence of flow-limiting dissections or perforations)
Target lesion is an in-stent restenosis or a post-DCB restenosis or has been previously treated with bypass surgery
Dilation before randomization resulted in a major ($\geq$ grade D) flow-limiting dissection (observed on 2 orthogonal views) or residual stenosis $>$ 70% and translesional peak gradient $>$ 10 mm Hg

CFA = common femoral artery; DCB = drug-coated balloon; PPA = proximal popliteal artery; SFA = superficial femoral artery.

Table E3. Baseline Participant and Lesion Characteristics of Participants Treated with DCB

Baseline Participant and Lesion Characteristics	Male DCB (n = 143 participants; n = 144 lesions)	Female DCB (n = 77 participants; n = 77 lesions)	*P* Value
Baseline Demographics*			
Age (y)	66.4 ± 9.1 (143)	69.4 ± 9.9 (77)	.025
BMI (kg/m^2)	27.6 ± 4.4 (143)	28.1 ± 5.6 (77)	.530
Obesity (BMI ≥ 30 kg/m^2)	23.8% (34/143)	35.1% (27/77)	.084
Hypertension	89.5% (128/143)	94.8% (73/77)	.217
Hyperlipidemia	84.6% (121/143)	84.4% (65/77)	1.000
Diabetes mellitus	40.6% (58/143)	40.3% (31/77)	1.000
Carotid artery disease	36.8% (49/133)	31.6% (24/76)	.456
Coronary heart disease	62.1% (87/140)	47.3% (35/74)	.043
Current smoker	41.3% (59/143)	33.8% (26/77)	.311
Renal insufficiency (baseline serum creatinine ≥ 1.5 ng/dL)	11.4% (16/140)	2.6% (2/77)	.037
On dialysis	0.7% (1/140)	0.0% (0/77)	1.000
Below-the-knee vascular disease of target leg (stenotic/occluded)	39.2% (56/143)	44.2% (34/77)	.477
Previous peripheral revascularization	44.8% (64/143)	41.6% (32/77)	.671
Previous limb amputation	0.0% (0/143)	2.6% (2/77)	.121
Rutherford Clinical Classification			.204
0	0.0% (0/143)	0.0% (0/77)	
1	0.0% (0/143)	0.0% (0/77)	
2	39.2% (56/143)	35.1% (27/77)	
3	58.7% (84/143)	54.5% (42/77)	
4	2.1% (3/143)	10.4% (8/77)	
5	0.0% (0/143)	0.0% (0/77)	
6	0.0% (0/143)	0.0% (0/77)	
ABI/TBI† (mm Hg ratio)	0.766 ± 0.239 (138)	0.773 ± 0.207 (71)	.846
Lesion Characteristics (site-reported)			
Outflow impaired	11.9% (17/143)	10.4% (8/77)	.826
Lesion type			.457
De novo	95.8% (137/143)	93.5% (72/77)	
Restenotic (no stent)	4.2% (6/143)	6.5% (5/77)	
Number of participants receiving provisional stent	7.0% (10/143)	7.8% (6/77)	.828
Lesion Characteristics (core laboratory–reported, per lesion)‡			
Vessel§			
SFA	96.5% (139/144)	100.0% (77/77)	.166
PPA	9.0% (13/144)	2.6% (2/77)	.093
Number of run-off vessels occluded			
0	39.4% (54/137)	45.3% (34/75)	.466
1	45.3% (62/137)	34.7% (26/75)	.147
2	12.4% (17/137)	16.0% (12/75)	.532
3	2.9% (4/137)	4.0% (3/75)	.700
Preprocedure Characteristics			
TASC lesion type			.595
A	55.6% (80/144)	58.4% (45/77)	
B	30.6% (44/144)	31.2% (24/77)	
C	13.9% (20/144)	9.1% (7/77)	
D	0.0% (0/144)	1.3% (1/77)	
RVD (mm)	4.785 ± 0.886 (144)	4.390 ± 0.682 (77)	< .001
MLD (mm)	0.900 ± 0.788 (144)	0.900 ± 0.759 (77)	.998
Occluded lesion (100% stenosis)	26.4% (38/144)	24.7% (19/77)	.872
Diameter stenosis (%)	81.8 ± 15.2 (144)	79.8 ± 16.2 (77)	.356
Lesion length (cm)	9.08 ± 4.90 (144)	8.69 ± 4.90 (77)	.576

continued

Table E3. Baseline Participant and Lesion Characteristics of Participants Treated with DCB *(continued)*

