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Low-dose Paclitaxel-coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease: 1-year Results of the ILLUMENATE European Randomized Clinical Trial

Running Title: *Schroeder et al; DCB vs. PTA for Femoropopliteal Disease*

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for the ILLUMENATE EU RCT Investigators

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Abstract

Background—Numerous studies have reported favorable outcomes using drug-coated balloons (DCBs) for treatment of symptomatic peripheral artery disease (PAD) of the superficial femoral and popliteal arteries. However, the treatment effect compared to an uncoated balloon has differed greatly amongst the randomized trials with better outcomes observed with higher-dose DCBs. This European trial was designed to assess the safety and effectiveness of a next-generation low dose (2 μg/mm^2 surface dose of paclitaxel) DCB.

Methods—This was a prospective, randomized, multi-center, single-blinded trial. Patients were randomized (3:1) to treatment with a low-dose DCB or an uncoated percutaneous transluminal angioplasty (PTA) balloon. The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months post-procedure. The primary effectiveness endpoint was primary patency at 12 months.

Results—Patients were randomized to treatment with a DCB (222 patients, 254 lesions) or uncoated PTA balloon (72 patients, 79 lesions) following successful pre-dilatation. Mean lesion length was 7.2 cm and 7.1 cm, and 19.2% and 19.0% of lesions represented total occlusions, respectively. The primary safety endpoint was met and superiority was demonstrated; freedom from a primary safety event was 94.1% (193/205) with DCB and 83.3% (50/60) with PTA, for a difference of 10.8% (95% CI: 0.9%—23.0%). The primary effectiveness endpoint was met and superiority of DCB over PTA was achieved [83.9% (188/224) vs. 60.6% (40/66), p<0.001]. Outcomes with DCB were also superior to PTA per Kaplan Meier estimate for primary patency (89.0% vs. 65.0% at 365 days, log rank p<0.001) and for rates of clinically-driven target lesion revascularization (5.9% vs 16.7%, p=0.014).

Conclusions—Superiority with a low dose DCB for femoropopliteal interventions was demonstrated over PTA for both the safety and effectiveness endpoints.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01858363.

Key Words: drug-eluting balloon; paclitaxel; peripheral artery disease; percutaneous treatment; randomized controlled trial;

Clinical Perspective

What is new?

- In symptomatic patients with superficial femoral and/or proximal popliteal artery disease, this low-dose drug-coated balloon is safer and more effective than uncoated percutaneous transluminal angioplasty balloon through 12 months of follow-up.

What are the clinical implications?

- A low-dose drug-coated balloon is a promising treatment option in symptomatic patients with superficial femoral and/or popliteal artery disease.

Peripheral artery disease (PAD) contributes to significant morbidity and mortality affecting approximately 27 million adults in Europe and North America.[1] The overall prevalence of PAD is estimated to be 3% - 10%, and increases to 15% - 20% in adults over 80 years of age.[2] The superficial femoral artery (SFA), the longest artery in the human body, is exposed to the highest levels of dynamic mechanical stress and is involved in the majority of patients with PAD. It is challenging to maintain patency following revascularization of the SFA. Primary patency rates of around 55% can be reached with optimal percutaneous transluminal angioplasty (PTA) at 1 year.[3, 4] Elective stenting has raised this towards 80%.[5] However, hesitance exists towards an elective use of stents given the burden of treating in-stent-restenosis and the desire to avoid an unnecessary permanent implant. Therefore, PTA with provisional stenting still represents the most widely adopted endovascular treatment in this patient population.

Stents coated with paclitaxel, an anti-proliferative agent, have proven safety and shown superior 12-month effectiveness as compared with bare-metal stents.[6, 7] Recent research suggests that paclitaxel drug-coated balloons (DCBs) are viable alternatives to drug-eluting stents, with the added advantage of avoidance of a permanent implant. Several studies demonstrate that DCBs are safe with durable clinical outcomes.[4, 8-11] Current commercially available DCBs all contain the same drug (paclitaxel), but have different doses or surface concentrations (2-3.5µg/mm^2), excipients, coating methods and drug formulations (crystalline, amorphous, or hybrid). Bench and pre-clinical tests confirm that drug tissue uptake, residency, drug loss and drug effect are different across DCB platforms.[12-14]

The first-in-human trial with this low-dose DCB was promising.[8] The primary patency rates were 89.5% and 80.3% at 12 and 24 months, respectively. The objective of the current study was to assess the safety and effectiveness this low-dose DCB compared with a standard

PTA balloon in symptomatic patients with superficial femoral and/or proximal popliteal artery disease.

Methods

Study Design

This was a multicenter, single-blinded, randomized controlled trial conducted at 18 centers in Germany and Austria to assess the safety and effectiveness of a low-dose DCB (Stellarex™, Spectranetics Corp., Colorado Springs, CO) versus a standard PTA balloon in symptomatic patients with superficial femoral and/or proximal popliteal artery disease. The study was approved by the ethics committee at each participating center and patients provided signed written informed consent before enrollment. The study was prospectively registered at URL: http://www.clinicaltrials.gov. Unique identifier: NCT01858363.

Patient Selection

Eligible patients reported moderate to severe claudication, or ischemic rest pain (Rutherford class 2 to 4) with angiographic evidence of >70% stenosis within the superficial femoral artery and/or popliteal artery, one or two *de novo* or restenotic lesions with cumulative length of 30 to 200 mm, and reference vessel diameter 4 to 6 mm. Important patient eligibility criteria are detailed in Supplemental Table 1.

Randomization, Blinding, and Data Quality

Following successful lesion crossing and pre-dilatation with ≤70% residual stenosis and no flow-limiting dissection, patients were randomized to treatment with DCB or PTA using blocked allocation with a 3:1 ratio stratified by site. Patients requiring provisional stent placement after pre-dilatation underwent post-dilatation with DCB and were not randomized, rather assigned to

the "stent cohort" and analyzed separately. Investigators and research staff at the study centers were not blinded to treatment assignment given visual differences in the study devices. Patients remained blinded to treatment assignment throughout the study.

Independent core laboratories analyzed all images including duplex ultrasound (DUS; VasCore, Massachusetts General Hospital, Boston, MA) and angiography (SynvaCor, Springfield, IL). Core laboratory readers remained blinded to treatment assignment. A blinded Clinical Events Committee who did not participate in the study adjudicated all adverse events. An independent Data Safety and Monitoring Board monitored the study for safety. Data were monitored for accuracy with 100% source document verification.

