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Determinants of Drug-Coated Balloon Failure in Patients Undergoing Femoropopliteal Arterial Intervention

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ABSTRACT

BACKGROUND Drug-coated balloons (DCB) are frequently used to treat femoropopliteal artery disease. However, patency loss occurs in ≥10% of patients within 12 months posttreatment with poor understanding of the underlying mechanisms.

OBJECTIVES The authors sought to investigate the determinants of DCB failure in femoropopliteal disease.

METHODS Data from randomized clinical trials (IN.PACT SFA, MDT-2113 SFA Japan) and 2 prespecified imaging cohorts of the IN.PACT Global Clinical Study were included. Influential procedural characteristics were evaluated by an independent angiographic core laboratory. The primary endpoint was DCB failure (patency loss during follow-up). Additional endpoints were binary restenosis and clinically driven target lesion revascularization. Multivariable analyses evaluated the clinical, anatomical, and procedural predictors of DCB failure.

RESULTS Included were 557 participants with single lesions and 12-month core laboratory–adjudicated duplex ultrasonography. Key clinical characteristics were as follows: mean age 68.8 years, 67.5% male, 87.6% with hypertension, 76.9% with hyperlipidemia, 40.5% with diabetes mellitus, 90.5% in Rutherford Classification Category (RCC) 2 to 3, and 9.5% in RCC 4 to 5. Average length and reference vessel diameter (RVD) were 16.37 cm and 4.66 mm, respectively; 49.7% of lesions were totally occluded. In multivariable analysis, only residual stenosis >30% was associated with patency loss, whereas residual stenosis >30% and smaller preprocedure RVD were associated with increased binary restenosis risk. RCC >3 and residual stenosis >30% were associated with increased 12-month clinically driven target lesion revascularization risk.

CONCLUSIONS Patency loss after DCB treatment was influenced by procedural and clinical factors. Residual stenosis >30%, smaller preprocedure RVD, and higher RCC may be considered predictors of increased risk of DCB failure and its components in femoropopliteal artery disease. (Randomized Trial of IN.PACT Admiral® Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease [INPACT SFA I]; NCT01175850; IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA] [INPACT SFA II]; NCT01566461; MDT-2113 Drug-Eluting Balloon vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery [MDT-2113 SFA]; NCT01947478; IN.PACT Global Clinical Study; NCT01609296) (J Am Coll Cardiol 2022;80:1241–1250) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

CD-TLR = clinically driven target lesion revascularization

DCB = drug-coated balloon

PAD = peripheral artery disease

PTA = percutaneous transluminal angioplasty

RCC = Rutherford Classification Category

RVD = reference vessel diameter

TBI = toe-brachial index

Contemporary endovascular treatment options for peripheral artery disease (PAD) involving the femoropopliteal segment include several strategies ranging from atherectomy to the use of scaffolds to optimize blood flow through the treated segment. The introduction of drug-coated balloon (DCB) technology in the treatment of femoropopliteal artery disease has changed the landscape of endovascular approaches in the treatment of PAD.[1-4] Currently, international guidelines recommend the use of DCB only in Trans-Atlantic Inter-Society Consensus Document A and B lesions.[5] However, the use of DCBs is increasingly being expanded to more complex lesions.[6,7] DCB use has been shown to improve primary patency and decrease target lesion revascularization compared with percutaneous transluminal angioplasty (PTA) out to 5 years.[1,8] Despite increasing data in the treatment of femoropopliteal arteries with DCB over recent years,[7] scarce data exist about the mechanism of DCB failure in this particular vascular bed.[9] Therefore, in this independent participant-level pooled analysis, we aimed to investigate the clinical characteristics, anatomical factors, and procedural variables associated with DCB failure in the femoropopliteal artery segment.

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METHODS

The included studies were conducted in accordance with the Declaration of Helsinki, good clinical practice, and all local regulatory requirements. The study protocols were approved by the Institutional Review Boards or ethics committees of all participating sites. All participants provided informed consent before enrollment.

STUDY DESIGN. This retrospective analysis pooled participant-level data of patients treated with the IN.PACT Admiral paclitaxel DCB (Medtronic) for symptomatic femoropopliteal PAD from randomized clinical trials (IN.PACT SFA [Randomized Trial of IN.PACT Admiral® Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease], NCT01175850 [Phase I]; INPACT SFA II [IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery (SFA) and Proximal Popliteal Artery (PPA)], NCT01566461 [Phase II][1,8]; and MDT-2113 SFA Japan [MDT-2113 Drug-Eluting Balloon vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery], NCT01947478),[10,11] and the prospective single-arm multicenter IN.PACT Global Clinical Study (NCT01609296).[12] In total, the pooled analysis represents data from 83 sites and 17 countries (**Figure 1**). The randomized clinical trials were the IN.PACT SFA and the MDT-2113 SFA Japan (IN.PACT SFA Japan) prospective, multicenter, randomized, single-blind trials comparing outcomes with IN.PACT Admiral DCB to PTA, of which the details have been previously reported.[1,8,10,11] IN.PACT Global was a prospective, multicenter, single-arm study on the use of IN.PACT Admiral DCB to treat femoropopliteal PAD in "real-world" lesions.[12] In order to provide a data set of angiographic core laboratory outcomes, only participants with single lesions from the long lesion[13] and chronic total occlusion[14] prespecified imaging cohorts of the IN.PACT Global study were included in the current analysis. The designs, inclusion and exclusion criteria, and endpoints of these studies are provided in Supplemental Table 1. All participants were required to be on dual antiplatelet therapy at the time of the index procedure and to continue for 1 month if receiving a DCB only or 3 months for participants with provisional stent implantation.