Baseline Participant and Lesion Characteristics	Male DCB (n = 143 participants; n = 144 lesions)	Female DCB (n = 77 participants; n = 77 lesions)	*P* Value
Postprocedure Characteristics			
MLD (mm)	3.999 ± 0.779 (144)	3.724 ± 0.659 (77)	.009
Diameter stenosis (%)	21.0 ± 10.5 (144)	17.8 ± 9.9 (77)	.028
Acute gain (mm)	3.099 ± 0.960 (144)	2.824 ± 0.794 (77)	.033

Note–Values are reported as % (counts/sample size) or mean ± SD (N).
ABI = ankle-brachial index; BMI = body mass index; DCB = drug-coated balloon; MLD = minimum lumen diameter; PPA = proximal popliteal artery; RVD = reference vessel diameter; SFA = superficial femoral artery; TASC = TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease; TBI = toe-brachial index.
*Baseline demographics are site-reported.
†TBI was not measured in IN.PACT SFA I phase.
‡Baseline lesion characteristics are core laboratory–reported. Key core laboratory definitions are as follows:
RVD—angiographic measurement of the normal artery proximal and/or distal to the lesion intended for treatment.
MLD—angiographic measurement of the tightest area of obstruction or stenosis located within the segment of interest or the intended area of treatment.
Lesion length—angiographic measurement from the proximal healthy vessel segment to the distal healthy vessel segment (eg, length of obstruction).
§All lesions within artery segment are counted. Note that the number of lesions is greater than the number of participants enrolled, as 2 DCB participants were assessed by sites as having tandem lesions treated during the index procedure and were assessed by the angiographic core laboratory as having 2 target lesions treated during the index procedure. In addition, 1 DCB participant did not have a baseline angiogram available for assessment by the angiographic core laboratory.

Table E4. Kaplan-Meier Estimate of Cause of Death Through 3 Years in Participants Treated with DCB

Cause of Death	Male DCB (n = 143 participants)	Female DCB (n = 77 participants)
Cardiovascular deaths*	4.5% (6)	4.4% (3)
Acute MI†	0.8% (1)	0.0% (0)
Sudden cardiac death‡	0.7% (1)	2.9% (2)
Heart failure§	1.6% (2)	1.5% (1)
Stroke‖	1.5% (2)	0.0% (0)
Noncardiovascular deaths¶	4.7% (6)	4.3% (3)
Pulmonary	0.8% (1)	0.0% (0)
Gastrointestinal	0.8% (1)	0.0% (0)
Infection/sepsis (includes inflammatory)*	3.2% (4)	0.0% (0)
Neurologic (noncardiovascular)††	0.0% (0)	1.5% (1)
Malignancy	0.0% (0)	2.8% (2)
Gastrointestinal	0.0% (0)	1.4% (1)
Bladder	0.0% (0)	1.4% (1)
Undetermined cause‡‡	0.8% (1)	3.0% (2)