Study Device and Procedure

The DCB coating includes a low-dose (2 μg/mm^2) of paclitaxel with a polyethylene glycol excipient. The DCB is coated while unfolded and partially inflated, then deflated and folded into final configuration. This coating method allows for most of the drug to be protected by the balloon folds during delivery to the target lesion and provides a uniform circumferential delivery to the artery. The DCB is available in 4-, 5-, and 6-mm diameters and 40-, 80-, and 120-mm lengths.

Patients received dual antiplatelet therapy before the procedure per hospital standard of care. Post-procedure, the study protocol required patients to take acetylsalicylic acid for the duration of the study and recommended the additional use of clopidogrel for 30-days post-procedure, or 90 days post-procedure if a stent was placed. Balloon length was required to be ≥10 mm longer than the pre-dilatation balloon length and balloon inflation time ≥1 minute in each group. Patients with residual stenosis >30% and/or flow-limiting dissection after treatment with the study device underwent post-dilatation. In the DCB group, post-dilatation was

performed with DCB or PTA. In the PTA group, post-dilatation was performed with an uncoated balloon catheter only. If post-dilatation was unsuccessful, provisional stent placement was performed.

Patient Follow-up

Patients returned for clinical visits at 1, 6, and 12 months which included clinical assessment, functional status (excluding 1 month), adverse events, medication compliance, and DUS examination. Patient follow-up is ongoing for up to five years, with the primary efficacy and safety results at 12-months of follow up presented here.

Outcomes

The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days post procedure, and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 12 months. The primary effectiveness endpoint was primary patency (per lesion) through 12 months, defined as the absence of target lesion restenosis (DUS determined peak systolic velocity ratio (PSVR) ≤ 2.5) and freedom from CD-TLR. CD-TLRs were adjudicated by a blinded clinical events committee and defined as a revascularization of the target lesion with peak systolic velocity ratio ≥2.5 by DUS (or percent diameter stenosis >50% by angiography) and worsening of Rutherford classification; or abnormal ABI that was clearly referable to the target lesion. Worsening was defined as Rutherford increase of at least 1 class from the earliest post-procedural measurement, or ABI decrease >0.15 from the maximum early post-procedural level. The degree of stenosis was determined by independent, blinded core laboratories. Technical success (per lesion) was defined as final in-lesion residual diameter stenosis ≤50% determined by the angiographic core laboratory without a device malfunction. Clinical success (per patient) required technical

success without a procedural major adverse event (MAE). Lesion success (per lesion) required final in-lesion residual diameter stenosis of ≤50% determined by the angiographic core laboratory. Procedural success (per patient) was defined as lesion success without a procedural MAE. Additional outcomes included MAE defined as cardiovascular death, target limb amputation, or CD-TLR, as adjudicated by the blinded clinical events committee. Other secondary endpoints included change in ABI, walking impairment questionnaire score, Rutherford classification and walking distance, compared with baseline. Ankle-brachial index was defined as the ratio of the highest ankle systolic pressure to the highest brachial systolic pressure. The change in the walking distance was assessed by a treadmill test or 6-minute walk test and calculated per subject, with the baseline result compared with the result at 12 months, using the same assessment method.

Statistical Analysis

The primary safety hypothesis was that freedom from a primary safety endpoint at 1 year with DCB would be non-inferior to PTA. A non-inferiority margin of 5% absolute difference was deemed a clinically nonsignificant difference. A priori, if non-inferiority was met and the lower 95% confidence limit > 0%, superiority would be claimed. The primary effectiveness hypothesis was that primary patency at 1 year would be superior with DCB versus PTA. Given 3:1 randomization, 90% power, one-sided alpha=0.025, absolute difference of 5% non-inferiority margin for safety, and estimated safety and effectiveness endpoint rates of 80% with DCB and 60% with PTA, 176 patients were required for the primary safety endpoint and 280 for the primary effectiveness endpoint.

Continuous data are reported as mean and standard deviation; categorical data are reported as frequency and percentage. Comparisons of baseline characteristics were performed

with independent samples t-test, Fisher's exact test, or chi square as appropriate. Non-inferiority was assessed with a Farrington-Manning exact test and superiority was evaluated with a chi-square test. The Kaplan-Meier method and log-rank tests were used to evaluate time-to-event outcomes including primary patency and freedom from clinically-driven TLR through 12-month follow-up. Time-to-event effectiveness outcomes are displayed through 395 days (12-month follow-up plus 30-day visit window). All analyses were pre-specified in a statistical analysis plan. Data were analyzed with SAS version 9.3 or higher (SAS Institute, Cary, NC).

Role of the Funding Source

The clinical trial was designed by the principal investigator (H.S.), Philippe Marco, MD and the study sponsor. Study data were collected, monitored, and analyzed by the study sponsor (currently The Spectranetics Corp). H.S. and M.B. prepared the first draft of the manuscript, which was then critically reviewed and edited by the other authors. The study sponsor had the right to review, but not to approve, the final manuscript. The authors had full access to all data and take full responsibility for the accuracy, completeness, and integrity of the reported analyses and data interpretation.

Results

Patient Enrollment and Follow-up

Between December 2012 and April 2015, 294 patients were randomized to DCB (222 patients, 254 lesions) or PTA (72 patients, 79 lesions) at 18 centers in Germany and Austria (listed in the appendix). Data are reported separately for 33 patients who underwent provisional stent placement after failed pre-dilatation. One patient who was not randomized was treated with DCB and excluded from all analyses (**Fig. 1**).

Patient and Procedural Data

No statistically significant differences were noted in baseline patient characteristics between groups (**Table 1**). Lesion characteristics were comparable across the randomized cohorts, including mean lesion length (7.2 vs. 7.1 cm), diameter stenosis (79% vs. 81%), and total occlusions (both 19%). The only significant difference between groups was noted in reference vessel diameter (5.0±0.8 vs. 4.8±0.7, p=0.01) (**Table 2**). Procedural outcomes were not statistically different between DCB and PTA, including flow-limiting dissection (0.4% vs. 0%), provisional stent placement (15% vs. 11%), and diameter stenosis post-procedure (24% vs. 23%) (**Table 3**). Comparing DCB with PTA acute success rates were as follows: technical success (99.2% vs. 100%), clinical success (99.1% vs. 100%), lesion success (99.6% vs. 100%), and procedural success (99.5% vs. 100%).