ENDPOINTS. The primary endpoint of the current analysis was DCB failure, defined as loss of primary patency during a 12-month follow-up. Primary patency was defined as freedom from clinically driven target lesion revascularization (CD-TLR) (due to symptoms and/or a decrease in ankle-brachial index [ABI] by ≥20% or >0.15 compared with post-procedure baseline ABI, or toe-brachial index [TBI]) and freedom from binary restenosis (as determined by a duplex ultrasonography-derived peak systolic velocity ratio of ≤2.4). Additional endpoints were binary restenosis determined by either peak systolic

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center. *Current address: University of California San Francisco, San Francisco, California, USA.

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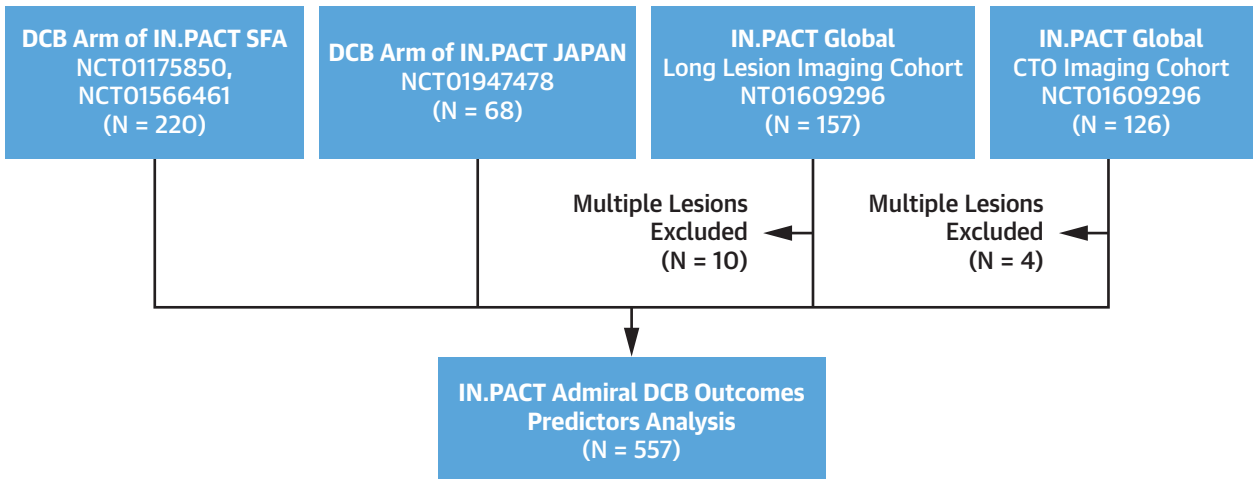
FIGURE 1 Study Flow Chart



Participants were pooled from the DCB arms of the IN.PACT SFA and IN.PACT SFA Japan randomized controlled trials and the prespecified angiographic cohorts of the prospective single-arm multicenter IN.PACT Global Clinical Study. The total pooled analysis includes data from 557 participants at 83 sites in 17 countries. CTO = chronic total occlusion; DCB = drug-coated balloon; IN.PACT SFA I = 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 II = 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 Japan = MDT-2113 Drug-Eluting Balloon vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery; SFA = superficial femoral artery.

velocity ratio >2.4 as assessed by an independent duplex ultrasonography core laboratory or >50% stenosis as assessed by an independent angiographic core laboratory and CD-TLR. Residual stenosis was measured based on the final assessment angiogram at the end of the index procedure, after any post-dilatation and provisional stenting.

ANGIOGRAPHIC ANALYSIS. Independent angiographic imaging assessment and adjudication were performed by an angiographic core laboratory (SynvaCor). Additionally, 3 endovascular specialists independently reviewed all anonymized angiograms to determine angiographic findings for the following factors: lesion calcification,[15] dissection, residual stenosis >30%, and need for stenting. All reviewers were blinded to all participant information. Independent duplex ultrasonography adjudication was performed by a core laboratory (VasCore, Massachusetts General Hospital, Boston, Massachusetts).

