Journal of the American Heart Association

ORIGINAL RESEARCH

Vessel Patency and Associated Factors of Drug-Coated Balloon for Femoropopliteal Lesion

Yoshimitsu Soga, MD, PhD; Mitsuyoshi Takahara, MD, PhD; Osamu Iida, MD, PhD; Yusuke Tomoi, MD; Daizo Kawasaki, MD, PhD; Akiko Tanaka, MD; Yasutaka Yamauchi, MD, PhD; Kazuki Tobita, MD; Amane Kozuki, MD, PhD; Masahiko Fujihara, MD; Kenji Ando, MD; on behalf of the POPCORN Investigators*

BACKGROUND: Although clinical trials have reported favorable outcomes after drug-coated balloon (DCB) therapy for femoropopliteal lesions, their real-world performance and predictors have not been well evaluated. This study aimed to elucidate 1-year freedom from restenosis and to explore the associated factors after a DCB for femoropopliteal lesions in clinical settings.

METHODS AND RESULTS: This multicenter, prospective cohort registered 3165 de novo or restenotic femoropopliteallesions (mean lesion length, 13.5±9.3 cm; chronic total occlusion, 25.9%; severe calcification, 14.6%) that underwent successful DCB (Lutonix [24.2%] and IN.PACT Admiral [75.8%]) treatment between March 2018 and December 2019. Patency was assessed at 12±2 months. The primary outcome measure was 1-year freedom from restenosis and its associated factors. Bailout stenting was performed in 3.5% of patients. The postprocedural slow flow phenomenon was observed in 3.9% of patients. During a median follow-up of 14.2 months, 811 patients experienced restenosis. The Kaplan–Meier estimate of freedom from restenosis was 84.5% at 12 months (79.7% at 14 months). Focal, tandem, diffuse, and occlusive restenosis accounted for 37.4%, 9.8%, 18.9%, and 33.9%, respectively. Freedom from target lesion revascularization was 91.5% at 12 months. Risk factors independently associated with 1-year restenosis were a history of revascularization, smaller distal reference vessel diameter, severe calcification, chronic total occlusion, low-dose DCB, and residual stenosis.

CONCLUSIONS: The 1-year clinical outcomes after DCB use for femoropopliteal lesions in real-world practice was favorable. The additive risk factors were associated with a lower rate of freedom from restenosis.

Key Words: drug-coated balloon ■ endovascular therapy ■ femoropopliteal lesions ■ peripheral artery disease ■ re-occlusion ■ restenosis ■ target lesion revascularization

In recent years, the advent of drug-eluting devices has dramatically reduced restenosis and target lesion revascularization (TLR) of femoropopliteal lesions after endovascular therapy (EVT) compared with conventional percutaneous transluminal angioplasty and bare-nitinol stent (BNS) implantation.[1–7] Currently, there are 2 types of drug-eluting devices: drug-coated balloons (DCBs)[2–4] and drug-eluting stents (DESs).[5–7] Although both are used in various clinical settings, DES is a permanent metallic implant, such as BNS, and shares a future risk of stent fractures.[8,9] Recently, aneurysmal degeneration after DES placement has been reported,[10] which is another concern regarding primary DES implantation. In contrast, DCBs are free from these concerns; however,

Correspondence to: Yoshimitsu Soga, MD, PhD, Department of Cardiology, Kokura Memorial Hospital, 3-2-1 Asano, Kokurakita-ku, Kitakyushu, Japan. Email: soga@circulation.jp

*A complete list of the POPCORN Investigators can be found in the Supplemental Material.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.025677

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrated the true performance of drug-coated balloons in real-world practice, with a very low rate of bailout stenting and no use of atherectomy devices.
- In addition, it also elucidated morphologies associated with restenosis and the risk factors for restenosis after using drug-coated balloons.

What Are the Clinical Implications?

- This large-scale multicenter prospective clinical drug-coated balloon study indicated that 12-month freedom from restenosis and target lesion revascularization was 84.5% and 91.5%.
- Two thirds of restenosis had a stenotic pattern, and independent predictors of restenosis were prior revascularization, smaller vessel, presence of severe calcification, chronic total occlusion, use of low-dose drug-coated balloons, and residual stenosis.

Nonstandard Abbreviations and Acronyms

BNS	bare-nitinol stent
CTO	chronic total occlusion
DCB	drug-coated balloons
DES	drug-eluting stents
EVT	endovascular therapy
TLR	target lesion revascularization

their restenosis rate reported in clinical trials are higher than those after DES implantation. Moreover, large-scale clinical studies on restenosis, its associated factors, and morphology after DCB use are warranted.

To assess the restenosis risk associated with a specific device, it is important to minimize the influence of other devices. In this context, evaluating the real-world efficacy of DCBs alone is difficult in Europe and North America, where bailout stenting is commonly performed, especially in complex lesions,[11] and atherectomy devices are also available.[12,13] However, in Japan, bailout stenting after DCBs is rare because it is not reimbursed, and no atherectomy devices have been approved yet. Therefore, Japan is an appropriate field for evaluating the true effectiveness of DCBs in real-world clinical practice.

This study aimed to elucidate the 1-year freedom from restenosis and to explore the associated factors after EVT with a DCB for symptomatic femoropopliteal lesions in real-world clinical settings.

METHODS

Study Population

This study used the clinical database of POPCORN (Prospective Multicenter Registry of Drug-Coated Balloon for Femoropopliteal Disease). POPCORN is an ongoing prospective multicenter observational study that registered patients (≥20 years) undergoing DCB treatment for femoropopliteal lesions (either de novo or restenotic) with symptomatic peripheral arterial disease (Rutherford category 2 to 5) at 81 cardiovascular centers across Japan between March 2018 and December 2019. Annual follow-ups with a time window of ±2 months for 5 years were scheduled. A total of 3165 lesions in 2827 limbs of 2507 patients undergoing treatment with Lutonix or IN.PACT Admiral were included in the registry. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of the participating centers. Informed consent was obtained from the participants or, if not possible, their families. This study reported the 1-year clinical outcomes from the registry. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Procedures and Follow-Up

All patients were recommended to receive dual antiplatelet therapy (aspirin 81–100 mg/day and clopidogrel 75 mg/day) the day before EVT or earlier. Either ipsilateral or contralateral femoral punctures were performed. After insertion of a 6- or 5-Fr sheath, an intra-arterial bolus of 5000 IU heparin was injected and supplemented as required to maintain an active clotting time of >200 seconds.

After the lesion was successfully crossed with a 0.035-, 0.018-, or 0.014-inch guidewire, predilatation was performed with a standard angioplasty balloon that was the same size as the reference vessel or 0.5–1 mm smaller. Following successful predilatation (without flow-limiting dissection and <50% of residual stenosis), 2 types of DCBs were used: Lutonix (Bard, New Hope, MN, USA) and IN.PACT Admiral (Medtronic, Santa Rosa, CA, USA). The DCB type was determined by each operator and the DCB size was the same as the reference vessel diameter. In principle, DCB was used to cover the entire lesion. Postdilation was performed if needed and sized appropriately according to reference vessel diameter. Intravascular ultrasound (IVUS) was performed at the discretion of the operators based on their usual practice. Atherectomy devices are not commercially available in Japan; therefore, they were not used in this study.

After the procedure, lifelong aspirin (81–100 mg/day) and prolonged (at least 1 month) clopidogrel (75 mg/day) were recommended. Restenosis was routinely monitored by duplex ultrasound at 1 month and 1 year, regardless of the presence of ischemic symptoms. The 1-year follow-up was scheduled at 12±2 months (ie, between 10 and 14 months) after the procedure.

Outcome Measures

The primary outcome measure was freedom from restenosis and its associated factors. The secondary outcome measures were freedom from TLR, limb salvage rate, freedom from any reintervention and major adverse limb events, and all-cause mortality.

Definitions

Restenosis was defined as >2.4 times of the peak systolic velocity ratio on duplex ultrasound or >50% of the arterial diameter based on angiography.[14] Restenosis was classified as focal (<30 mm), tandem (multiple focal), diffuse (>30 mm), and occlusive. An undetectable signal in the treated segments on duplex ultrasound was graded as a complete occlusion. TLR was clinically driven and defined as reintervention performed for lesions with >50% diameter stenosis identified by angiography within ±5 mm of the target lesion after the documentation of recurrent clinical symptoms.[14] Therefore, all TLR cases were included as restenosis cases. Residual stenosis was defined as ≥25% stenosis after DCB, based on angiography findings. The dissection grade was determined based on angiographic dissection patterns.[15] Severe dissection was defined as grade D or greater. Limb salvage was freedom from major amputation, which was defined as surgical excision of the limb above the ankle.[16] Major adverse limb events were defined as a composite of major amputation, bypass conversion, or any reintervention during the study period. Arterial calcification was assessed using angiography before the procedure, and below-the-knee runoffs were angiographically assessed after femoropopliteal treatment. Arterial calcification was graded using the peripheral arterial calcium scoring system[17] and severe calcification was denoted as grade 4. The reference vessel diameter was assessed via angiography at healthy distal sites, free of atherosclerotic plaques. Chronic kidney disease was referred to as an estimated glomerular filtration rate of <60 mL/min per 1.76 m^2.