Safety Outcomes

Freedom from a primary safety event was 94.1% (193/205) with DCB and 83.3% (50/60) with PTA, for a difference of 10.8% (95% CI: 0.9%—23.0%). The lower limit of the 95% confidence interval difference was greater than -5%; thus, non-inferiority was established. Additionally, superiority of DCB was also established since the lower confidence interval limit exceeded 0. The Kaplan-Meier freedom from clinically-driven TLR estimates were 94.8% for DCB and 85.3% for PTA at 365 days (log-rank p-value=0.010) (**Fig. 2**). A total of 20 major adverse events (MAEs) were reported in 14 (6.8%) DCB patients and 12 MAEs were reported in 11 (18.0%) PTA patients (p = 0.008). Comparing DCB with PTA, CD-TLR was 5.9% vs. 16.7% (p=0.014); cardiovascular death was 1.0% vs. 1.6% (p=0.542); and target limb amputation was 0.5% vs. 0% (p > 0.99). The target limb amputation was a minor amputation (toe) 354 days post-procedure. No major amputations were reported in either cohort.

Effectiveness Outcomes

The primary effectiveness outcome, primary patency proportional rates, per assessable lesion, through 12-month follow-up (day 395), was 83.9% (188/224) for DCB and 60.6% (40/66) for PTA, for a difference of 23.3% (95% CI: 10.6%—36.1%, p<0.001). Therefore, the primary effectiveness endpoint was also met and superiority over PTA was demonstrated.

The Kaplan-Meier primary patency rate was 89.0% for DCB and 65.0% for PTA at day 365 (log-rank p-value<0.001) (**Fig. 3**). Additionally, significantly favorable outcomes were observed with the DCB when evaluating primary patency by sex (**Fig. 4**) and diabetes status (**Fig. 5**). The primary patency rate in the DCB cohort was 89.2% in patients with diabetes and 88.8% in patients without diabetes (p=0.4724). Likewise, there was no statistical difference in the primary patency rates observed in the DCB cohort when stratified by sex (90.4% in men and 85.3% in women, p= 0.3064).

This study allowed post-dilatation with a DCB, in the DCB arm. This occurred in 24 lesions (17%). When these lesions are excluded from the analysis, the primary patency rate at day 365 is 88.4%. To assess the impact of the statistically significant difference between groups in baseline RVD (p=0.012) on the primary endpoints, logistic regression models were used to provide both adjusted and unadjusted comparisons. For both primary efficacy and safety, baseline RVD is significantly associated with the outcomes. However, there is no statistical evidence of interaction effects and the impact on the treatment group comparisons is minimal with unadjusted odds ratios for DCB vs. PTA vs adjusted odds ratios of 3.394 vs 3.105 for patency and 3.217 vs 2.827 for the safety. Therefore this difference does not affect the overall study conclusions.

At 12 months, a similar percentage of patients in both the DCB and PTA cohorts had improvements in ABI (83.9% and 76.8%), Rutherford classification (89.2% and 86.2%) and walking distance (77.1% and 72.1%). ABI improvement was similar with DCB (0.71 ± 0.20 to 0.93 ± 0.14) and PTA (0.66 ± 0.27 to 0.90 ± 0.16) through 12 months. These similar outcomes were achieved with a significantly, almost 3-fold lower rate of CD-TLR in the DCB cohort [5.9% (12/205) vs. 16.7% (10/60), p = 0.014].

Outcomes with Provisional Stent Placement

A total of 33 patients were enrolled in a nonrandomized cohort following provisional stent placement for suboptimal pre-dilatation. Following sub-optimal pre-dilatation, these patients were not randomized; all were stented and then treated with a DCB. The majority of these patients (75.8%) were men with a mean age of 66±8 years. Comorbidities included hypertension (78.8%), hyperlipidemia (69.7%), diabetes (36.4%) and previous coronary revascularization (30.3%). The mean lesion length was 8.8 cm, 54.5% were CTOs, and 15.6% were severely calcified. At 12 months, primary patency was 78.8% (26/33) and CD-TLR rate was 12.1% (4/33).

Within the randomized DCB cohort, a bail-out stent was placed in 38 patients (39 of the 42 target lesions in this subgroup). The mean lesion length was 8.4cm, 40.5% were CTOs and 11.9% were severely calcified. The 12-month primary patency rate was 75.0% (30/40) in this cohort. A total of 181 patients with 209 lesions were treated with a DCB and not stented. The mean lesion length was 6.9 cm, 14.9% were CTOs and 12.9% were severely calcified. The primary patency rate in this cohort was 85.9% (158/184). Primary patency was not statistically different patients treated with vs. without bail-out stent placement in the DCB group (p=0.09).

Discussion

This was the first randomized controlled trial to assess the effectiveness and safety of the Stellarex DCB vs. standard uncoated PTA to treat SFA and/or popliteal disease. The trial demonstrated superior safety and effectiveness outcomes in the DCB arm and validated the results of the previously reported first-in-human study.[8] The core-lab adjudicated primary patency rate at day 365 was 89.0% in the DCB arm of this trial, a comparable rate to that observed in the first-in-human study (89.5%), validating those early promising outcomes. Uniquely, this study allowed post-dilatation with a DCB, in the DCB arm. When these lesions are excluded from the patency analysis, there is a negligible change in the patency rate a day 365 (88.4%).

There are two other published randomized trials comparing DCB and PTA in similar patient populations and characterized by the same rigorous trial design and conduct related to two DCBs of different drug doses, 2.0 µg/mm^2 and 3.5µg/mm.[3, 4] Outcomes in the current study are comparable with the IN.PACT SFA Trial,[4, 10] which assessed the IN.PACT Admiral DCB vs. PTA with a very similar trial design, endpoint definitions and rigorous conduct. The IN.PACT SFA Trial randomized 331 patients with a mean lesion length of ~ 9cm and demonstrated significantly higher patency rates for the DCB arm at 360 days, per Kaplan Meier estimate (87.5% vs. 66.8%). Two-year data for this trial have been reported and no late catch-up was observed; 2-year patency rates were 78.9% vs 50.1% in the PTA arm (log rank p <0.001), demonstrating a sustained clinical benefit following acute exposure to an effective DCB. The most important differentiator between the IN.PACT Admiral DCB and the Stellarex DCB is the amount of paclitaxel on the balloon surface. The IN.PACT Admiral DCB has a drug dose surface concentration of 3.5µg/mm^2 as compared with 2µg/mm^2 on the Stellarex DCB. Drug

pharmacokinetics is a key variable impacting DCB performance. Optimization of drug tissue uptake and retention while minimizing drug loss during transit and inflation remain the key goals of modern DCB technologies.[12, 15] The ILLUMENATE EU RCT is the first trial to demonstrate that angioplasty with a low-dose DCB is able to achieve comparable clinical outcomes to that of a DCB with 75% more drug. The clinical implications of the higher drug dose coating formulation are unclear; however, low-dose DCBs carry the potential to reduce distal drug embolization[16] which may translate into a safety advantage in specific patient populations and anatomical settings.