Note–Numbers are Kaplan-Meier estimate (number of participants with event); definitions are from Hicks et al (12).
DCB = drug-coated balloon; MI = myocardial infarction.
*Cardiovascular deaths include acute MI, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage, cardiovascular disease, other cardiovascular causes, and unknown cardiovascular causes.
†Death by any cardiovascular mechanism (eg, arrhythmia, sudden death, heart failure, stroke, pulmonary embolism, peripheral arterial disease) ≤ 30 days after MI, related to the immediate consequence of MI. For simplicity, if a cardiovascular death occurs ≤ 30 days of MI, it will be considered a death due to MI. Death resulting from a procedure to treat MI (percutaneous coronary intervention, coronary artery bypass graft) or treat complication resulting from MI should also be considered death due to acute MI. Death resulting from elective coronary procedure to treat myocardial ischemia (chronic stable angina) or death due to MI that is a direct consequence of a cardiovascular procedure/operation should be considered as death due to cardiovascular procedure.
‡Unexpected death not within 30 days of acute MI death, defined as follows:
Witnessed with or without new or worsening symptoms.
Witnessed within 60 minutes of onset of new or worsening cardiac symptoms (unless symptoms suggest acute MI).
Witnessed and attributed to an identified arrhythmia (captured on electrocardiogram, witnessed on monitor, or unwitnessed but found on implantable cardioverter defibrillator review).
After unsuccessful resuscitation from cardiac arrest.
After successful resuscitation from cardiac arrest and without identification of specific cardiac or noncardiac etiology.
Unwitnessed in participant seen alive and clinically stable ≤ 24 hours before being found without evidence of specific noncardiovascular cause of death, or if participant was not observed alive within 24 hours of death, undetermined cause of death should be recorded.
§Clinically worsening symptoms and/or signs of heart failure regardless of heart failure etiology.
‖Death as direct consequence of stroke or complications of stroke.
¶Categories of noncardiovascular deaths include pulmonary, renal, gastrointestinal, pancreatic, hepatobiliary, infection/sepsis (includes inflammatory), hemorrhage (excluding cardiovascular bleed or stroke), noncardiovascular procedure or surgery, trauma (including homicide), suicide, neurologic (noncardiovascular), drug reaction or overdose (may include anaphylaxis), other noncardiovascular, other noncardiovascular unknown, and malignancies (lung, gastrointestinal, prostate, breast, brain, bone [primary], undetermined neoplasm, bladder, ovarian, uterine/cervical, renal, sarcoma, hepatic, pancreatic, throat/nasopharyngeal, other).
**For example, systemic inflammatory response syndrome/immune (including autoimmune), may include anaphylaxis from environmental antigen (eg, food allergies).
††Excludes cardiovascular death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or cardiovascular hemorrhage of central nervous system.
‡‡Refers to a death not attributed to one of the above categories of cardiovascular death or to a noncardiovascular cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death.

Table E5. Baseline Participant and Lesion Characteristics of Participants Treated with PTA