STATISTICAL ANALYSIS. All analyses were performed independently by the Baim Institute for Clinical Research (Boston, Massachusetts) using SAS software version 9.4 (SAS Inc). Analyses were based on the intent-to-treat principle as specified in the study protocols with evaluable data. Continuous variables were reported as mean ± SD; dichotomous and categorical variables were reported as frequencies and percentages. Clinical and angiographic outcomes were reported on a per-participant basis. The primary patency endpoint was based on participants with evaluable data for CD-TLR and binary restenosis at 12-month follow-up. The Kaplan-Meier method was used to evaluate the time-to-event data for freedom from CD-TLR, freedom from binary restenosis, and primary patency through the 12-month follow-up period. Univariate and multivariable Cox proportional hazards regression models were used to determine the predictors of CD-TLR, binary restenosis, and loss of primary patency. For the multivariable Cox proportional hazards regression analyses, CD-TLR was censored at 360 days, whereas primary patency and binary restenosis were censored at 390 days. Candidate variables for the multivariable models were selected based on: 1) $P < 0.20$ on the univariate analysis; 2) <20% missing data; and 3) a manual review conducted to focus on clinically relevant, procedurally actionable variables among the variables meeting these 2 criteria. For covariates with missing values in the multivariable analysis, a simple sex-specific imputation using the mean for continuous variables or median value for dichotomous or categorical variables of the nonmissing values was performed. A full list of covariates included in the univariate and multivariable analyses is presented in Supplemental Tables 2 to 4. No adjustment was

TABLE 1 Baseline Clinical Characteristics (N = 557)

Age, y	68.8 ± 10.0/70.0 [62.0-76.0]
BMI, kg/m^2	26.7 ± 4.9/26.3 [23.5-29.3]
Obesity, BMI ≥30 kg/m^2	21.6 (119/552)
Male	67.5 (376/557)
Hypertension	87.6 (486/555)
Hyperlipidemia	76.9 (419/545)
Diabetes mellitus	40.5 (225/555)
Insulin-dependent diabetes mellitus	16.6 (92/555)
Carotid artery disease	26.6 (132/497)
Coronary heart disease	48.0 (258/538)
Smoking	
Active	38.2 (213/557)
Previous	33.4 (186/557)
Never	28.4 (158/557)
Renal insufficiency, baseline serum creatinine ≥1.5 mg/dL	10.2 (54/528)
On dialysis	1.3 (7/552)
Below-the-knee vascular disease of target leg, stenotic/occluded	41.6 (222/534)
Previous peripheral revascularization	46.1 (257/557)
Iliac	17.2 (96/557)
Common femoral	5.9 (33/557)
Femoral profunda	0.9 (5/557)
Superficial femoral	33.2 (185/557)
Popliteal	8.4 (47/557)
Below-the-knee	3.4 (19/557)
Rutherford category	
1	0.0 (0/556)
2	33.3 (185/556)
3	57.2 (318/556)
4	7.2 (40/556)
5	2.3 (13/556)
6	0.0 (0/556)
Target limb ABI/TBI, mm Hg ratio, per participant	0.71 ± 0.22/0.70 [0.58-0.83]

Values are mean ± SD/median [IQR] or % (n/N).
ABI = ankle-brachial index; BMI = body mass index; TBI = toe-brachial index.

applied for multiple comparisons, and the level of statistical significance was set at $P < 0.05$.

RESULTS

BASELINE CLINICAL AND LESION CHARACTERISTICS. A total of 557 participants with single lesions treated with the IN.PACT Admiral DCB were identified and included in this independent participant-level analysis. The mean age of the study population was 68.8 ± 10.0 years (median 70.0 years; IQR: 62.0-76.0 years), and 67.5% (n = 376 of 557) were male. Baseline clinical characteristics are summarized in Table 1. Cardiovascular risk factors included hypertension in 87.6% (n = 486 of 555), hyperlipidemia in 76.9% (n = 419 of 545), diabetes mellitus in 40.5% (n = 225 of 555), and active smoking in 38.2% (n = 213 of 557). Renal insufficiency with serum creatinine ≥1.5 mg/dL was present in 10.2% of participants (n = 54 of 528). Previous peripheral revascularization was documented in 46.1% of participants (n = 257 of 557), but only 2 participants had a history of previous amputation of the target limb (0.4%). The majority of participants presented with intermittent claudication (Rutherford Classification Category [RCC] 2 in 33.3% [n = 185 of 556]) and RCC 3 in 57.2% [n = 318 of 556]), whereas 7.2% (n = 40 of 556) and 2.3% (n = 13 of 556) were RCC 4 and 5, respectively. The mean target limb ABI or TBI ratio per participant was 0.71 ± 0.22 mm Hg (median 0.70 mm Hg; IQR: 0.58-0.83 mm Hg).