LEVANT 2 assessed the safety and effectiveness of the Lutonix DCB, which also has a 2μg/mm^2 surface concentration of paclitaxel.[3] This trial also had a blinded duplex ultrasound core lab assessing patency and the same peak systolic velocity ratio threshold to determine patency in a binary fashion. The trial randomized 476 patients with a mean lesion length of 6.3cm in both groups. At 12 months, the patency rate was significantly higher in the DCB arm (73.5% vs 56.8%; p<0.001), though considerably lower than the rate observed in the present trial and in the IN.PACT SFA trial. There was no statistical difference between groups for rates of target lesion revascularization (12.3% vs. 16.8%, p=0.21). To date, 2-year outcomes have not been published, but have been reported.[17] The primary patency rate was 58.6% vs. 53.0% (log rank p=0.05) and freedom from CD-TLR was 82% vs. 79% (p=NS) at 2 years, questioning the durability of outcomes with this low-dose DCB.

The effectiveness of a DCB may be impacted by several components including the anti-restenotic drug, excipient, drug morphology, balloon material, manufacturing process, as well as the drug pharmacokinetic properties and bioavailability.[15] More studies are needed to better understand the contribution of each of these factors and their role in DCB effectiveness.

Post-hoc analyses show the DCB maintained a significant treatment effect vs. PTA in both critical subsets of women and patients with diabetes. These findings are important because diabetes has been identified as an independent predictor of decreased long-term primary patency after PTA/stenting,[18] and there was no treatment effect observed for the Lutonix DCB in females in the LEVANT 2 Trial.[19]

The PTA data indicate the control arm treatment was optimal with high acute success rates and a relatively high patency rate. At 12 months, the patency rate was 65.0%, which is consistent with previous control arm data in prior randomized controlled DCB trials (IN.Pact SFA PTA arm patency rate = 66.8%), but nearly twice that for PTA used in previously published bare metal stent trials (33%).[20] Despite these optimal results, superiority was demonstrated with the DCB.

Limitations

There were several limitations of this study that deserve further discussion. While the CEC, DSMB, and core lab personnel were blinded to treatment, physicians were not blinded due to the visible coating on the DCB catheter. These data cannot be generalized to other DCBs as head-to-head comparative trials have not been completed. Finally, patients were selected using strict inclusion and exclusion criteria; therefore, generalizability of these data to real-world cases may be limited.

Conclusions

This randomized trial of a low-dose DCB demonstrated superior safety and effectiveness outcomes over standard PTA in the treatment of symptomatic SFA and/or popliteal PAD.

Appendix

List of enrolling centers and principal investigators in the ILLUMENATE EU RCT Trial

Site	Location	Principal Investigator
Jüdisches Krankenhaus	Berlin, Germany	Dr. Henrik Schroeder
St Joseph Krankenhaus	Berlin, Germany	Dr. Beata Lux
Evangelisches Krankenhaus Hubertus	Berlin, Germany	Dr. Dirk-Roelfs Meyer
LKH Univ.- Klinikum Graz	Graz, Austria	Prof. Marianne Brodmann
Vivantes Humboldt-Klinikum	Berlin, Germany	Dr. Karsten Krueger
Vivantes Klinikum Spandau	Berlin, Germany	Dr. Karsten Krueger
SRH Sentralklinikum	Berlin, Germany	Dr. Volker Sesselmann
Ammerland-Klinik GMbH	Westerstede, Germany	Prof. Martin Zwaan
Vivantes-Klinikum Neukölln	Berlin, Germany	Prof. Thomas Albrecht
Klinik Altona-Asklepios	Hamburg, Germany	Prof. Roman Fischbach
Klinikum Karlsruhe	Karlsruhe, Germany	Prof. Peter Reimer
Krankenhaus Nordwest GmbH	Frankfurt, Germany	Prof. Markus Duex
Klinikum Robert Koch Gehrden	Gehrden, Germany	Dr. Goetz Voshage
Sint. Franziskus-Hospital GmbH	Muenster, Germany	Prof. Giovanni Torsello
Romed Klinikum – Rosenheim	Rosenheim, Germany	Prof. Gunnar Tepe
Evangelisches Krankenhaus Mulheim	Mulheim, Germany	Prof. Claus Nolte-Ernsting
Universitatsklinik – Vienna	Vienna, Austria	Prof. Christian Loewe
Hanusch Krankenhaus Wr.GKK Heinrich Collin-Vienna	Vienna, Austria	Dr. Martin Werner

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Dr. Schröder and Dr. Martin Werner have received research grants and speaking and consulting honoraria from Spectranetics. Prof. Marianne Brodmann has received speaking honoraria from BARD, Medtronic, BAYER Health Care, Daiichi, and Böhringer Ingelheim. She has also participated on Scientific Advisory Boards for Medtronic, Spectranetics and Intact Vascular. Dr.

Jaff has served as a non-compensated advisor to Abbott Vascular, Boston Scientific, Cordis and Medtronic Vascular and has served as a board member of VIVA Physicians, a 501 c 3 a not for profit education and research organization. All other authors have reported that they have no relationships relevant to the contents of this paper.

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Table 1. Baseline Patient Characteristics

Variable	DCB (n=222)	PTA (n=72)	P-value
Demographics			
Age, y	67 ± 9	69 ± 9	0.08
Men	160 (72)	49 (68)	0.51
Body mass index, kg/m^2	27 ± 5	28 ± 5	0.38
Clinical presentation			
Rutherford class			0.53
2	34 (15)	15 (21)	
3	183 (83)	55 (77)	
4	4 (2)	1 (1)	
Ankle-brachial index	0.72 ± 0.21	0.69 ± 0.26	0.25
Non-compressible	7 (3)	1 (1)	0.69
Medical history			
Smoking	198 (89)	60 (83)	0.19
Hypertension	173 (78)	60 (83)	0.33
Hyperlipidemia	137 (62)	49 (68)	0.33
Diabetes	83 (37)	26 (36)	0.85
Obesity	56 (25)	19 (26)	0.84
Cerebrovascular disease	38 (17)	15 (21)	0.48
Chronic obstructive pulmonary disease	36 (16)	6 (8)	0.10
Myocardial infarction	29 (13)	12 (17)	0.44
Renal Insufficiency	20 (9)	6 (8)	0.86
Previous revascularization			
Any lower limb	101 (45)	33 (46)	0.96
Treated limb	49 (22)	19 (26)	0.47
Coronary	46 (21)	16 (22)	0.79

DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.
Data reported as mean ± standard deviation or n (%).

Table 2. Baseline Lesion Characteristics

Variable	**DCB** (n=254)	**PTA** (n=79)	**P-value**
Lesion type			0.53
de novo	234 (92)	71 (90)	
Restenotic	20 (8)	8 (10)	
Lesion location			0.55
Proximal SFA	38 (15)	11 (14)	
Mid SFA	97 (39)	30 (38)	
Distal SFA	89 (35)	28 (35)	
Proximal popliteal	21 (8)	5 (6)	
Mid popliteal	6 (2)	5 (6)	
Lesion length, cm	7.2± 5.2	7.1 ± 5.3	0.878
Reference vessel diameter, mm	5.0 ± 0.8	4.8 ± 0.7	0.01
Diameter stenosis, %	79 ± 16	81 ± 16	0.30
Total occlusion	48 (19)	15 (19)	0.97
Calcification			0.78
None/mild	140 (56)	47 (59)	
Moderate	79 (31)	24 (30)	
Severe	32 (13)	8 (10)	
Number of patent run-off vessels			0.17
0	18 (10)	3 (5)	
1	34 (18)	9 (15)	
2	56 (30)	28 (45)	
3	76 (41)	22 (35)	

DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty; SFA: superficial femoral artery. Data reported as mean ± standard deviation or n (%).

Table 3. Procedural Data

Variable	**DCB** (222 patients, 254 lesions)	**PTA** (72 patients, 79 lesions)	**P-value**
Procedure time*, min	66 ± 35	63 ± 33	0.56
Fluoroscopy time*, min	9.8 ± 8.0	9.2 ± 6.7	0.60
Pre-dilatation performed	254 (100)	78 (99)	0.24
Total inflation time (min)	2.4 ± 1.2	2.2 ± 1.1	0.07
Flow-limiting dissection	1 (0.4)	0	1.0
Post-dilatation (w/ PTA)	85 (33)	27 (34)	0.91
Post-dilatation (w/ DCB)	42 (17)	N/A	N/A
Bail-out stent placement	39 (15)	9 (11)	0.38
Diameter stenosis post-procedure	24 ± 11	23 ± 10	0.72

*Per subject
DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.
Data reported as mean ± standard deviation or n (%).

Figure Legends

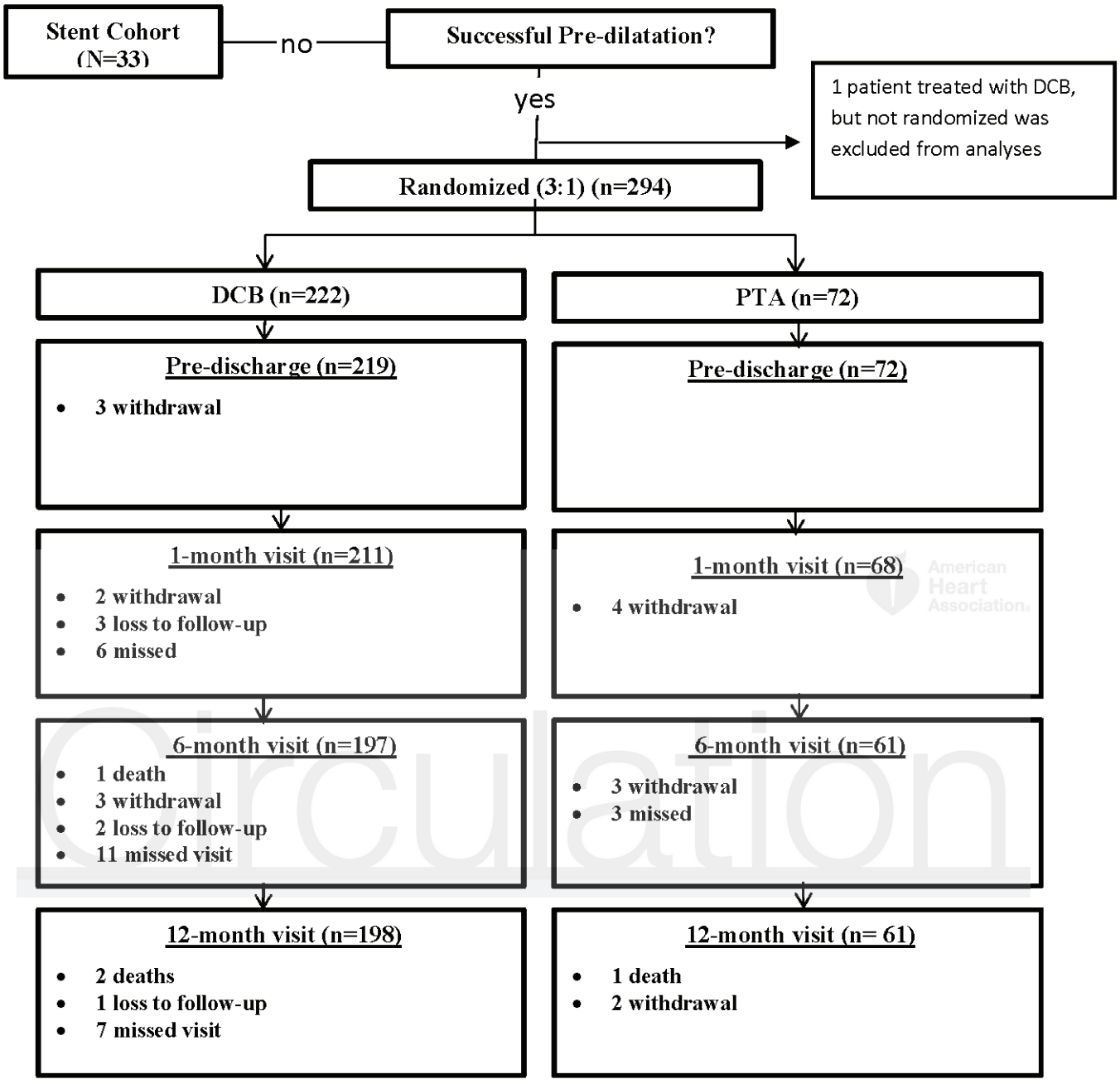
Figure 1. Patient flow diagram. Twelve-month follow-up visit completed in 89% treated with DCB and 85% treated with PTA. DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.