Baseline Participant and Lesion Characteristics	Male PTA (n = 75 participants; n = 77 lesions)	Female PTA (n = 36 participants; n = 36 lesions)	*P* Value
Baseline Demographics*			
Age, y	66.9 ± 9.5 (75)	70.4 ± 8.3 (36)	.063
BMI, kg/m^2	27.9 ± 4.4 (75)	25.9 ± 5.4 (36)	.036
Obesity (BMI ≥ 30 kg/m^2)	26.7% (20/75)	22.2% (8/36)	.816
Hypertension	88.0% (66/75)	88.9% (32/36)	1.000
Hyperlipidemia	81.3% (61/75)	83.3% (30/36)	1.000
Diabetes mellitus	53.3% (40/75)	38.9% (14/36)	.163
Carotid artery disease	32.3% (21/65)	30.6% (11/36)	1.000
Coronary heart disease	56.8% (42/74)	51.4% (18/35)	.682
Current smoker	41.3% (31/75)	25.0% (9/36)	.139
Renal insufficiency (baseline serum creatinine ≥ 1.5 ng/dL)	8.1% (6/74)	2.9% (1/35)	.426
On dialysis	0.0% (0/75)	0.0% (0/36)	> .999
Below-the-knee vascular disease of target leg (stenotic/occluded)	56.0% (42/75)	47.2% (17/36)	.421
Previous peripheral revascularization	49.3% (37/75)	52.8% (19/36)	.840
Previous limb amputation	4.0% (3/75)	0.0% (0/36)	.550
Rutherford Clinical Classification			.011
0	0.0% (0/75)	0.0% (0/36)	
1	0.0% (0/75)	0.0% (0/36)	
2	45.3% (34/75)	22.2% (8/36)	
3	50.7% (38/75)	66.7% (24/36)	
4	4.0% (3/75)	8.3% (3/36)	
5	0.0% (0/75)	2.8% (1/36)	
6	0.0% (0/75)	0.0% (0/36)	
ABI/TBI† (mm Hg ratio)	0.737 ± 0.190 (72)	0.760 ± 0.187 (34)	.557
Lesion Characteristics (site reported)			
Outflow impaired	14.9% (11/74)	11.1% (4/36)	.770
Lesion type			.006
De novo	98.7% (74/75)	86.1% (31/36)	
Restenotic (no stent)	1.3% (1/75)	13.9% (5/36)	
Number of participants receiving provisional stent	16.0% (12/75)	5.6% (2/36)	.121
Lesion Characteristics (angiographic core laboratory–reported, per lesion)‡			
Vessel§			
SFA	97.4% (75/77)	88.9% (32/36)	.080
PPA	5.2% (4/77)	11.1% (4/36)	.263
Number of run-off vessels occluded			
0	39.5% (30/76)	27.8% (10/36)	.292
1	31.6% (24/76)	36.1% (13/36)	.671
2	23.7% (18/76)	33.3% (12/36)	.361
3	5.3% (4/76)	2.8% (1/36)	1.000
Preprocedure Characteristics			
TASC lesion type			.006
A	54.5% (42/77)	80.6% (29/36)	
B	31.2% (24/77)	16.7% (6/36)	
C	14.3% (11/77)	2.8% (1/36)	
D	0.0% (0/77)	0.0% (0/36)	
RVD (mm)	4.892 ± 0.771 (77)	4.229 ± 0.770 (36)	< .001
MLD (mm)	0.969 ± 0.846 (77)	0.858 ± 0.582 (36)	.419
Occluded lesion (100% stenosis)	22.1% (17/77)	13.9% (5/36)	.445
Diameter stenosis (%)	81.8 ± 13.9 (77)	80.1 ± 13.2 (36)	.535
Lesion length (cm)	9.20 ± 5.22 (77)	7.97 ± 4.86 (36)	.233

continued

Table E5. Baseline Participant and Lesion Characteristics of Participants Treated with PTA *(continued)*

Baseline Participant and Lesion Characteristics	Male PTA (n = 75 participants; n = 77 lesions)	Female PTA (n = 36 participants; n = 36 lesions)	*P* Value
Postprocedure Characteristics			
MLD (mm)	3.948 ± 0.711 (77)	3.678 ± 0.753 (36)	.068
Diameter stenosis (%)	20.8 ± 10.8 (77)	15.5 ± 8.3 (36)	.011
Acute gain (mm)	2.979 ± 0.937 (77)	2.820 ± 0.760 (36)	.376

Note–Values are reported as % (counts/sample size) or mean ± SD (N).
ABI = ankle-brachial index; BMI = body mass index; MLD = minimum lumen diameter; PPA = proximal popliteal artery; PTA = percutaneous transluminal angioplasty; RVD = reference vessel diameter; SFA = superficial femoral artery; TASC = TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease; TBI = toe-brachial index.
*Baseline demographics are site-reported.
†TBI was not measured in IN.PACT SFA I phase.
‡Baseline lesion characteristics are core laboratory–reported. Key core laboratory definitions are as follows:
RVD—angiographic measurement of the normal artery proximal and/or distal to the lesion intended for treatment.
MLD—angiographic measurement of the tightest area of obstruction or stenosis located within the segment of interest or the intended area of treatment.
Lesion length—angiographic measurement from the proximal healthy vessel segment to the distal healthy vessel segment (eg, length of obstruction).
§All lesions within artery segment are counted. Note that the number of lesions is greater than the number of participants enrolled, as 2 PTA participants were assessed by sites as having tandem lesions treated during the index procedure and were assessed by the angiographic core laboratory as having 2 target lesions treated during the index procedure.