Angiographic and procedural characteristics are presented in Table 2. The target lesion type was de novo in 90.7% (n = 505 of 557) and nonstented restenotic in 9.3% of participants (n = 52 of 557). Total occlusion of the target lesion was present in 49.7% of participants (n = 275 of 553), and the mean lesion length was 16.37 ± 10.68 cm (median 14.45 cm; IQR: 7.90-23.50 cm). Severe calcification was detected in 56.4% (n = 304 of 539). The mean preprocedure reference vessel diameter (RVD) was 4.66 ± 0.83 mm (median 4.59 mm; IQR: 4.08-5.19 mm]) and the mean minimal lumen diameter was 0.74 ± 0.76 mm (median 0.56 mm; IQR: 0.00-1.32 mm).

PROCEDURAL CHARACTERISTICS. The mean postprocedure mean minimal lumen diameter was 3.93 ± 0.75 mm (median 3.93 mm; IQR: 3.43-4.47 mm) with a mean acute gain of 3.01 ± 0.90 mm (median 3.00 mm; IQR: 2.40-3.64 mm). A residual stenosis of >30% postindex procedure was present in 12.8% of participants (n = 69 of 538).

Predilatation was performed in 94.6% of participants (n = 526 of 556), whereas postdilatation was performed in 34.7% of participants (n = 193 of 556). Provisional stenting was required in 24.1% of participants (n = 134 of 556). Among the 134 participants receiving provisional stenting, the reasons for provisional stenting included persistent residual stenosis ≥50% in 56.0% (n = 75 of 134), persistent gradient >10 mm Hg across the lesion in 1.5% (n = 2 of 134), and flow-limiting dissection in 60.4% (n = 81 of 134). Postprocedure dual antiplatelet medication compliance rates are included in Supplemental Table 5.

OUTCOMES AND PREDICTORS OF DCB FAILURE. Based on Kaplan-Meier estimates, primary patency loss through 12-month follow-up in the pooled analysis was 17.5% (86 events). Binary restenosis occurred in 15.6% (76 events), and CD-TLR occurred in 5.3% (28 events). Supplemental Tables 2 to 4 summarize the univariate analyses for loss of primary patency, binary restenosis, and CD-TLR. Figure 2 presents the

multivariable Cox proportional hazards regression analysis for patency loss, binary restenosis, and CD-TLR through 12-month follow-up, respectively. Residual stenosis >30% was identified as a statistically significant predictor of increased risk in loss of primary patency through 12 months (HR: 2.94; 95% CI: 1.76-4.92; $P < 0.001$). Residual stenosis of >30% (HR: 2.73; 95% CI: 1.60-4.65; $P < 0.001$) and smaller preprocedure RVD (in 1-mm decreasing increments; HR: 1.57; 95% CI: 1.01-2.46; $P = 0.046$) were associated with increased risk of having binary restenosis through 12 months. Residual stenosis >30% (HR: 5.67; 95% CI: 2.32-13.85; $P < 0.001$) and RCC >3 (vs ≤3; HR: 4.19; 95% CI: 1.68-10.46; $P = 0.002$) were identified as predictors of increased risk in CD-TLR through 12 months.

The **Central Illustration** shows the impact of having 0, 1, or 2 of the risk factors (residual stenosis >30%, RCC >3, and smaller preprocedure RVD) identified by the multivariable predictor analyses. Among participants with both residual stenosis >30% and RCC >3, 33.3% (n = 2 of 6) had a CD-TLR event, compared with 11.8% of participants (n = 13 of 110) with either residual stenosis >30% or RCC >3 and 2.9% of participants (n = 13 of 441) with neither of those risk factors. For binary restenosis, 40.0% of participants (n = 8 of 20) with both residual stenosis >30% and a preprocedure RVD in the lowest tercile had binary restenosis, compared with 18.6% of participants (n = 38 of 204) with only 1 of those risk factors and 9.0% (n = 30 of 333) of participants with neither of those risk factors.

DISCUSSION

In the present study, we investigated the predictors of DCB failure in the femoropopliteal segment from a pooled participant-level database. Multivariable Cox proportional hazards regression analyses suggested that residual stenosis >30% is associated with increased risk of patency loss, binary restenosis, and CD-TLR through 12 months. Additionally, smaller RVD and RCC >3 were shown to be associated with increased risk of binary restenosis and CD-TLR. Furthermore we found that these predictors exert an additive effect on the occurrence of binary restenosis and CD-TLR.