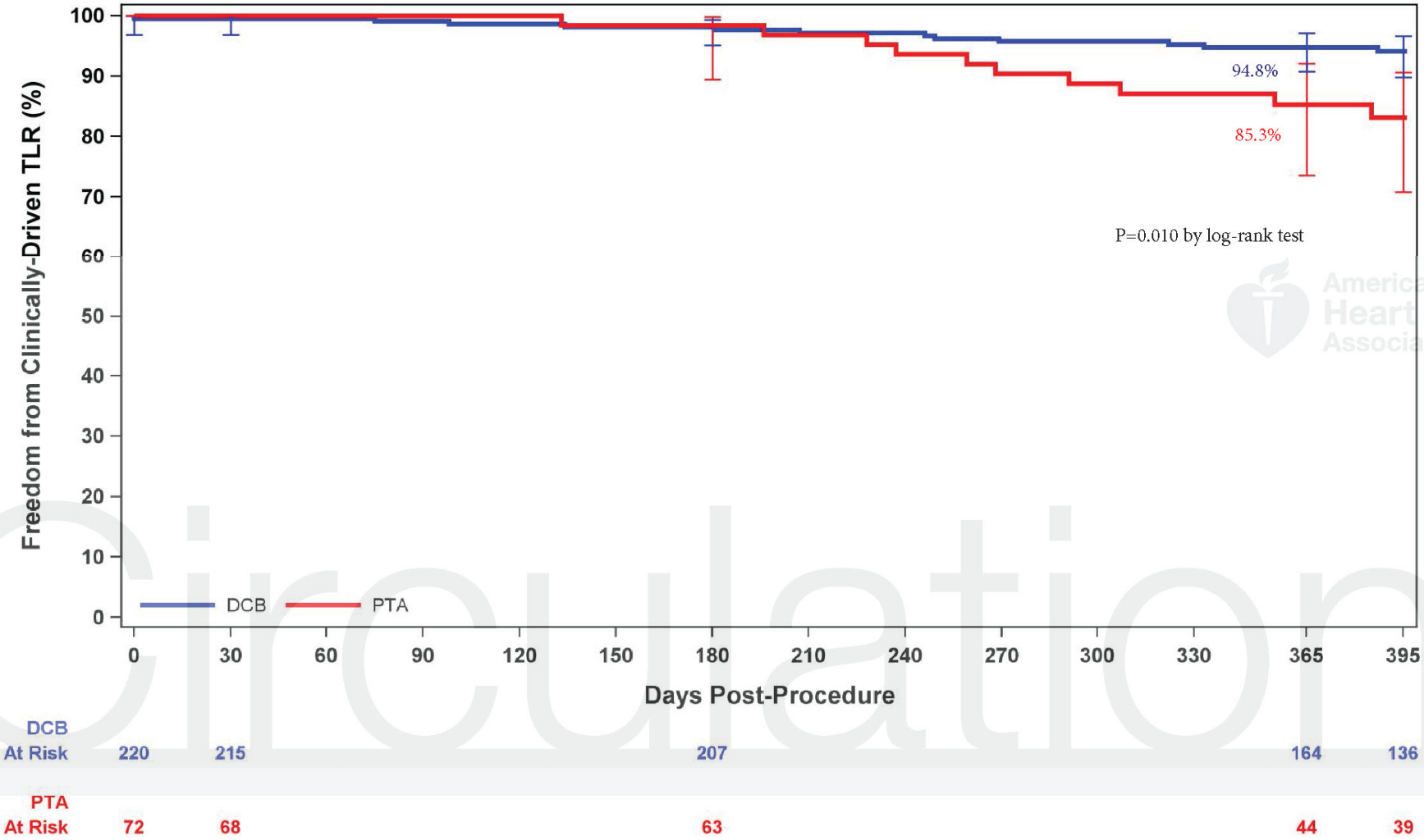
Figure 2. Freedom from clinically-driven TLR by Kaplan-Meier was significantly higher in the DCB group vs. the PTA group (P=0.010 by log-rank test; 94.8% vs. 85.3% at day 365). Bars represent 95% confidence intervals. TLR: target lesion revascularization; DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.

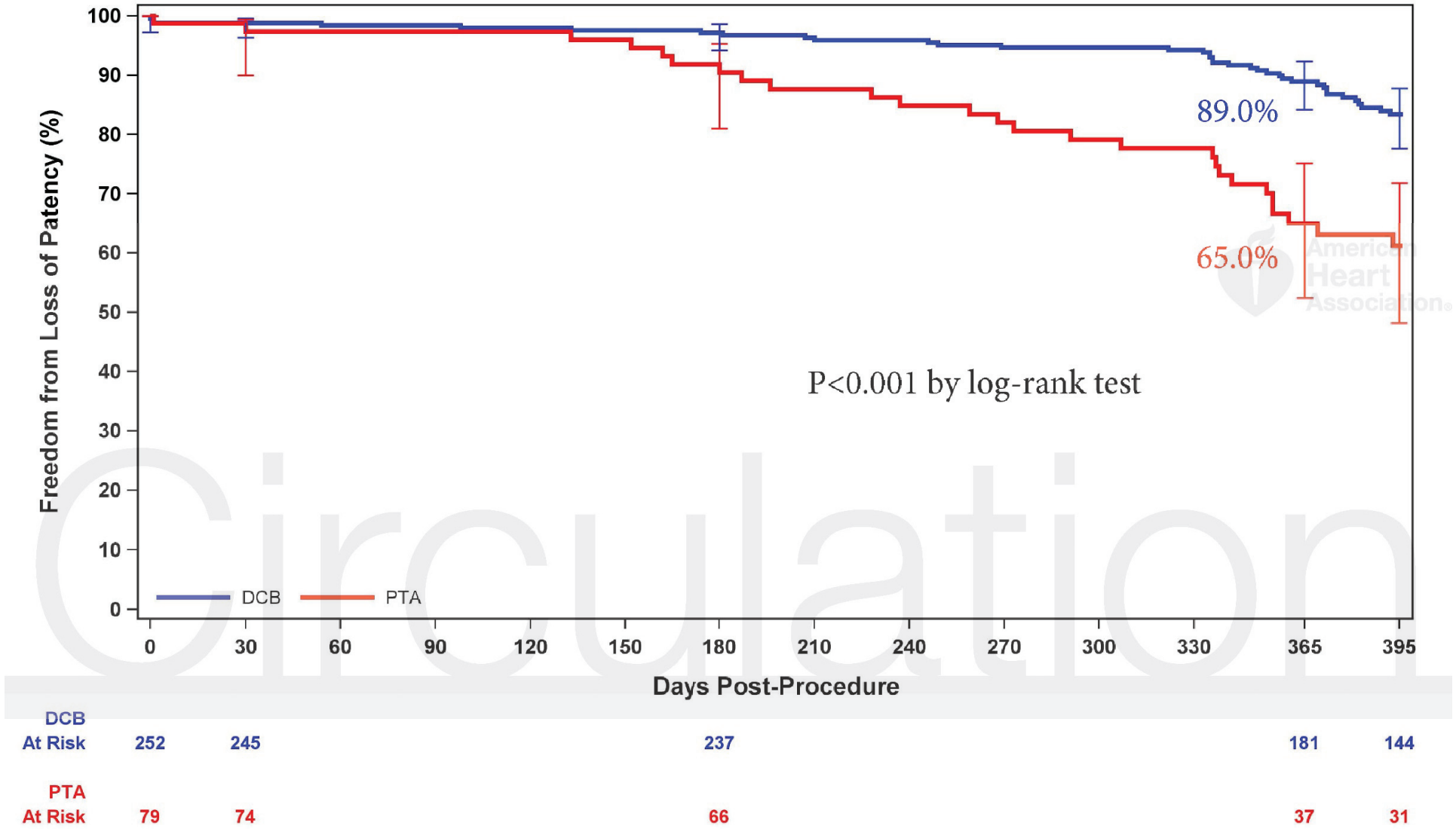
Figure 3. Primary patency by Kaplan-Meier was significantly higher in the DCB group vs. the PTA group (P<0.001 by log-rank test; 89.0% vs. 65.0% at day 365). Bars represent 95% confidence intervals. DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.

Figure 4. Primary patency by Kaplan Meier was similar between men and women (P=0.31 by log-rank test; 90.4% vs. 85.3% at day 365) in the DCB cohort. DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.

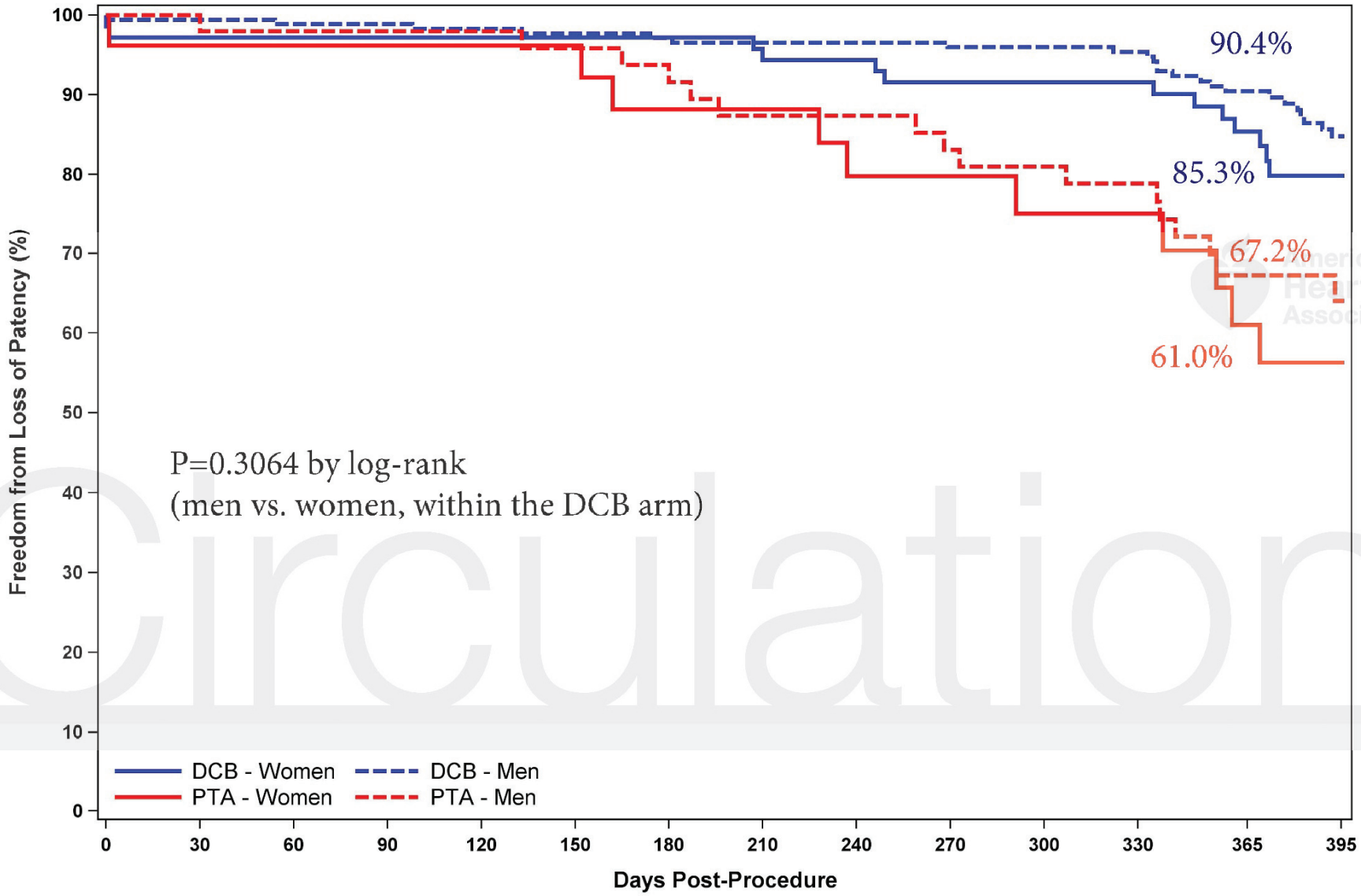
Figure 5. Primary patency by Kaplan Meier was similar between patients with and without diabetes (P=0.47 by log-rank test; 89.2% vs. 88.8% at day 365) in the DCB cohort. DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty.

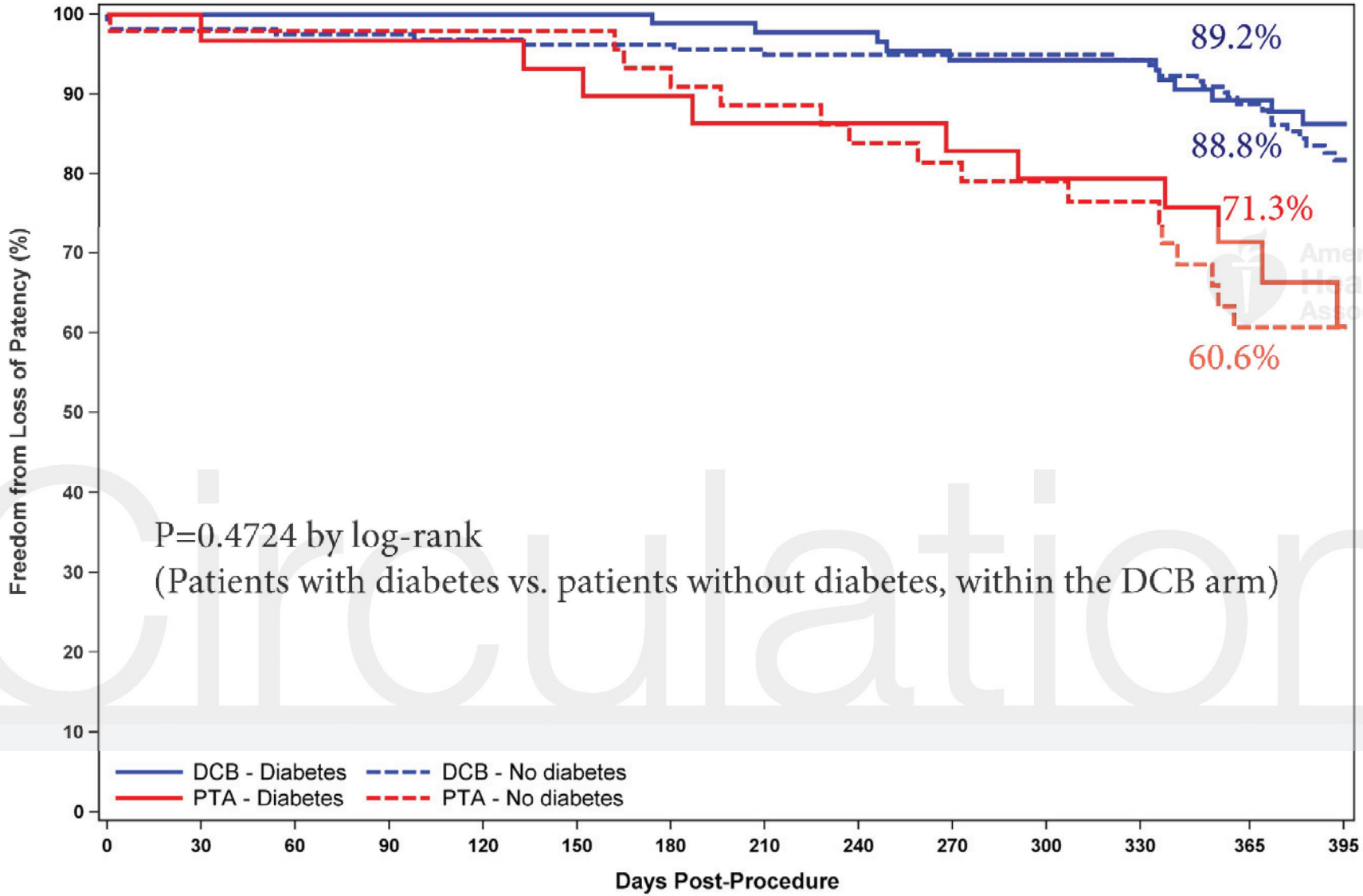

Stent Cohort (N=33)
no
Successful Pre-dilatation?
yes
1 patient treated with DCB, but not randomized was excluded from analyses
Randomized (3:1) (n=294)
DCB (n=222)
PTA (n=72)
Pre-discharge (n=219)
3 withdrawal
Pre-discharge (n=72)
1-month visit (n=211)
2 withdrawal
3 loss to follow-up
6 missed
1-month visit (n=68)
4 withdrawal
6-month visit (n=197)
1 death
3 withdrawal
2 loss to follow-up
11 missed visit
6-month visit (n=61)
3 withdrawal
3 missed
12-month visit (n=198)
2 deaths
1 loss to follow-up
7 missed visit
12-month visit (n= 61)
1 death
2 withdrawal





DCB At Risk	252	245					237					181	144
PTA At Risk	79	74					66					37	31





Supplemental Material: ILLUMENATE EU RCT Study

Supplemental Table 1. Key inclusion and exclusion criteria

Key Inclusion Criteria	Key Exclusion Criteria
Clinical criteria	
▪ Symptomatic leg ischemia requiring treatment of superficial femoral artery and/or popliteal artery ▪ Age ≥ 18 years ▪ Life expectancy > 1 year ▪ Rutherford-Becker classification 2-4	▪ Female who is pregnant, lactating, or intends to become pregnant; male intending to father children during study ▪ Aneurysm in target vessel, iliac artery, or popliteal artery ▪ Contraindication to dual anti-platelet therapy ▪ Hemorrhagic stroke within 3 months ▪ Planned vascular interventions within 14 days before or 30 days after treatment ▪ Previous vascular surgery of target lesion ▪ Unstable angina pectoris, myocardial infarction, liver failure, renal failure, or chronic kidney disease within 30 days of procedure
Angiographic criteria	
▪ De novo or restenotic lesion >70% stenosis within superficial femoral artery and/or popliteal artery ▪ Lesion length 3-20 cm ▪ Lesion treatable by no more than two devices ▪ Successful wire crossing of lesion ▪ Target reference vessel diameter 4-6 mm ▪ Patent (<50% stenosis) inflow artery ▪ At least one patent (<50% stenosis) tibio-peroneal run-off artery	▪ Severe calcification precluding adequate percutaneous transluminal angioplasty ▪ Acute or sub-acute thrombus in target vessel ▪ Prior stent placement in target vessel ▪ Adjunctive therapies (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy) in the target lesion or vessel