Table E6. Kaplan-Meier Estimate of Cause of Death Through 3 Years in Participants Treated with PTA

Cause of Death	Male PTA (n = 74 participants)	Female PTA (n = 36 participants)
Cardiovascular deaths*	0.0% (0)	0.0% (0)
Noncardiovascular deaths†	1.4% (1)	0.0% (0)
Malignancy	1.4% (1)	0.0% (0)
Gastrointestinal	1.4% (1)	0.0% (0)
Undetermined cause‡	0.0% (0)	3.0% (1)

Note–Numbers are Kaplan-Meier estimates (number of participants with event); definitions are from Hicks et al (12).
PTA = percutaneous transluminal angioplasty.
*Cardiovascular deaths include acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage, cardiovascular disease, other cardiovascular causes, and unknown cardiovascular causes.
†Categories of noncardiovascular deaths include pulmonary, renal, gastrointestinal, pancreatic, hepatobiliary, infection/sepsis (includes inflammatory), hemorrhage (excluding cardiovascular bleed or stroke), noncardiovascular procedure or surgery, trauma (including homicide), suicide, neurologic (noncardiovascular), drug reaction or overdose (may include anaphylaxis), other noncardiovascular, other noncardiovascular unknown, and malignancies (lung, gastrointestinal, prostate, breast, brain, bone [primary], undetermined neoplasm, bladder, ovarian, uterine/cervical, renal, sarcoma, hepatic, pancreatic, throat/nasopharyngeal, other).
‡Refers to a death not attributed to one of the above categories of cardiovascular death or to a noncardiovascular cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death.

Table E7. DCB Outcomes by Sex in Other Trials

	Male DCB	Male PTA	Female DCB	Female PTA	Statistical Analyses
THUNDER (13,14)					
Cotavance DCB (no longer on the market)					
102 total participants from 3 German study centers, enrollment period 2004–2005					
Number enrolled	31 (30%)	34 (33%)	17 (17%)	20 (20%)	—
LLL at 6 mo	0.42 mm	1.76 mm	0.37 mm	1.61 mm	None provided
TLR at 5 y	17% (4/24)	71% (20/28)	38% (6/16)	52% (10/19)	None provided
PACIFIER (15)					
IN.PACT Pacific DCB					
91 total participants from 3 German study centers, enrollment period 2010–2011					
Number enrolled	26 (28%)	30 (33%)	18 (20%)	17 (19%)	—
LLL at 6 mo	−0.23 mm [−0.58, 0.12]	0.53 mm [0.18, 0.89]	0.36 mm [−0.10, 0.82]	0.85 mm [−0.58, 1.30]	Men: $P = .003$ Women: $P = .13$
TLR at 12 mo	0% [0]	24.1% [7]	16.7% [3]	35.7% [5]	Men: $P = .012$ Women: $P = .252$
LEVANT 2 (16)					
Lutonix DCB					
476 total participants from 54 study centers across the globe, enrollment period 2011–2012					
Number enrolled	193 (41%)	107 (22%)	123 (26%)	53 (11%)	—
Freedom from primary safety event at 1 y (all)	86.2% (150/174)	84.5% (82/97)	80.4% (90/112)	67.4% (31/46)	Men difference = 1.7% Women difference = 13.0%
Freedom from primary safety event at 1 y (United States only)	86.3% (88/102)	85.0% (51/60)	74.4% (58/78)	80.0% (24/30)	Men difference = 1.3% Women difference = -5.6
Primary patency at 1 y (all)	70.6% (115/163)	48.4% (44/91)	56.4% (57/101)	61.4% (27/44)	Men difference = 22.2% Women difference = −4.9%
Primary patency at 1 y (United States only)	71.9% (69/96)	50.0% (29/58)	50.7% (36/71)	70.4% (19/27)	Men difference = 21.9% Women difference = −19.7%
LEVANT 2 German Substudy (17)					
Lutonix DCB					
126 total participants from 8 German centers, enrollment period 2011–2012 (476 in full trial)					
Total enrolled	50 (40%)	29 (23%)	33 (26%)	14 (11%)	—
Primary patency through 395 d	76.2% (32/42)	54.5% (12/22)	68.0% (17/25)	42.9% (6/14)	Men difference 21.6%: $P = .079$ Women difference 25.1%: $P = .126$
Freedom from TLR through 395 d	93.3% (42/45)	88.5% (23/26)	93.1% (27/29)	53.8% (7/13)	Men difference 4.9%: $P = .484$ Women difference 39.3%: $P = .004$
Composite safety end point through 395 d	88.9% (40/45)	80.8% (21/26)	93.1% (27/29)	38.5% (5/13)	Men difference 8.1%: $P = .060$ Women difference 54.6%: $P < .001$
Lutonix Global SFA (18)					
691 total participants from 38 study centers globally, enrollment period 2012–2014					
Total enrolled	67.9% (469)	—	32.1% (222)	—	—
12-mo TLR-free rate by KM	—	—	88.9% (83.9–92.4)	—	—
24-mo TLR-free rate by KM	—	—	85.8% (80.2–89.8)	—	—
Retrospective IN.PACT Registry (19)					
IN.PACT Pacific DCB or IN.PACT Admiral DCB					
260 total participants, single German center, retrospective analysis of participants treated 2009–2012					
Total enrolled	63% (164)	—	37% (96)	—	—
Primary patency at 1 y	83.6 ± 3.0	—	71.6 ± 4.8	—	Male vs female: $P = .002$
Primary patency at 2 y	61.7 ± 4.1	—	39.8 ± 5.6	—	
Freedom from TLR at 1 y	88.5 ± 2.4	—	79.9 ± 4.0	—	Male vs female: $P = .001$
Freedom from TLR at 2 y	75.6 ± 3.4	—	55.6 ± 5.5	—	