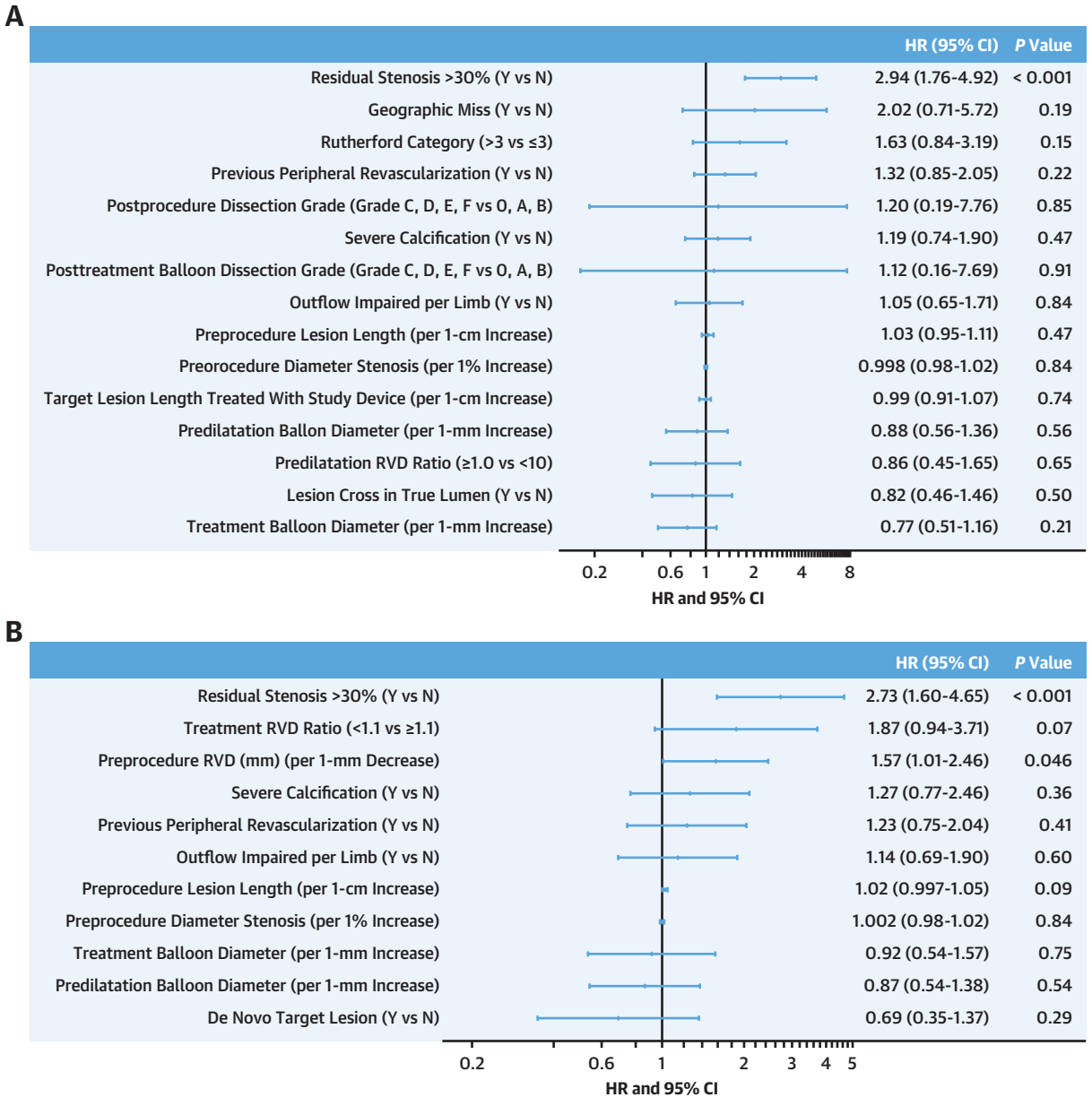
Within the last 2 decades, endovascular intervention has evolved as a safe and effective treatment for femoropopliteal PAD.[7] International societies have issued guidelines recommending surgical revascularization for more complex lesions, and both surgical and endovascular interventions for less complex lesions.[5,16,17] Nevertheless, most recently, endovascular

TABLE 2 Quantitative Angiographic Analysis and Procedural Characteristics (N = 557)

Target lesion type per lesion	
De novo	90.7 (505/557)
Restenotic, nonstented	9.3 (52/557)
Occluded lesion, 100% stenosis	49.7 (275/553)
Severe calcification	56.4 (304/539)
Preprocedure angiographic core laboratory	
RVD, mm	4.66 ± 0.83/4.59 [4.08-5.19]
MLD, mm	0.74 ± 0.76/0.56 [0.00-1.32]
Diameter stenosis, %	87.78 ± 15.03/98.00 [77.00-100.00]
Lesion length, cm	16.37 ± 10.68/14.45 [7.90-23.50]
Postprocedure angiographic core laboratory	
MLD, mm, postintervention	3.93 ± 0.75/3.93 [3.43-4.47]
Diameter stenosis, %	20.24 ± 10.13/20.00 [14.00-27.00]
Acute gain, mm	3.01 ± 0.90/3.00 [2.40-3.64]
Residual stenosis >30%	12.8 (69/538)
Lesion access, per lesion	
Ipsilateral antegrade	32.0 (178/557)
Contralateral retrograde	66.6 (371/557)
Other	3.0 (8/269)
Lesion crossed with guidewire, per lesion	100.0 (537/537)
True lumen	80.4 (432/537)
Subintimal	19.6 (105/537)
Participants with predilatation	94.6 (526/556)
Participants with postdilatation	34.7 (193/556)
Reason for postdilatation, per lesion	
None	26.4 (51/193)
Persistent ≥50% residual stenosis	37.8 (73/193)
Translesional gradient >10 mm Hg	1.6 (3/193)
Flow-limiting dissection	37.8 (73/193)
Other	16.9 (20/118)
Participants receiving provisional stents	24.1 (134/556)
1st lesion length tercile, range 1.0-9.9 cm	7.9 (14/177)
2nd lesion length tercile, range 10.0-19.8 cm	18.3 (33/180)
3rd lesion length tercile, range 20.0-53.0 cm	46.1 (83/180)
Participants who received provisional stents and no postdilatation	11.2 (62/556)
Reason for provisional stenting, per participant	
Persistent ≥50% residual stenosis	56.0 (75/134)
Translesional gradient >10 mm Hg	1.5 (2/134)
Flow-limiting dissection	60.4 (81/134)
Other	4.2 (5/118)
Provisional stenting coverage	
Spot	31.3 (36/115)
Partial	34.8 (40/115)
Total	33.9 (39/115)
Provisional stent length, mm (n = 134)	147.0 ± 97.6/ 140.0 [60.0-200.0]
Stent-to-lesion length ratio	0.7 ± 0.5/ 0.7 [0.4-1.0]
Posttreatment dissection grade	35.0 (195/557)
Grade A	19.5 (38/195)
Grade B	28.2 (55/195)
Grade C	10.8 (21/195)
Grade D	4.6 (9/195)
Grade E	5.1 (10/195)
Grade F	1.0 (2/195)

Values are % (n/N) or mean ± SD/median [IQR].
MLD = minimal lumen diameter; RVD = reference vessel diameter.

FIGURE 2 **Predictors of Patency Loss, Binary Restenosis, and Clinically Driven Target Lesion Revascularization**



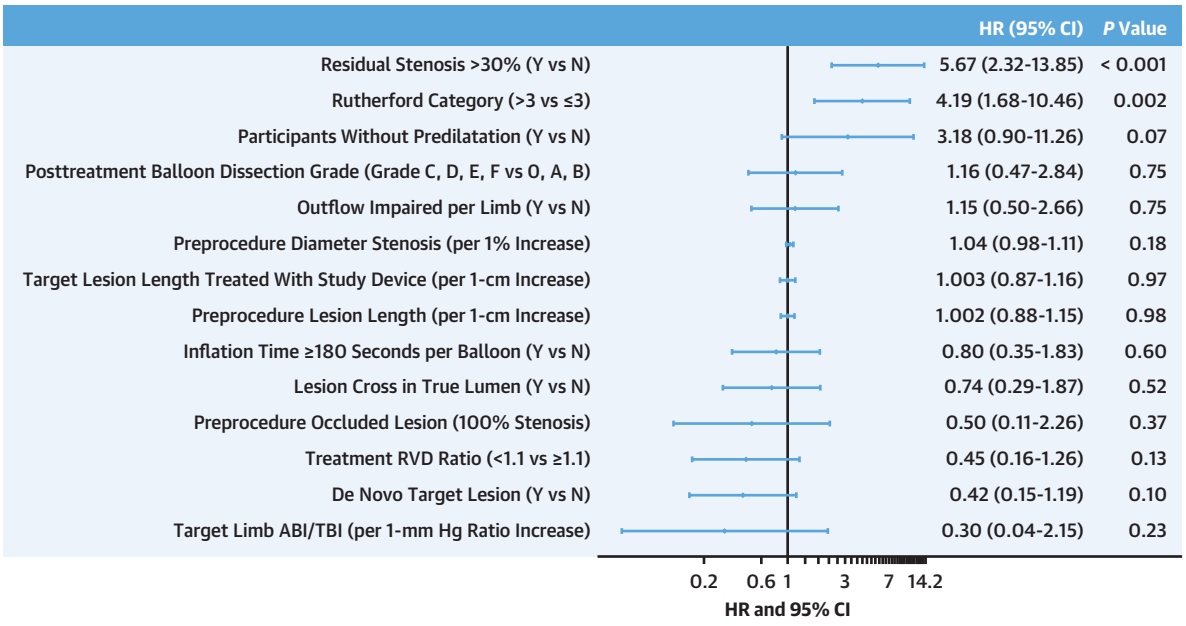
Multivariable Cox regression models were used to evaluate the clinical, anatomical, and procedural factors associated with patency loss **(A)**, binary restenosis **(B)**, and clinically driven target lesion revascularization **(C)**. Only residual stenosis >30% was associated with increased risk of loss of primary patency, whereas residual stenosis >30% and smaller preprocedure RVD were associated with increased binary restenosis risk. RCC >3 and residual stenosis >30% were associated with increased risk of 12-month clinically driven target lesion revascularization. The **vertical line** indicates an HR of 1.0. ABI = ankle-brachial index; DCB = drug-coated balloon; RVD = reference vessel diameter; TBI = toe-brachial index.

Continued on the next page

interventions have been increasingly expanded to more complex lesions, with investigations of various endovascular devices showing promising results also in long and occlusive lesions with patency rates similar to bypass surgery.[7] In addition, there is no universal definition of PAD complexity.[5,18] The currently available definitions base their criteria mostly on lesion length and degree of lumen narrowing (stenotic vs

FIGURE 2 Continued

C

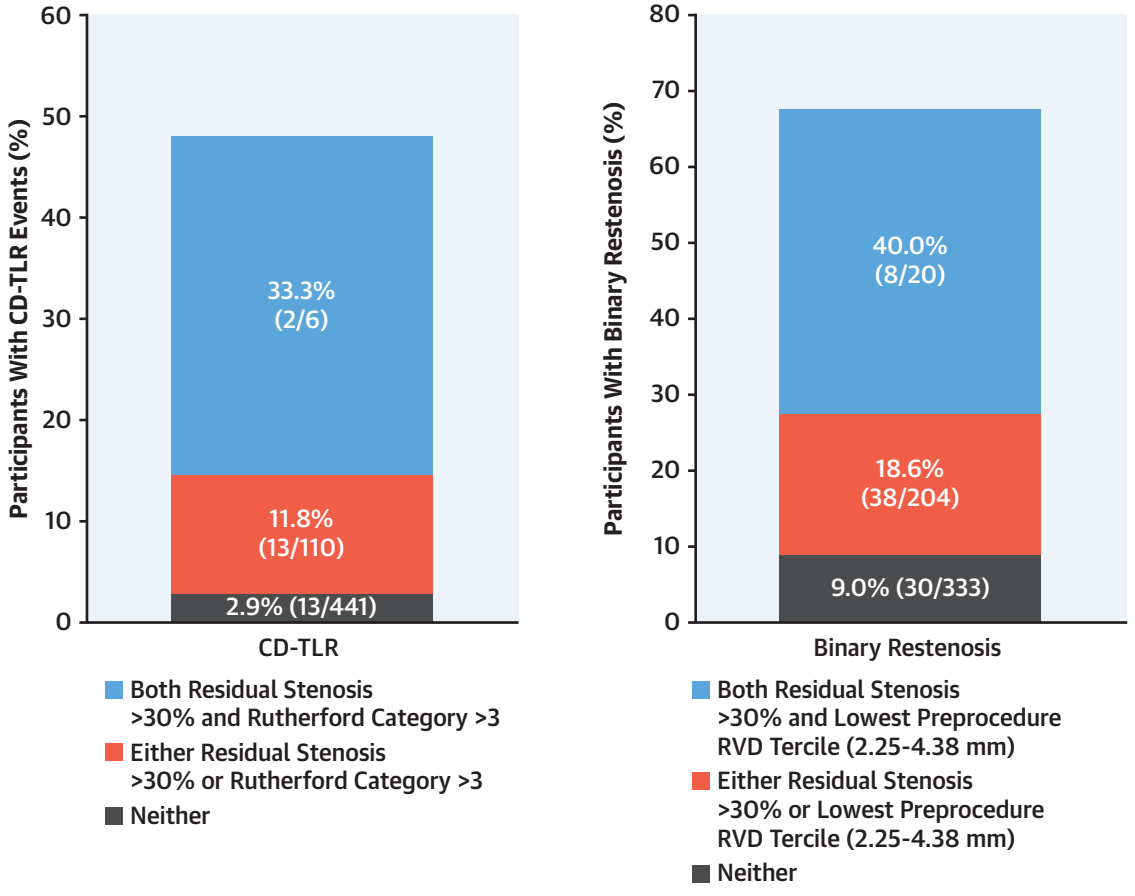


occlusive),[5,18] factors that have repeatedly been reported as independent predictors of patency loss and restenosis.[5,18,19] However, additional factors may affect outcomes after endovascular revascularization. Vessel dimension at the lesion site has been shown to be a predictor of poor outcome after stenting with bare-metal and drug-eluting stents,[20,21] and after DCB treatment.[9] With regard to the latter, in a retrospective study of 164 patients treated with DCB for femoropopliteal artery disease with popliteal artery involvement was associated with higher risk of DCB failure (~60%).[9] Our study demonstrates that smaller RVD was associated with binary restenosis regardless of the location of the lesion.

Similar to our findings, the presentation of PAD patients with chronic limb ischemia vs intermittent claudication has been shown to impact outcomes in previous analyses.[22,23] Residual stenosis after PTA is frequently found and associated with the need for further treatment with additional PTA or even a scaffold.[24,25] Our finding that residual stenosis >30% is associated with higher risk of DCB failure is novel.

Compared with these previous studies, our analysis provides nuanced insights with respect to differences in the predictive value of RCC (>3 vs ≤3), RVD, and residual stenosis (>30% vs ≤30%), endpoints that were adjudicated by independent core laboratories. Our study demonstrates that loss of primary patency and binary restenosis, which are considered imaging outcomes, are associated with lesion and procedural parameters, whereas CD-TLR, a clinical endpoint driven by patients' symptoms, was associated with clinical presentation and by residual stenosis >30%. Because DCB failure defined by imaging endpoints is merely associated with lesion and procedural characteristics, it may be important to routinely consider clinical outcomes for a comprehensive evaluation of DCB failure and acknowledge clinical presentation for prognostic purposes. These findings become of greater importance as those predictors exert an additive effect on the occurrence of DCB failure. Paradoxically, several other lesion characteristics and procedural parameters that are considered to contribute to lesion complexity and revascularization failure in the femoropopliteal segment were not predictive of DCB failure. Specifically, lesion length, degree of calcification, dissection, or provisional stenting, which have been shown to impact patency after endovascular intervention in previous studies,[1,19,20,26] were not associated with DCB failure in our study. However, longer lesions (lesion length ≥20 cm) in the present study were more frequently treated by provisional stenting, which limits the generalizability of our findings in very long lesions.

CENTRAL ILLUSTRATION **Independent Predictors of Clinically Driven Target Lesion Revascularization and Binary Restenosis**



Krishnan P, et al. J Am Coll Cardiol. 2022;80(13):1241–1250.

A patient-level pooled analysis of randomized clinical trials and the prespecified imaging cohorts of a prospective single-arm study was used to identify the predictors of drug-coated balloon failure, including binary restenosis and CD-TLR. Influential procedural characteristics were evaluated by an independent angiographic core laboratory. Among the factors found to be statistically significant in multivariable models (residual stenosis >30%, Rutherford clinical category >3, and smaller RVD), participants with 2 risk factors had a higher risk of CD-TLR or binary restenosis than participants with only 1 risk factor or no risk factors. CD-TLR = clinically driven target lesion revascularization; RVD = reference vessel diameter.

Endovascular revascularization for PAD involving the femoropopliteal artery segment has become a standard technique to improve quality of life in patients with intermittent claudication and reduce the risk of limb loss and mortality in patients with critical limb ischemia.[27] Certain clinical and lesion characteristics can impact the intermediate- and long-term success of such interventions. The additive impact of those characteristics should be acknowledged and accounted for when attempting revascularization with DCB. The results of the present study may have the potential to improve planning of and outcomes after endovascular intervention with DCB in femoropopliteal artery segment. Because lesion length is a nonmodifiable factor, endovascular intervention with DCB should in particular focus on parameters such as residual stenosis. Despite lacking evidence from largescale randomized trials, advanced imaging employing intravascular ultrasound may identify residual stenosis >30% post-DCB treatment so that adjunctive therapy may be considered.[28] Finally, the role of medical and conservative treatment should not be neglected, because the clinical presentation of the patients with PAD is an independent predictor of CD-TLR.[16,29,30] Physicians treating PAD should apply guideline-directed medical management for PAD patients and thereby attempt to avoid a progression to critical limb ischemia.[16,29,30]

STUDY LIMITATIONS. Several limitations of the present study should be acknowledged before interpreting the presented findings. Despite the utilization of an independent angiographic core lab, the analysis was conducted retrospectively from participant-level pooled analysis, and therefore, we cannot exclude the influence of unmeasured confounders. The analysis focused only on 1 type of DCB, and further studies are needed to identify a potential class effect. Therefore, our results cannot be extrapolated to other available DCB platforms. This analysis also did not evaluate the predictors of failure following PTA use. Additionally, as provisional stenting was more frequently used in subjects with long lesions (>20 cm) in the present study, the mode of failure of DCB in these lesions remains to be investigated further.

CONCLUSIONS

In this population, patency loss after DCB treatment was determined by procedural characteristics and clinical factors. Residual stenosis (>30%) as well as small RVD and clinical presentation (RCC class >3) may be considered predictors of increased risk of DCB failure and its components. In the femoropopliteal segment, careful consideration of the impact of clinical presentation and lesion characteristics may result in more favorable outcomes with the use of DCB.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients undergoing endovascular femoropopliteal arterial intervention using drug-coated balloons, the severity of ischemic at presentation, reference vessel diameter, and >30% residual stenosis are associated with adverse outcomes.

TRANSLATIONAL OUTLOOK: Prospective trials are needed to evaluate strategies addressing each of these predictors, including case and device selection, to improve the long-term patency and clinical outcomes of endovascular femoropopliteal interventions.

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APPENDIX For supplemental tables, please see the online version of this paper.