Statistical Analysis

Data were presented as mean±SD for continuous variables and as percentage for categorical variables, unless otherwise indicated. A P value <0.05 was considered statistically significant, and 95% CIs were reported when appropriate. Time-to-event was estimated using the Kaplan–Meier method. The Kaplan–Meier method was originally used for right-censored data. In contrast, data on restenosis were interval censored; restenosis, especially asymptomatic restenosis, could not be confirmed without examination. In other words, restenosis was overlooked unless objectively evaluated. When the interval-censored data were analyzed by the Kaplan–Meier method, cases in which restenosis had developed but was left undetected were treated as those free from restenosis, resulting in an artificially high event-free rate (or low event incidence rate). As mentioned, in the current registry, the 1-year follow-up was scheduled at 12±2 months, and not all participants were expected to complete the 1-year examination at 12 months. Therefore, we presented the Kaplan–Meier estimate of freedom from restenosis not only at 12 months, but also at 14 months, when the scheduled 1-year examination was completed.

The association of baseline characteristics with the 1-year restenosis risk was investigated using the Cox mixed-effect model, in which the interhospital variability was treated as random effects, whereas baseline characteristics were treated as fixed effects. The R package *coxme* was used for model development. The hazard ratio (HR) of a baseline characteristic without adjustment for the other baseline characteristics, named an "unadjusted" HR, was obtained from the mixed model, whose fixed effect was the covariate alone. We conveniently named this model the "univariate" model. We also developed a mixed model, in which all baseline characteristics were entered as fixed effects. This model was named the "multivariate" model, and the HRs derived from the model were called adjusted HRs. Missing data were addressed using multiple imputations by the chained equations method during model development. In this procedure, we generated 5 imputed data sets and combined the analytic results based on Rubin's rule. The predictive performance of the multivariate model was evaluated using the C-statistic, which was calculated as the area under the time-dependent receiver operating characteristic curve.[18] Based on the multivariate model, we tentatively developed a simple risk score that was calculated as the number of accumulated independent risk factors. The predictive performance of the risk score was also assessed using the C-statistic. The 95% CIs and P values for C-statistics were obtained using a 2000-time bootstrapping method. All statistical analyses were performed using software R, version 4.1.1 (R Development Core Team, Vienna, Austria).

RESULTS

The patient (n=2507), limb (n=2827), and lesion (n=3165) characteristics of the study population are summarized

in Table 1. The mean patient age was 75±9 years, and 64.9% of the study participants were men. The prevalence of patients with diabetes and chronic kidney disease on dialysis was 65.4% and 29.0%, respectively. Chronic limb-threatening ischemia accounted for 31.2% of the cases. The mean lesion length and distal reference vessel diameter were 13.5±9.3 cm and 4.8±0.9 mm, respectively. The frequencies of chronic total occlusion (CTO) and severe calcification were 25.9% and 14.6%, respectively.

Perioperative outcomes are shown in Table 2. Slow flow or no reflow after DCB was observed in 3.9% of the patients. Severe dissection after DCB was found in 4.6% (95% CI, 3.9%–5.4%), and bailout stenting was performed in 3.5% (95% CI, 2.9%–4.2%). Perioperative complications were observed in 3.6% (95% CI, 2.9%–4.3%) of patients, of which the incidence of distal emboli and acute occlusion were similar with 0.6% (95% CI, 0.3%–0.9%).

Outcome Measures

During the follow-up period, 172 patients died and 206 patients were lost to follow-up. One-year follow-up rate was 84.9% (2129/2507) on a patient basis. The median follow-up period was 14.2 (interquartile range, 10.1–23.0) months. Restenosis was detected in 811 patients, of whom 545 were found to have restenosis in the first year post procedure. Figures 1 and 2 illustrate the lesion, limb, and patient prognoses after EVT. The Kaplan–Meier estimate of freedom from restenosis was 84.5% (95% CIs, 83.1%–85.8%) at 12 months (79.7% [95% CI, 78.1%–81.2%] at 14 months). Focal, tandem, diffuse, and occlusive restenosis accounted for 37.4% (95% CI, 29.9%–44.9%), 9.8% (95% CI, 8.4%–11.2%), 18.9% (95% CI, 17.0%–20.9%), and 33.9% (95% CI, 26.0%–41.8%) of restenosis cases, respectively (Figure 1A). The 12-month rate of freedom from TLR was 91.5% (95% CI, 90.5%–92.5%) (Figure 1B).

The 12-month Kaplan–Meier estimates of limb salvage (Figure 2A), freedom from any reintervention (Figure 2B), and freedom from major adverse limb events (Figure 2C) was 98.6% (95% CI, 98.2%–99.1%), 91.1% (95% CI, 90.0%–92.2%), and 90.0% (95% CI, 88.9%–91.2%), respectively. The 12-month cumulative incidence rate of all-cause mortality was 9.5% (95% CI, 7.4%–9.7%) (Figure 2D).

Table 3 demonstrates the association between baseline characteristics and the 1-year risk of restenosis. Baseline characteristics that were independently associated with 1-year restenosis were history of revascularization (1.32 [95% CI, 1.01–1.73] for 1 EVT and 1.70 [95% CI, 1.23–2.34] for more EVTs versus de novo lesions; P=0.044 and 0.001), distal reference vessel diameter (0.87 [95% CI, 0.78–0.97] per 1-mm increase; P=0.012), severe calcification (1.29 [95% CI, 1.03–1.63]; P=0.027), CTO (1.28 [95% CI, 1.04–1.58]; P=0.021),

Table 1. Baseline Characteristics

Patient characteristics	(n=2507)
Age, y	75±9
Male sex	1626 (64.9%)
Nonambulatory	323 (12.9%)
Smoking	516 (20.6%)
Diabetes	1639 (65.4%)
CKD*	
None	762 (30.4%)
CKD without dialysis	1015 (40.5%)
CKD on dialysis	728 (29.1%)
Heart failure*	463 (18.5%)
Aspirin use*	1964 (78.9%)
P2Y12 inhibitor use*	2155 (86.3%)
Cilostazol use*	623 (25.2%)
Anticoagulant use*	
None	2050 (82.2%)
Warfarin use	191 (7.7%)
Direct oral anticoagulant use	254 (10.2%)
Statin use*	1514 (61.0%)
Limb characteristics	**(n = 2827)**
Rutherford classification	
Category 2	739 (26.1%)
Category 3	1207 (42.7%)
Category 4	291 (10.3%)
Category 5	590 (20.9%)
Ankle-brachial index*	0.61±0.23
Aortoiliac lesion*	616 (22.0%)
No below-the-knee runoff*	357 (12.7%)
Lesion characteristics	**(n=3165)**
History of EVT	
None (de novo)	2370 (74.9%)
1 EVT	474 (15.0%)
≥2 EVTs	321 (10.1%)
In-stent restenosis*	442 (14.0%)
Popliteal lesion	1069 (33.8%)
Distal reference vessel diameter (mm)*	4.8±0.9
Lesion length (cm)*	13.5±9.3
Severe calcification (peripheral arterial calcium scoring system grade 4)*	463 (14.6%)
Chronic total occlusion*	819 (25.9%)
Lutonix use	765 (24.2%)
Intravascular ultrasound use*	2196 (73.4%)

CKD indicates chronic kidney disease; and EVT, endovascular therapy.
*<5.5% of values were missing.

Lutonix use (1.97 [95% CI, 1.61–2.41] versus IN.PACT Admiral use; P<0.001), and residual stenosis (1.51 [95% CI, 1.24–1.83]; P<0.001). The C-statistic of the multivariate model was (0.71 [95% CI, 0.68–0.74]; P<0.001) (Figure 3A). The C-statistic of the simple risk score (ie,

Table 2. Perioperative Outcomes

Clinical outcome	Estimate [95% CI]
Perioperative outcomes	
Residual stenosis (≥25%)	26.4% [24.8%–27.9%]
Blood flow after DCB	
No change	96.0% [95.4%–96.7%]
Slow flow	2.8% [2.2%–3.4%]
No reflow	1.1% [0.8%–1.5%]
Dissection after DCB	
None	33.4% [31.8%–35.1%]
Grade A	27.1% [25.5%–28.6%]
Grade B	23.6% [22.2%–25.1%]
Grade C	11.2% [10.1%–12.3%]
Grade D	3.9% [3.2%–4.5%]
Grade E	0.6% [0.4%–0.9%]
Grade F	0.1% [0.0%–0.3%]
Dissection grade C or greater	15.8% [14.6%–17.1%]
Dissection grade D or greater	4.6% [3.9%–5.4%]
Bailout stenting	3.5% [2.9%–4.2%]
Mean ankle-brachial index after the procedure	0.89 [0.88–0.89]
Perioperative complication	3.6% [2.9%–4.3%]
Perioperative death	1.0% [0.6%–1.4%]
Target lesion revascularization (endovascular therapy)	0.7% [0.4%–1.0%]
Target lesion revascularization (bypass)	0.0% [0.0%–0.1%]
Distal embolism	0.6% [0.3%–0.9%]
Transfusion for bleeding	0.6% [0.3%–0.9%]
Acute occlusion	0.6% [0.3%–0.8%]
Vessel rupture	0.1% [0.0%–0.2%]
Blue toe syndrome	0.1% [0.0%–0.3%]
Major amputation	0.2% [0.0%–0.4%]
Myocardial infarction	0.2% [0.0%–0.4%]
Stroke	0.1% [0.0%–0.3%]
Renal impairment	0.2% [0.0%–0.3%]

DCB indicates drug-coated balloon.

the number of accumulated independent risk scores) was 0.66 (95% CI, 0.63–0.69); it was smaller than that of the multivariate model (the difference, −0.05 [95% CI, −0.07 to −0.03]; $P<0.001$), but was still significantly larger than 0.5 ($P<0.001$) (Figure 3A). Accumulation of these risk factors was associated with a lower rate of freedom from restenosis (Figure 3B).Rutherford classification and ankle-brachial index significantly improved at 1-year follow-up (Table 4).

DISCUSSION

Our multicenter, prospective, observational study documented the 1-year clinical outcomes of DCB treatment for femoropopliteal lesions. The study included a large number of patients (3165 lesions in 2507 patients) and used real -world registry data. It included patients with both short femoropopliteal lesions and CTOs, which have traditionally not been included in prior studies. The proportion of bailout stenting in this study was extremely low (3.5%), reflecting the fact that bailout stenting was not reimbursed in Japan. In addition, atherectomy devices have not yet been approved. Therefore, we believe that the results of this study illustrate the true efficacy of DCBs in femoropopliteal lesions. The 1-year rates of freedom from restenosis and TLR were clinically favorable. It was also of note that two thirds of restenosis cases were nonocclusive.

The restenosis morphology after BNS implantation was reported to be focal (≤5 cm) in 29%, diffuse (>5 cm) in 38%, and occlusive in 33%, with approximately two thirds showing the stenotic pattern.[19] Patency after EVT for stenotic restenosis was better than that for occlusive restenosis,[19] suggesting that the stenotic pattern is the preferred form of restenosis. In this study, approximately two thirds of the restenosis cases presented with a stenotic pattern. Reintervention would be easier and the patency rate would be higher for stenotic restenosis than for occlusive restenosis. The treatment strategy (DCB, DES, etc.) for stenotic and occlusive restenosis after DCB remains unclear and further studies are needed.

It has been reported that DCB does not work well for circumferential calcification.[20] In this study, severe calcification was a predictor of restenosis. Residual stenosis (>25%) was also a significant predictor of patency loss. DCB alone may be insufficient to treat patients with highly calcified lesions that were difficult to be dilated by predilatation.

In this study, factors such as the Rutherford category class, CTO, and ankle-brachial index were not independent predictors of 1-year freedom from restenosis. The results were considered favorable compared with those of the previous BNS era (the 12-month patency efficacy goal after femoropopliteal BNS was 66%).[21] Favorable 1-year clinical outcomes after the latest DES have been reported, despite the more complex lesions (1-year freedom from restenosis, 87.1%).[22] Although this study was not a direct comparison to DES, it may be considered a treatment option for more complex lesions.

This study showed that patency rate was reduced in patients with risk factors of multiple restenosis (Figure 3). However, the 1-year patency rate reached approximately 80%, even in those with 2 restenosis risks (85.8% at 12 months and 80.3% at 14 months), which was considered clinically acceptable. Considering the performance goal of the 1-year primary patency after femoropopliteal bare-nitinol stenting,[21] the efficacy of DCBs may not be sufficient in patients with 3 (65.8% at 14 months) or more risk factors (58.6% at 14 months).

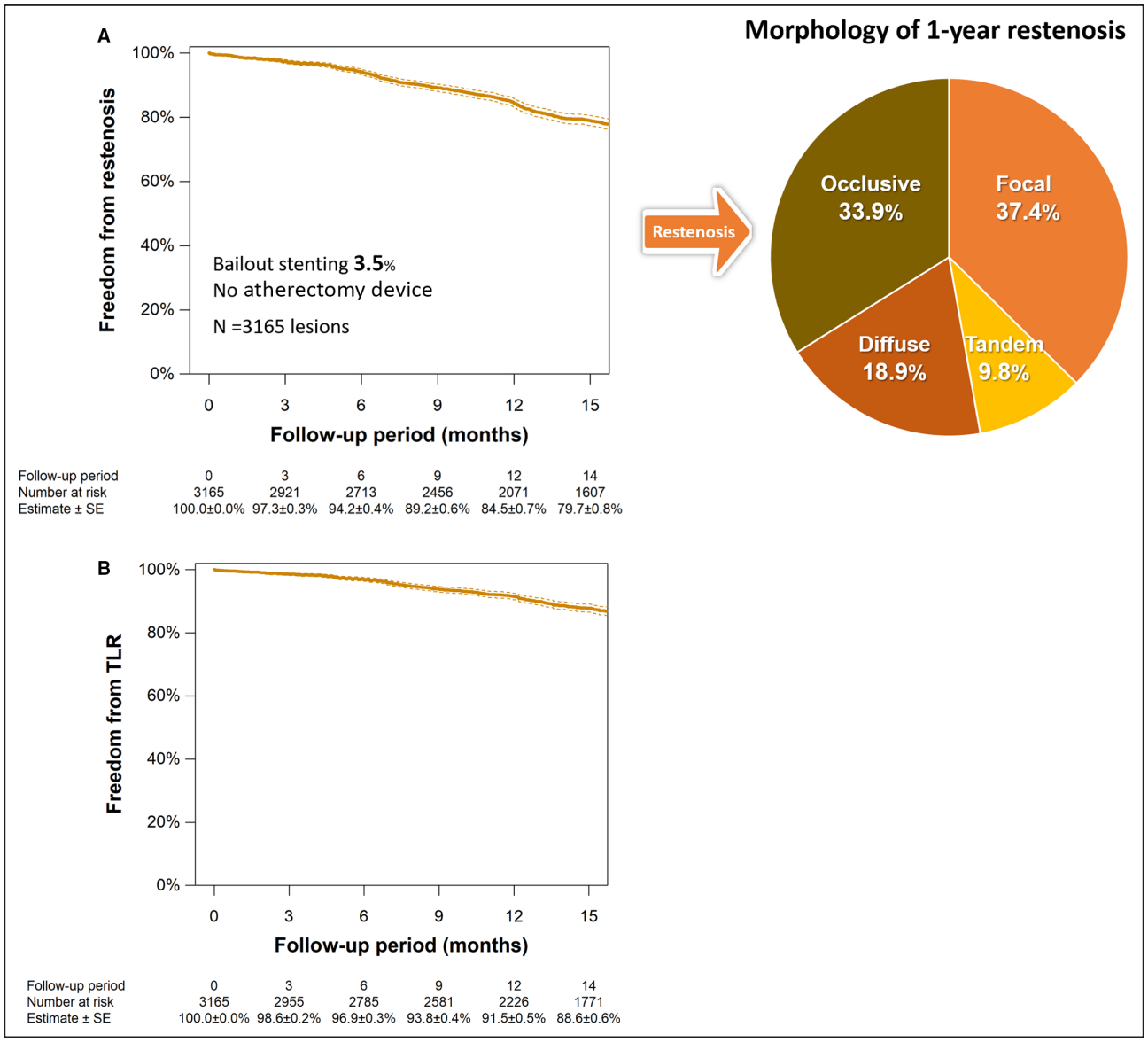


Figure 1. Freedom from restenosis and TLR.
A, Kaplan–Meier estimates of 1-year freedom from restenosis and morphology of restenosis. **B**, Kaplan–Meier estimates of 1-year freedom from TLR. Dotted lines represent 95% CIs. TLR indicates target lesion revascularization.

Such risk stratification systems play an important role in deciding the treatment strategies for individual cases. It remains unclear whether DES would be effective in cases in whom a lower rate of freedom from restenosis after DCB use was expected. Further studies are required to address this issue.

Although there are some reports of pseudoaneurysms after DCB treatment,[23,24] this study was not designed to evaluate aneurysmal changes after DCB. Further studies are required to clarify these details.

One reason for the favorable outcomes in this study would be the common use of IVUS (73.4%). The study had a high rate of IVUS usage for sizing (73%). In the present multivariate analysis, the use of IVUS was marginally but not significantly associated with a reduced risk of restenosis (Figure S1). It has been reported that there is a discrepancy in vessel diameter by approximately 1 mm between IVUS and angiography; this discrepancy is marked in small vessels.[25] The use of IVUS may provide adequate dilatation.[26] In addition to CTO and circumferential calcification, postprocedural IVUS-measured minimal lumen area has been reported to be a significant predictor of restenosis after DCB. This report recommended a minimal lumen area ≥12.7 mm^2.[27] The use of IVUS might help in the selection of DCBs with diameters larger than the angiographically measured vessel diameter, which may have contributed to the reduction of residual stenosis. In the future, it is

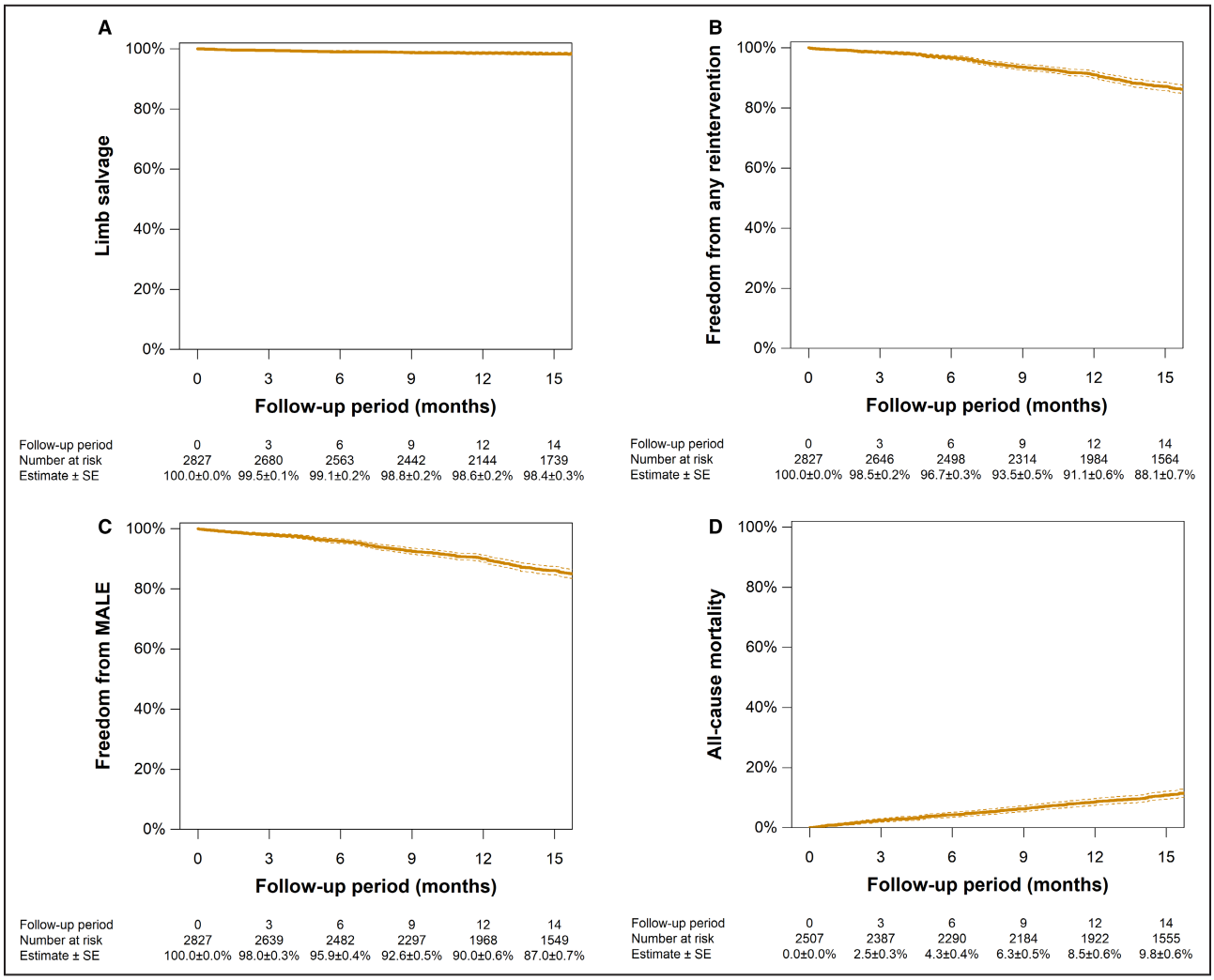


Figure 2. Limb salvage, freedom from any reintervention and MALE, and all-cause mortality.
A, Kaplan–Meier estimates of 1-year limb salvage. **B**, Kaplan–Meier estimates of 1-year freedom from any reintervention. **C**, Kaplan–Meier estimates of 1-year freedom from MALE. **D**, Kaplan–Meier estimates of 1-year all-cause mortality. Dotted lines represent 95% CIs. MALE indicates major adverse limb event (major amputation, bypass conversion, and reintervention).

necessary to investigate the IVUS parameters associated with restenosis risk. In terms of medication, anticoagulant and statin were not significantly associated with a reduced risk of restenosis (Figure S2 and S3).

Low-dose DCB (Lutonix) use in comparison with high-dose DCB (IN.PACT Admiral) use was associated with an increased risk of restenosis (Table 3). Indeed, the 12-month Kaplan–Meier estimate of primary patency was72.7% (69.3% to 76.2%) for Lutonix versus 88.0% (86.7% to 89.4%) for IN.PACT Admiral (P<0.001), and the corresponding estimate of freedom from TLR was 83.8% (81.0% to 86.7%) for Lutonix versus 93.8% (92.8% to 94.8%) for IN.PACT Admiral (P<0.001) (data not shown). The results were similar to the 1-year results of the respective DCB clinical trials conducted in Japan.[28–30] It has been reported that high-dose DCBs are associated with a lower risk of restenosis and TLR.[31,32] The results of the current study would support those findings. Because our study design did not directly compare the 2 types of DCBs, a randomized clinical trial is needed to confirm the results.

The number of patients with severe calcification (peripheral arterial calcium scoring system grade IV) was only 14.6% as compared with 46% in IN. PACT SFA trial.[33] It was considered that the main reason for this was that there is no reimbursement for bailout stent in Japan. Therefore, successful standard percutaneous transluminal angioplasty (<50% of residual stenosis without severe dissection) was needed to avoid stenting. If suboptimal result occurred after percutaneous transluminal angioplasty, the treatment strategy would be changed to stent-first. It is also known that the Japanese population has less incidence of medial calcinosis; the current population was associated with

Table 3. Association of Baseline Characteristics With 1-Year Restenosis Risk

	Unadjusted hazard ratio	Adjusted hazard ratio
Age (per 10 y)	0.88 [0.81–0.97] (*P*=0.008)	0.91 [0.82–1.01] (*P*=0.071)
Male sex	1.05 [0.87–1.25] (*P*=0.62)	1.18 [0.97–1.42] (*P*=0.093)
Nonambulatory	1.46 [1.14–1.86] (*P*=0.003)	1.15 [0.88–1.51] (*P*=0.30)
Smoking	0.97 [0.78–1.20] (*P*=0.76)	0.94 [0.75–1.18] (*P*=0.57)
Diabetes	1.18 [0.98–1.42] (*P*=0.073)	1.07 [0.88–1.30] (*P*=0.48)
CKD		
CKD without dialysis	0.88 [0.71–1.10] (*P*=0.27)	0.92 [0.74–1.16] (*P*=0.49)
CKD on dialysis	1.48 [1.20–1.82] (*P*<0.001)	1.19 [0.93–1.51] (*P*=0.16)
Heart failure	0.98 [0.79–1.23] (*P*=0.89)	0.83 [0.65–1.04] (*P*=0.11)
Aspirin use	0.93 [0.75–1.15] (*P*=0.48)	0.96 [0.75–1.23] (*P*=0.73)
P2Y12 inhibitor use	0.97 [0.74–1.26] (*P*=0.80)	0.99 [0.74–1.33] (*P*=0.96)
Cilostazol use	0.90 [0.73–1.12] (*P*=0.35)	0.87 [0.68–1.11] (*P*=0.26)
Anticoagulant use		
Warfarin use	1.36 [1.02–1.80] (*P*=0.034)	1.21 [0.89–1.63] (*P*=0.22)
Direct oral anticoagulant use	0.86 [0.63–1.17] (*P*=0.33)	0.93 [0.66–1.31] (*P*=0.68)
Statin use	0.93 [0.78–1.10] (*P*=0.39)	0.99 [0.82–1.19] (*P*=0.89)
Rutherford classification	1.27 [1.18–1.38] (*P*<0.001)	1.09 [0.99–1.20] (*P*=0.073)
Aortoiliac lesion	1.12 [0.91–1.37] (*P*=0.27)	1.17 [0.95–1.44] (*P*=0.14)
No below-the-knee runoff	1.63 [1.30–2.04] (*P*<0.001)	1.26 [0.99–1.60] (*P*=0.065)
History of revascularization		
1 EVT	1.28 [1.02–1.60] (*P*=0.035)	1.32 [1.01–1.73] (*P*=0.044)
≥2 EVTs	1.71 [1.33–2.20] (*P*<0.001)	1.70 [1.23–2.34] (*P*=0.001)
In-stent restenosis	1.18 [0.94–1.48] (*P*=0.15)	0.91 [0.66–1.24] (*P*=0.54)
Popliteal lesion	1.53 [1.29–1.82] (*P*<0.001)	1.20 [0.99–1.45] (*P*=0.063)
Reference vessel diameter (per 1 mm)	0.76 [0.69–0.83] (*P*<0.001)	0.87 [0.78–0.97] (*P*=0.012)
Lesion length (per 10 cm)	1.22 [1.12–1.34] (*P*<0.001)	1.09 [0.98–1.22] (*P*=0.098)
Severe calcification	1.63 [1.31–2.02] (*P*<0.001)	1.29 [1.03–1.63] (*P*=0.027)
Chronic total occlusion	1.42 [1.18–1.71] (*P*<0.001)	1.28 [1.04–1.58] (*P*=0.021)
Lutonix use	2.06 [1.69–2.51] (*P*<0.001)	1.97 [1.61–2.41] (*P*<0.001)
Intravascular ultrasound use	0.72 [0.57–0.91] (*P*=0.007)	0.80 [0.64–1.01] (*P*=0.056)
Residual stenosis	1.69 [1.40–2.05] (*P*<0.001)	1.51 [1.24–1.83] (*P*<0.001)
Blood flow after drug-coated balloon (vs no change)		
Slow flow	0.72 [0.38–1.36] (*P*=0.31)	0.63 [0.33–1.19] (*P*=0.16)
No reflow	1.42 [0.66–3.05] (*P*=0.37)	1.55 [0.72–3.35] (*P*=0.26)
Dissection	1.09 [1.02–1.18] (*P*=0.016)	1.04 [0.96–1.13] (*P*=0.29)

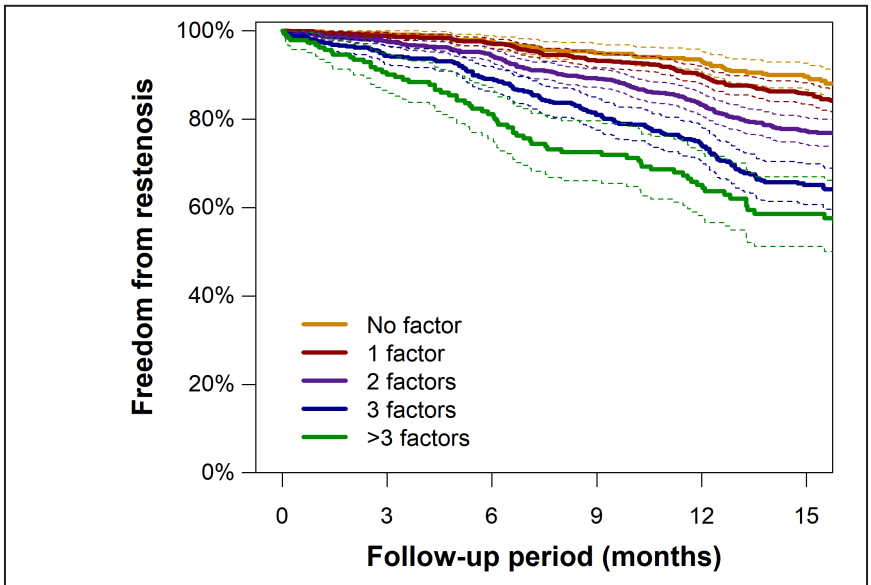
Data are hazard ratios [95% CIs] (*P* values), derived from the Cox mixed-effect model in which the intersubject variability was treated as the random effects. Severe calcification was referred to as peripheral arterial calcium scoring system classification grade 4, whereas severe dissection indicated grade C or more severe. CKD indicates chronic kidney disease; EVT, endovascular therapy; and N/I, not included.

less calcification and good outcomes despite not using atherectomy. As known severe calcification was an independent predictor of restenosis it should be kept in mind that these results cannot be generalized to other populations with a higher degree of vascular calcium.

There was substantial loss to follow-up and 1-year follow-up was 84.9% of patients. All-cause mortality at 1 year in the current study was higher (9.5%) compared with other clinical trials (2.5%–3%).[33,34] However, this study was a real-world clinical study, with older mean age (75±9 years), more diabetes (65.4%), and more chronic kidney disease (69.6%). This may have affected the mortality rate.

Limitations

This study has several limitations that may have affected the clinical outcomes. First, although we enrolled almost all consecutive patients who underwent DCB, we did not enroll patients with unsuccessful predilatation. In addition, bailout stents were not reimbursed and complex lesions that required stenting may have been minimally enrolled.



Follow-up period	0	3	6	9	12	14
Number at risk						
No factor	492	467	445	421	367	292
1 factor	1004	954	900	833	717	565
2 factors	929	859	791	706	578	449
3 factors	520	457	418	361	301	221
>3 factors	190	161	134	114	89	64
Estimate ± SE						
No factor	100.0±0.0%	99.4±0.4%	97.4±0.7%	95.0±1.0%	93.1±1.2%	90.0±1.5%
1 factor	100.0±0.0%	98.9±0.3%	97.1±0.5%	93.2±0.8%	89.9±1.0%	86.3±1.2%
2 factors	100.0±0.0%	97.6±0.5%	94.4±0.8%	89.3±1.1%	83.3±1.3%	78.5±1.5%
3 factors	100.0±0.0%	94.4±1.0%	89.1±1.4%	81.0±1.8%	74.0±2.1%	65.8±2.3%
>3 factors	100.0±0.0%	90.1±2.2%	81.2±3.0%	72.6±3.4%	65.2±3.7%	58.6±4.0%

Figure 3. Prediction of 1-year restenosis risk.
The simple risk score was calculated as the number of accumulated independent risk factors, that is, history of EVT, distal reference vessel diameter <5 mm, severe classification (PACSS classification grade 4), chronic total occlusion, Lutonix use, and residual stenosis (see Table 3). Kaplan–Meier estimates of 1-year primary patency by the simple risk score. Dotted lines represent 95% CIs. EVT indicates endovascular therapy; and PACSS, peripheral arterial calcium scoring system.

This likely introduced selection bias, as this is an underestimation of what would be seen in the US or European practice. Unfortunately, we could not eliminate the selection bias completely. Furthermore, in order to clarify the true effectiveness of DCBs, a contemporary cohort of patients with primary percutaneous transluminal angioplasty in whom the same standards for inclusion into the registry were needed. Second, core laboratories were not used in this study. Although this may compromise the reliability of restenosis and other clinical assessments, participating sites had sufficient experience in clinical trials, and we believe their experience will minimize variability. Finally, only 2 types of DCBs (Lutonix and IN. PACT Admiral) were used in the treatment. It is not clear whether similar results can be obtained with other types of DCBs. Additionally, in this study, freedom from restenosis and its associated factors was selected as the primary end point in contrast to the prior trails. In the 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) trial,[33] the primary outcome was clinically driven TLR, and in the LEVANT 2 (A Prospective, Multicenter Registry of the Lutonix Drug Coated Balloon for Treatment of Femoropopliteal Arteries) trial[34] was primary patency of the target lesion (which included binary restenosis and freedom from TLR). These differences in primary end points among studies are also an important limitation for comparative evaluation.

CONCLUSIONS

Our data demonstrated 1-year freedom from restenosis after DCB therapy for femoropopliteal lesions in a real-world setting. Independent predictors of 1-year restenosis were a history of revascularization, smaller

Table 4. Rutherford Classification and Ankle-Brachial Index at 1 Year Versus Baseline

	Baseline	1 year	*P* value
Rutherford classification			<0.001
Category 0	0.0% [0.0%–0.0%]	46.8% [44.3%–49.2%]	
Category 1	0.0% [0.0%–0.0%]	26.5% [24.5%–28.5%]	
Category 2	25.7% [24.2%–27.2%]	9.6% [8.4%–10.8%]	
Category 3	42.4% [40.7%–44.2%]	5.3% [4.0%–6.5%]	
Category 4	10.7% [9.6%–11.8%]	3.1% [2.0%–4.2%]	
Category 5	21.2% [19.7%–22.6%]	7.8% [6.4%–9.2%]	
Category 6	0.0% [0.0%–0.0%]	1.0% [0.2%–1.7%]	
Mean ankle-brachial index	0.61 [0.60–0.61]	0.85 [0.83–0.87]	<0.001

Data are estimates [95% CIs], derived from the multiple imputation.

distal reference vessel diameter, severe calcification (peripheral arterial calcium scoring system grade 4), Lutonix use (versus IN.PACT Admiral use), and residual stenosis. The presence of these risk factors was associated with a lower rate of freedom from restenosis.

ARTICLE INFORMATION

Received July 22, 2022; accepted October 11, 2022.

Affiliations

Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan (Y.S., Y.T., K.A.); Department of Metabolic Medicine (M.T.); and Department of Diabetes Care Medicine (M.T.), Osaka University Graduate School of Medicine, Suita, Japan; Kansai Rosai Hospital, Cardiovascular Center, Amagasaki, Japan (O.I.); Department of Cardiology, Morinomiya Hospital, Osaka, Japan (D.K.); Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan (A.T.); Cardiovascular Center, Takatsu General Hospital, Kawasaki, Japan (Y.Y.); Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Japan (K.T.); Division of Cardiology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan (A.K.); Department of Cardiology, Kishiwada Tokushukai Hospital, Kishiwada, Japan (M.F.).

Sources of Funding

The POPCORN study was supported by the Research Association for Lower Limb Artery Revascularization (LIBERAL).

Disclosures

Drs Soga, Iida, Kawasaki, and Kozuki received honoraria from BARD Japan and Medtronic Japan. Drs Tobita, Dr Fujihara, and Ando received honoraria from Medtronic Japan. Dr Tanaka received honoraria from BARD Japan. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Figures S1–S3

REFERENCES

1. Soga Y, Iida O, Hirano K, Yokoi H, Nanto S, Nobuyoshi M. Mid-term clinical outcome and predictors of vessel patency after femoropopliteal stenting with self-expandable nitinol stent. *J Vasc Surg*. 2010;52:608–615. doi: 10.1016/j.jvs.2010.03.050
2. Schneider PA, Laird JR, Tepe G, Brodmann M, Zeller T, Scheinert D, Metzger C, Micari A, Sachar R, Jaff MR, et al. Treatment effect of drug-coated balloons is durable to 3 years in the femoropopliteal arteries: long-term results of the IN.PACT SFA Randomized Trial. *Circ Cardiovasc Interv*. 2018;11:e005891. doi: 10.1161/CIRCINTERVENTIONS.117.005891
3. Micari A, Brodmann M, Keirse K, Peeters P, Tepe G, Frost M, Wang H, Zeller T; IN.PACT Global Study Investigators. Drug-coated balloon treatment of femoropopliteal lesions for patients with intermittent claudication and ischemic rest pain: 2-year results from the IN.PACT Global Study. *JACC Cardiovasc Interv*. 2018;11:945–953. doi: 10.1016/j.jcin.2018.02.019
4. Shishehbor MH, Schneider PA, Zeller T, Razavi MK, Laird JR, Wang H, Tieché C, Parikh SA, Iida O, Jaff MR. Total IN.PACT drug-coated balloon initiative reporting pooled imaging and propensity-matched cohorts. *J Vasc Surg*. 2019;70:1177–1191. doi: 10.1016/j.jvs.2019.02.030
5. Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y, Schroeder H, Prem JT, Holden A, Popma J, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018;392:1541–1551. doi: 10.1016/S0140-6736(18)32262-1
6. Müller-Hülsbeck S, Benko A, Soga Y, Fujihara M, Iida O, Babaev A, O'Connor D, Zeller T, Dulas DD, Diaz-Cartelle J, et al. Two-year efficacy and safety results from the IMPERIAL Randomized Study of the eluvia polymer-coated drug-eluting stent and the zilver PTX polymer-free drug-coated stent. *Cardiovasc Intervent Radiol*. 2021;44:368–375. doi: 10.1007/s00270-020-02693-1
7. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Machan LS, Snyder SA, O'Leary EE, Ragheb AO, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation*. 2016;133:1472–1483. doi: 10.1161/CIRCULATIONAHA.115.016900
8. Scheinert D, Scheinert S, Sax J, Piorkowski C, Bräunlich S, Ulrich M, Biamino G, Schmidt A. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. *J Am Coll Cardiol*. 2005;45:312–315. doi: 10.1016/j.jacc.2004.11.026
9. Schlager O, Dick P, Sabeti S, Amighi J, Mlekusch W, Minar E, Schillinger M. Long-segment SFA stenting–the dark sides: in-stent restenosis, clinical deterioration, and stent fractures. *J Endovasc Ther*. 2005;12:676–684. doi: 10.1583/05-1672.1
10. Bisdas T, Beropoulis E, Argyriou A, Torsello G, Stavroulakis K. 1-year all-comers analysis of the eluvia drug-eluting stent for long femoropopliteal lesions after suboptimal angioplasty. *JACC Cardiovasc Interv*. 2018;11:957–966. doi: 10.1016/j.jcin.2018.03.046
11. Steiner S, Schmidt A, Zeller T, Tepe G, Thieme M, Maiwald L, Schröder H, Euringer W, Ulrich M, Brechtel K, et al. COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions. *Eur Heart J*. 2020;41:2541–2552. doi: 10.1093/eurheartj/ehaa049
12. Mittleider D, Russell E. Peripheral atherectomy: applications and techniques. *Tech Vasc Interv Radiol*. 2016;19:123–135. doi: 10.1053/j.tvir.2016.04.005
13. Zeller T, Langhoff R, Rocha-Singh KJ, Jaff MR, Blessing E, Amann-Vesti B, Krzanowski M, Peeters P, Scheinert D, Torsello G, et al. Directional atherectomy followed by a paclitaxel-coated balloon to inhibit restenosis and maintain vessel patency: twelve-month results of the DEFINITIVE AR Study. *Circ Cardiovasc Interv*. 2017;10:e004848. doi: 10.1161/CIRCINTERVENTIONS.116.004848
14. Patel MR, Conte MS, Cutlip DE, Dib N, Geraghty P, Gray W, Hiatt WR, Ho M, Ikeda K, Ikeno F, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC). *J Am Coll Cardiol*. 2015;65:931–941. doi: 10.1016/j.jacc.2014.12.036
15. Fujihara M, Takahara M, Sasaki S, Nanto K, Utsunomiya M, Iida O, Yokoi Y. Angiographic dissection patterns and patency outcomes after balloon angioplasty for superficial femoral artery disease. *J Endovasc Ther*. 2017;24:367–375. doi: 10.1177/1526602817698634
16. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;43:S1–S67. doi: 10.1016/j.jvs.2006.12.037
17. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv*. 2014;83:E212–E220. doi: 10.1002/ccd.25387
18. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics*. 2000;56:337–344. doi: 10.1111/j.0006-341X.2000.00337.x
19. Tosaka A, Soga Y, Iida O, Ishihara T, Hirano K, Suzuki K, Yokoi H, Nanto S, Nobuyoshi M. Classification and clinical impact of restenosis

after femoropopliteal stenting. *J Am Coll Cardiol*. 2012;59:16–23. doi: 10.1016/j.jacc.2011.09.036
20. Fanelli F, Cannavale A, Gazzetti M, Lucatelli P, Wlderk A, Cirelli C, d'Adamo A, Salvatori FM. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. *Cardiovasc Intervent Radiol*. 2014;37:898–907. doi: 10.1007/s00270-014-0904-3
21. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G; VIVA Physicians, Inc. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. *Catheter Cardiovasc Interv*. 2007;69:910–919. doi: 10.1002/ccd.21104
22. Iida O, Takahara M, Soga Y, Yamaoka T, Fujihara M, Kawasaki D, Ichihashi S, Kozuki A, Nanto S, Sakata Y, et al. 1-Year outcomes of fluoropolymer-based drug-eluting stent in femoropopliteal practice: predictors of restenosis and aneurysmal degeneration. *JACC Cardiovasc Interv*. 2022;15:630–638. doi: 10.1016/j.jcin.2022.01.019
23. Dinh K, Singla A, Masuda H, Nguyen D. Multiple superficial femoral artery pseudoanurysms following sub intimal application of paclitaxel coated technology. *Radiol Case Rep*. 2021;16:3628–3630. doi: 10.1016/j.radcr.2021.08.073
24. Golouh V, Kobilica N, Breznik S. Superficial femoral artery pseudoaneurysm and arterial wall destruction after drug-coated balloon treatment. *Cureus*. 2020;12:e10527. doi: 10.7759/cureus.10527
25. Iida O, Takahara M, Soga Y, Fujihara M, Kawasaki D, Hirano K, Choi D, Mano T. Vessel diameter evaluated by intravascular ultrasound versus angiography. *J Endovasc Ther*. 2022;29:343–349. doi: 10.1177/15266028211047946
26. Allan RB, Puckridge PJ, Spark JI, Delaney CL. The impact of intravascular ultrasound on femoropopliteal artery endovascular interventions: a randomized controlled trial. *JACC Cardiovasc Interv*. 2022;15:536–546. doi: 10.1016/j.jcin.2022.01.001
27. Horie K, Tanaka A, Taguri M, Inoue N. Impact of baseline and post-procedural intravascular ultrasound findings on 1-year primary patency after drug-coated balloon treatment of femoropopliteal lesions. *J Endovasc Ther*. 2022;29:66–75. doi: 10.1177/15266028211058683
28. Iida O, Soga Y, Urasawa K, Saito S, Jaff MR, Wang H, Ookubo H, Yokoi H; MDT-2113 SFA Japan Investigators. Drug-coated balloon vs standard percutaneous transluminal angioplasty for the treatment of atherosclerotic lesions in the superficial femoral and proximal popliteal arteries: one-year results of the MDT-2113 SFA japan randomized trial. *J Endovasc Ther*. 2018;25:109–117. doi: 10.1177/1526602817745565
29. Soga Y, Iida O, Fujihara M, Kawasaki D, Saito S, Urasawa K, Yokoi H, Fernandez EJ, Guo J, Nakamura M, et al. real-world clinical outcomes of IN.PACT admiral drug-coated balloon for femoropopliteal artery disease - 12-month results from Japan Post-Market Surveillance Study. *Circ J*. 2021;85:2149–2156. doi: 10.1253/circj.CJ-21-0491
30. PMDA. http://www.pmda.go.jp/medical_devices/2017/M20170830001/780045000_22900BZX00252000_A100_1.pdf. Accessed May 2018.
31. Cassese S, Ndrepepa G, Fusaro M, Kufner S, Xhepa E, Fusaro M. Paclitaxel density and clinical efficacy of drug-coated balloon angioplasty for femoropopliteal artery disease: meta-analysis and adjusted indirect comparison of 20 randomised trials. *EuroIntervention*. 2019;15:e560–e562. doi: 10.4244/EIJ-D-18-00550
32. Katsanos K, Spiliopoulos S, Paraskevopoulos I, Diamantopoulos A, Karnabatidis D. Systematic review and meta-analysis of randomized controlled trials of paclitaxel-coated balloon angioplasty in the femoropopliteal arteries: role of paclitaxel dose and bioavailability. *J Endovasc Ther*. 2016;23:356–370. doi: 10.1177/1526602815626557
33. Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, Metzger C, Scheinert D, Zeller T, Cohen DJ, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131:495–502. doi: 10.1161/CIRCULATIONAHA.114.011004
34. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, Brodmann M, Pilger E, Zeller T, Krishnan P, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med*. 2015;373:145–153. doi: 10.1056/NEJMoa1406235

Supplemental Material

Data S1.

POPCORN Participating Centers and Investigators:

Aomori Prefectural Central Hospital: Motoi Kushibki

Asahi General Hospital: Naoki Hayakawa

Chikamori Hospital: Shuichi Seki

Fujimoto General Hospital: Hideaki Otsuji

Fukuoka University Hospital: Makoto Sugihara

Fukuoka Wajiro Hospital: Yuki Imoto

Fukuyama Cardiovascular Hospital: Masato Taniguchi

Fukuyama City Hospital: Yasunori Arai

Funabashi Municipal Medical Center: Yo Iwata

Gifu Prefectural General Medical Center: Tai Kojima

Hakodate Municipal Hospital: Tsuyoshi Shibata

Hoshi General Hospital: Yoshitane Seino

Ichinomiyanishi Hospital: Kei Ichihashi

JCHO Hitoyoshi Medical Center: Hirofumi Kurokawa

JCHO Kobe Central Hospital: Toru Mazaki

JCHO Kumamoto General Hospital: Takashi Uemura

Japanese Red Cross Society Kyoto Daini Hospital: Yoshinori Tsubakimoto

Japanese Red Cross Society Nagano Hospital: Yusuke Miyashita

Jichi Medical Unicersity: Yukako Ogoyama

JR Sapporo Hospital: Toru Hasegawa

Juntendo University Graduate School of Medicine: Shinya Okazaki

Kasukabe Central General Hospital: Nobuhito Kaneko

Kanazawa Medical University Hospital: Taketsugu Tsuchiya

Kawaguchi Cardiovascular and Respiratory Hospital: Hideo Tokuyama

Kawakita General Hospital: Atsushi Tosaka

Kansai Rosai Hospital: Osamu Iida, Taku Toyoshima

Kitano Hospital: Yuhei Yamaji

Kishiwada Tokushukai Hospital: Masahiko Fujihara

Kokura Memorial Hospital: Yoshimitsu Soga, Yusuke Tomoi

Kumamoto Rosai Hospital: Hideki Doi

Kumamoto Red Cross Hospital: Tomokazu Ikemoto

Kurashiki Central Hospital: Takenobu Shimada, Hiroyuki Tanaka

Kyoto University Hospital: Yasuaki Takeji

Matsunami General Hospital: Hiroki Kondo

Matsuyama Red Cross Hospital: Terutoshi Yamaoka

Mito kyodo Hospital: Eiji Kojima

Miyazaki Medical Association Hospital: Kenji Ogata

Morinomiya Hospital: Daizo Kawasaki

Nagano Municipal Hospital: Takashi Miura, Tomoaki Mochidome

National Hospital Organization Kagoshima Medical Center: Kensaku Higashi

New Tokyo Hospital: Koji Hozawa

Nihonkai General Hospital: Koki Ohmi

Oita Oka Hospital: Toshinobu Ishikawa

Oji General Hospital: Nobuo Kato, Takahito Itoh

Okayama University: Hironobu Toda

Okinawa Chubu Hospital: Jun Nakazato

Omihachiman Community Medical center: Kuniyoshi Fukai

Osaka Red Cross Hospital: Yohei Kobayashi

Osaka University Graduate School of Medicine: Tatsuya Shiraki

Osaka Saiseikai Nakatsu Hospital: Amane Kozuki

Rakuwakai Otowa Hospital: Taku Kato

Saga Prefectural Hospital Koseikan: Yunosuke Nishihara

Saiseikai Fukuoka General Hospital: Nobuhiro Suematsu

Saiseikai Kumamoto Hospital: Eiji Taguchi

Saiseikai Yokohama City Eastern Hospital: Shinsuke Mori

Saka General Hospital: Shinya Sasaki

Sapporo Cardio Vascular Clinic: Takuya Haraguchi

Shimonoseki City Hospital: Eiji Karashima

Shonan Kamakura General Hospital: Kazuki Tobita

Showa University School of Medicine: Hiroaki Tsujita

Shin Koga Hospital: Kazuki Haraguchi

Shinshu University School of Medicine: Tamon Kato

Sendai Kousei Hospital: Akiko Tanaka

Sunagawa City Medical Center: Norihiro Shimizu

Takai Hospital: Seiji Matsuhisa

Takatsu General Hospital: Yasutaka Yamauchi

Tenri Hospital: Soichiro Enomoto

Tenyokai Central Hospital: Junichiro Takaoka, Tatsuro Takei

Toho University Ohashi Medical Center: Makoto Utsunomiya

Tokushima Red Cross Hospital: Kenichiro Yuba

Tokyo Saiseikai Central Hospital: Kenji Suzuki

Tokyo Bay Urayasu Ichikawa Medical Center: Tatsuya Nakama

Tokyo Medical University: Naotaka Murata

Tokeidai Memorial Hospital: Michinao Tan

Tomishiro Central Hospital: Tomohiro Arakaki

Toyohashi Heart Center: Ryoji koshida

Tsukuba Medical Center Hospital: Hideaki Aihara

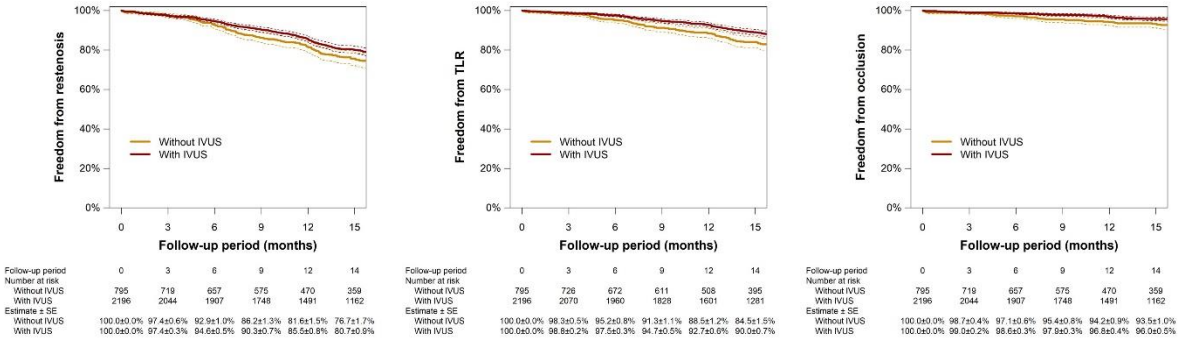
Urasoe General Hospital: Tomoyuki Kawashima

Yamagata Prefectural Central Hospital: Hyuuma Daidouji

Yamagata University: Hiroki Takahashi, Taku Shikama

Yamato Seiwa Hospital: Tatsuki Doijiri

Figure S1. Kaplan-Meier estimates of freedom from restenosis, TLR and occlusion with and without IVUS.



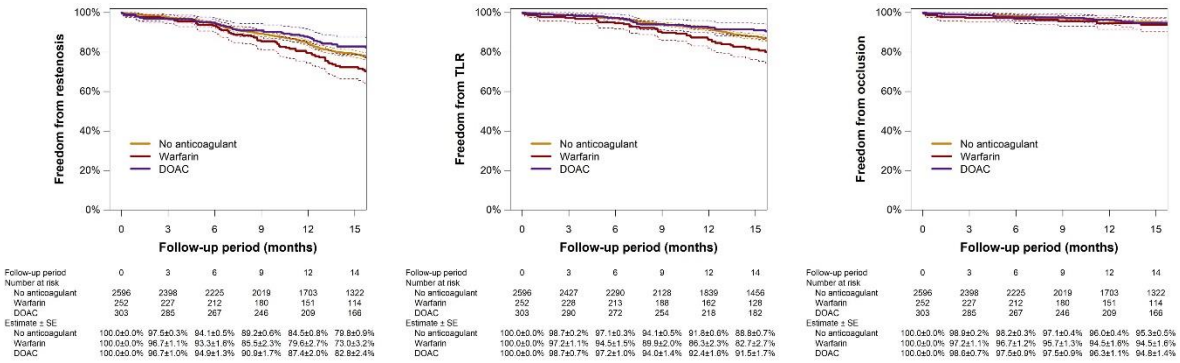
Follow-up period	0	3	6	9	12	14
Number at risk						
Without IVUS	795	719	657	575	470	359
With IVUS	2196	2044	1907	1748	1491	1162
Estimate ± SE						
Without IVUS	100.0±0.0%	97.4±0.6%	92.9±1.0%	86.2±1.3%	81.6±1.5%	76.7±1.7%
With IVUS	100.0±0.0%	97.4±0.3%	94.6±0.5%	90.3±0.7%	85.5±0.8%	80.7±0.9%

Follow-up period	0	3	6	9	12	14
Number at risk						
Without IVUS	795	726	672	611	508	395
With IVUS	2196	2070	1960	1828	1601	1281
Estimate ± SE						
Without IVUS	100.0±0.0%	98.3±0.5%	95.2±0.8%	91.3±1.1%	88.5±1.2%	84.5±1.5%
With IVUS	100.0±0.0%	98.8±0.2%	97.5±0.3%	94.7±0.5%	92.7±0.6%	90.0±0.7%

Follow-up period	0	3	6	9	12	14
Number at risk						
Without IVUS	795	719	657	575	470	359
With IVUS	2196	2044	1907	1748	1491	1162
Estimate ± SE						
Without IVUS	100.0±0.0%	98.7±0.4%	97.1±0.6%	95.4±0.8%	94.2±0.9%	93.5±1.0%
With IVUS	100.0±0.0%	99.0±0.2%	98.6±0.3%	97.9±0.3%	96.8±0.4%	96.0±0.5%

TLR; target lesion revascularization, IVUS; intravascular ultrasound

Figure S2. Kaplan-Meier estimates of freedom from restenosis, TLR and occlusion among no anticoagulant, warfarin and DOAC.



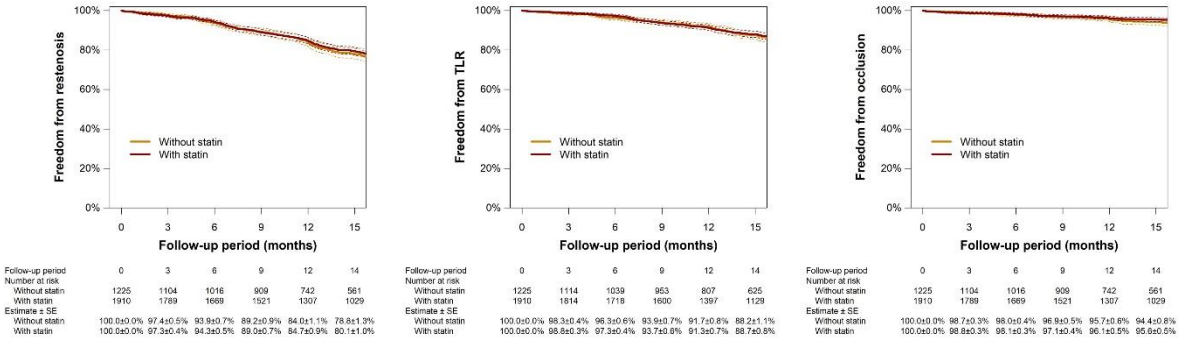
Follow-up period	0	3	6	9	12	14
Number at risk						
No anticoagulant	2596	2398	2225	2019	1703	1322
Warfarin	252	227	212	180	151	114
DOAC	303	285	267	246	209	166
Estimate ± SE						
No anticoagulant	100.0±0.0%	97.5±0.3%	94.1±0.5%	89.2±0.6%	84.5±0.8%	79.8±0.9%
Warfarin	100.0±0.0%	96.7±1.1%	93.3±1.8%	85.5±2.3%	79.6±2.7%	73.0±3.2%
DOAC	100.0±0.0%	96.7±1.0%	94.9±1.3%	90.9±1.7%	87.4±2.0%	82.8±2.4%

Follow-up period	0	3	6	9	12	14
Number at risk						
No anticoagulant	2596	2427	2290	2128	1839	1456
Warfarin	252	228	213	188	162	128
DOAC	303	290	272	254	218	182
Estimate ± SE						
No anticoagulant	100.0±0.0%	98.7±0.2%	97.1±0.3%	94.1±0.5%	91.8±0.6%	88.8±0.7%
Warfarin	100.0±0.0%	97.2±1.1%	94.5±1.5%	89.9±2.0%	86.3±2.3%	82.7±2.7%
DOAC	100.0±0.0%	98.7±0.7%	97.2±1.0%	94.0±1.4%	92.4±1.6%	91.5±1.7%

Follow-up period	0	3	6	9	12	14
Number at risk						
No anticoagulant	2596	2398	2225	2019	1703	1322
Warfarin	252	227	212	180	151	114
DOAC	303	285	267	246	209	166
Estimate ± SE						
No anticoagulant	100.0±0.0%	98.9±0.2%	98.2±0.3%	97.1±0.4%	96.0±0.4%	95.3±0.5%
Warfarin	100.0±0.0%	97.2±1.1%	96.7±1.2%	95.7±1.3%	94.5±1.6%	94.5±1.6%
DOAC	100.0±0.0%	98.8±0.7%	97.5±0.9%	97.5±0.9%	96.3±1.1%	94.8±1.4%

TLR; target lesion revascularization, , DOAC; direct oral anticoagulant

Figure S3. Kaplan-Meier estimates of freedom from restenosis, TLR and occlusion with and without statin.



Follow-up period	0	3	6	9	12	14
Number at risk						
Without statin	1225	1104	1016	909	742	561
With statin	1910	1789	1669	1521	1307	1029
Estimate ± SE						
Without statin	100.0±0.0%	97.4±0.5%	93.9±0.7%	89.2±0.9%	84.0±1.1%	78.8±1.3%
With statin	100.0±0.0%	97.3±0.4%	94.3±0.5%	89.0±0.7%	84.7±0.9%	80.1±1.0%

Follow-up period	0	3	6	9	12	14
Number at risk						
Without statin	1225	1114	1039	953	807	625
With statin	1910	1814	1718	1600	1397	1129
Estimate ± SE						
Without statin	100.0±0.0%	98.3±0.4%	96.3±0.6%	93.9±0.7%	91.7±0.8%	88.2±1.1%
With statin	100.0±0.0%	98.8±0.3%	97.3±0.4%	93.7±0.8%	91.3±0.7%	88.7±0.8%

Follow-up period	0	3	6	9	12	14
Number at risk						
Without statin	1225	1104	1016	909	742	561
With statin	1910	1789	1669	1521	1307	1029
Estimate ± SE						
Without statin	100.0±0.0%	98.7±0.3%	98.0±0.4%	96.9±0.5%	95.7±0.6%	94.4±0.8%
With statin	100.0±0.0%	98.8±0.3%	98.1±0.3%	97.1±0.4%	96.1±0.5%	95.6±0.5%

TLR; target lesion revascularization