continued

Table E7. DCB Outcomes by Sex in Other Trials *(continued)*

	Male DCB	Male PTA	Female DCB	Female PTA	Statistical Analyses
ILLUMENATE US (9)					
300 total participants from 43 study centers in United States and Austria, enrollment period 2013–2015					
Total enrolled	112 (37%)	64 (21%)	88 (29%)	36 (12%)	—
Primary patency through 12 mo	75.2% (76/101)	57.4% (35/61)	77.6% (59/76)	58.1% (18/31)	—
Primary patency through 12 mo by KM	80.9 ± 4.0	71.2 ± 6.2	84.1 ± 4.1	70.2 ± 8.0	Log-rank *P* for difference by sex through 410 days within DCB cohort: .4851
CD-TLR at 12 mo	5.7% (6/105)	14.5% (9/62)	10.7% (9/84)	21.2% (7/33)	—
ILLUMENATE Global (20)					
371 total participants from 37 European/Australia and New Zealand study centers, enrollment period 2013–2015					
Total enrollment	271 (73%)	—	100 (27%)	—	—
Primary patency at 365 d by KM	84.5%	—	72.8%	—	Log-rank $P = .015$
Freedom from CD-TLR through 1 y	96.2%	—	90.7%	—	Log-rank $P = .0370$
IN.PACT SFA (reported in this study) (5)					
331 total participants from 13 European and 44 US study centers, enrollment period 2010–2013					
Total enrolled	143 (43%)	75 (23%)	77 (23%)	36 (11%)	—
Primary patency through 3 y by KM	71.8%	46.7%	65.4%	42.3%	Male DCB to female DCB: $P = .302$ Male PTA to female PTA: $P = .551$
Freedom from CD-TLR through 3 y by KM	86.4%	75.5%	81.1%	59.4%	Male DCB to female DCB: $P = .285$ Male PTA to female PTA: $P = .109$
Primary safety composite through 3 y	83.6%	70.0%	76.8%	51.5%	Male DCB to female DCB: $P = .257$ Male PTA to female PTA: $P = .081$

CD = clinically driven; DCB = drug-coated balloon; KM = Kaplan-Meier; LLL = late lumen loss; PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization.