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Peripheral Arterial Occlusive Disease

Feasibility and Mid-Term Outcomes of Drug-Coated Balloon Angioplasty Between Intermittent Claudication and Critical Limb Ischemia in Patients with Femoropopliteal Disease

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Background: The efficacy of drug-coated balloons (DCBs) in critical limb ischemia (CLI) is unclear. To investigate the clinical characteristics and outcomes of DCBs in symptomatic femoropopliteal disease between patients with intermittent claudication (IC) and CLI.

Methods: Data were retrospectively collected from three centers in Taiwan on patients who received DCBs for femoropopliteal lesions between March 2013 and June 2017. We compared the clinical characteristics and outcomes regarding binary restenosis, amputation-free survival (AFS), and major adverse limb events (MALEs) between groups. Cox proportional hazards analysis was used to identify predictors of outcome endpoints.

Results: We enrolled a total of 200 affected limbs in 174 patients, including 83 limbs in 71 patients with IC and 117 limbs in 103 patients with CLI. Compared to the patients with claudication, those with CLI were older and had higher proportions of medical comorbidities, tissue inflammation, poor runoff, and vessel calcification. The 3-year rates of freedom from binary restenosis (57% vs. 59%, p = 0.781), and MALEs (77% vs. 67%, p = 0.507) were similar between the two groups. However, the 3-year AFS was significantly higher in the IC group compared to the CLI group (91% vs. 73%, p = 0.001). Lesion length and severe calcification independently predicted binary restenosis, and restenotic lesion predicted MALEs. Age, congestive heart failure, and dialysis were independently associated with AFS.

Conclusions: Despite advanced limb ischemia and comorbidities, the mid-term outcomes in surviving CLI patients were similar to those in the IC patients after treatment with DCBs for femoropopliteal disease.

Key Words: Amputation-free survival • Binary restenosis • Critical limb ischemia • Drug-coated balloon • Major adverse limb event

INTRODUCTION

Peripheral artery disease (PAD) affects up to 200 million people worldwide,[1] and is associated with significant morbidity and mortality.[2,3] Critical limb ischemia (CLI), an advanced form of low extremity arterial disease, presents with ischemic resting pain and tissue loss. It is important because of the higher risk of limb loss and cardiovascular events than asymptomatic and intermittent claudication (IC).[2,4]

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Recent advances in devices and techniques has led to EVT becoming the treatment of choice for PAD of variable severity.[5] EVT has been shown to reduce limb pain, improve quality of life, and prolong walking distance of those with claudication, and it has been associated with reduced amputation rates among those with CLI.[6-10] Proof-of-concept evidence has demonstrated that the use of drug-coated balloons (DCBs) results in low rates of restenosis and repeated EVT in comparison with uncoated balloon angioplasty.[11-14] Although DCBs have gained significant momentum in treating femoropopliteal segments, most trials have focused on claudicants with short, not severely calcified lesions. However, such anatomical disease is uncommonin real-world CLI populations, and thus the performance of DCBs may not be robust when used in CLI patients. This study aimed to compare the clinical characteristics and mid-term clinical outcomes of DCBs between IC and CLI patients over a 60-month follow-up period.

METHODS

Study population

The main subjects for this study were derived from the Tzuchi Registry of ENDovascular Intervention for Peripheral Artery Disease (TRENDPAD), which is an ongoing, prospective, physician-initiated, single-center observational registry of patients who have undergone EVT for lower limb ischemia since July 2005. A total of 177 legs in 151 patients who underwent DCB angioplasty for symptomatic femoropopliteal disease between March 2013 and June 2017 were identified. We also recruited 12 patients from Tainan Municipal Hospital and 11 from Chang Gang Memorial Hospital from June 2013 to January 2017. The angiographic inclusion criteria were de novo, restenotic and in-stent stenotic or occlusive femoropopliteal lesions. Concomitant interventions for iliac or tibial lesions were allowed in the study patients. After EVT, the patients were required to have either preexisting or re-established adequate runoff vessels with evidence of at least one patent crural vessel to the foot.

The exclusion criteria were acute or subacute thrombotic occlusions, prior use of a drug-eluting stent or covered stent, prior bypass graft anastomotic lesions, contraindications for aspirin or clopidogrel, life-threatening infections, and a follow-up duration < 3 months in the surviving patients. The flowchart of study enrollment is shown in Figure 1. We obtained informed consent from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the human research committee of each participating institution (06-X17-067).

The pre-interventional study included a clinical examination, hemodynamic evaluation (ankle or toe pressure, pulse volume recording, and duplex ultrasound), and anatomic assessments including computed tomographic angiography, magnetic resonance angiography, or diagnostic angiography. Toe pressures, pulse volume recording, and Doppler waveform patterns were obtained to measure hemodynamic changes in the patients with falsely elevated ankle-brachial index (ABI) values.

Interventional procedure

The EVT strategy depended on the treating physicians. Three kinds of paclitaxel-coated balloons were used in this study, including 340 IN.PACT Admiral (3.5 $\mu g/mm^2$, Medtronic Ireland, Galway, Ireland), 14 Lutonix (2 $\mu g/mm^2$, Bard, Wexford, Ireland), and 32 Ranger^{TM} (2 $\mu g/mm^2$, Boston, Wűrselen, Germany) balloons. The details of the interventional procedures have been described previously.[15,16] We implanted bare metal stents (BMSs) in cases of suboptimal angiographic results or flow-limiting dissections after treatment with the DCBs, which was determined by residual diameter stenosis (DS) > 50%, and translesion pressure gradient $\geq$ 10 mmHg.

Quantitative angiograms were acquired in at least two orthogonal views at baseline and after the intervention. A radiopaque ruler was used to calibrate angiographic measurements, including the length and minimal luminal diameter (MLD) of the target lesion and the mean proximal and distal reference vessel diameters (RVDs). Percent DS was calculated [%DS = (1 – MLD/RVD) $\times$ 100] at baseline and after EVT. Dual antiplatelet therapy with aspirin 100 mg and clopidogrel 300 mg was recommended before EVT and continued for three months after the use of a DCB. Antiplatelet therapy and anticoagulant regimens were used according to the physician's discretion based on the patient's condition.

Definitions

Binary restenosis was defined as DS > 50% by angio-

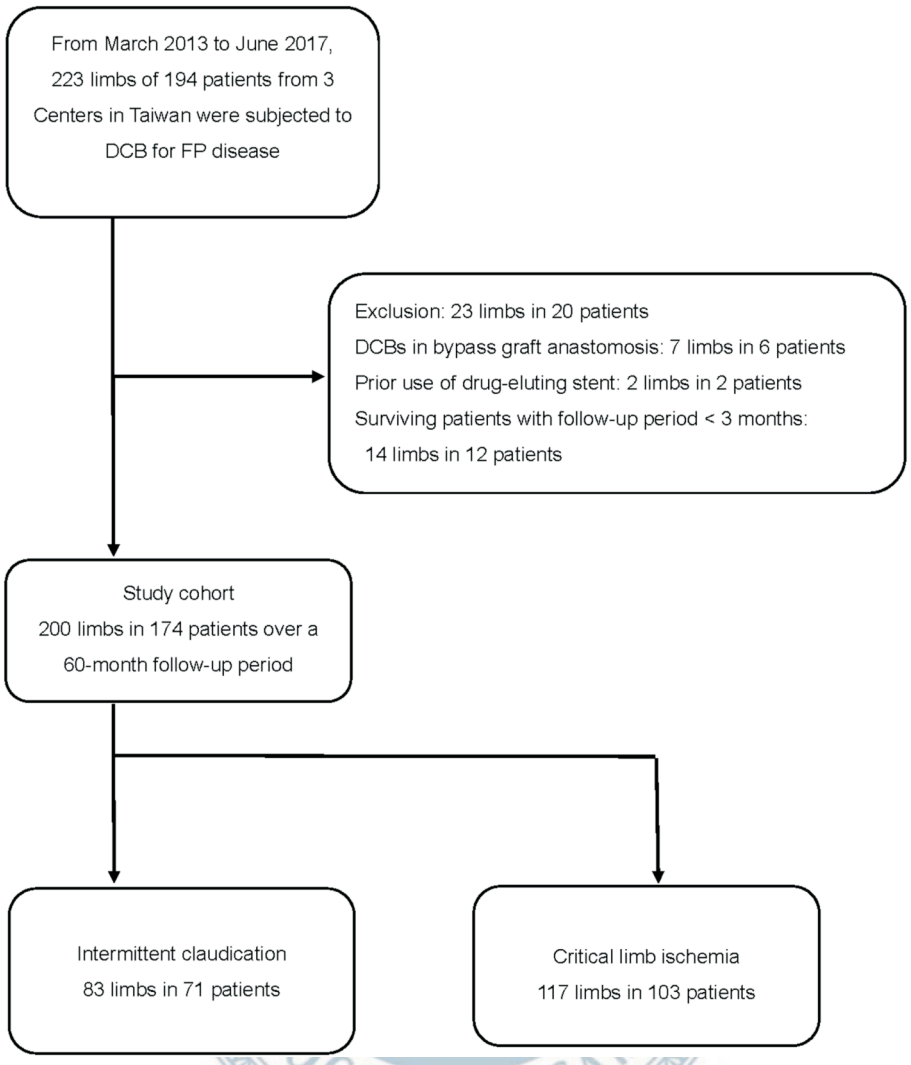


Figure 1. *Flow chart of study participants. DCB, drug-coated balloon; FP, femoropopliteal.*

graphy or peak systolic velocity ratio ≥ 2.4, which were determined by duplex ultrasound. We defined lumen gain as the change in MLD at each vessel before and after EVT. The severity of vessel calcification was graded according to the peripheral artery calcification scoring system.[16] Clinically driven target lesion revascularization was defined as a reintervention performed for > 50% DS within 5 mm of the target lesion after the documentation of recurrent clinical symptoms after the index procedure. Risk stratification was based on female sex, dialysis, CLI, lesion length (LL) > 150 mm, and poor runoff (FeDCLIP) score, which has been shown to be useful in stratifying vessel patency and the risk of mortality after superficial femoral artery EVT.[17] Amputation-free survival (AFS) was defined as freedom from all-cause deaths and above-the-ankle amputation of treated limbs. Major adverse limb events (MALEs) were defined as recurrent symptoms requiring endovascular or surgical revascularization and major amputation. The primary endpoint was binary restenosis, and the secondary endpoints were AFS and MALEs.

Patient follow-up

Vessel patency after EVT was regularly assessed during the follow-up period with clinical examinations and noninvasive studies, including ankle or toe brachial pressure index and duplex ultrasound at one week, one month, and every three months thereafter. The indication for a reintervention was clinically driven, and asymptomatic patients with DCB restenosis or reocclusion did

not undergo repeat revascularization. The main events (death, amputation, any endovascular or surgical revascularization, or other vascular events) were documented at discharge and during follow-up visits. The alternate data sources used when office follow-up was not feasible were telephone interviews, data from medical records, local electronic medical databases, and referring physicians. We used the follow-up index to examine the completeness of follow-up and reduce vulnerability to attrition bias as previously reported.[18]

Statistical analysis

We used SPSS statistical package for Windows version 21.0 (SPSS, Chicago, IL, USA) for all statistical analyses. Descriptive statistics were listed as a mean ± standard deviation for continuous variables and frequency (percent) for categorical variables. Discrete and categorical data were analyzed using the Pearson chi-square test. Parametric continuous variables were statistically analyzed between groups using the independent *t*-test, whereas the Mann-Whitney U test was used to analyze non-parametric continuous and ordinal data. Complete blood cell and differential counts, and level of C-reactive protein (CRP) are presented as median and interquartile range, and were logarithmically transformed before statistical analysis. Kaplan-Meier survival curves were used to determine the rates of AFS, freedom from binary restenosis, and MALEs after a reintervention and compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards model, entering clinically and anatomically relevant variables to identify the independent predictors associated with the endpoints. The variables with a p-value of < 0.25 in the univariate analysis and variables that were considered to be clinically significant were assessed in the multivariate analysis, including sex, body mass index, diabetes mellitus, coronary artery disease, dialysis dependence, vessel calcification, chronic total occlusion, lesion type, LL, lumen gain of the popliteal artery and laboratory data. A p value < 0.05 was considered to be statistically significant.

RESULTS

Baseline demographics

Table 1 summarizes the baseline demographics of the study participants. Compared to the IC group, the CLI group were older and had lower proportions of hyperlipidemia and thin stature as well as higher proportions of cerebrovascular disease and dialysis. Regarding the laboratory data and medications, the CLI patients had more tissue inflammation including higher white cell and platelet counts, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and CRP, lower levels of hemoglobin and serum albumin, and less use of statins. The follow-up index in this study cohort was 0.95 ± 0.17, and there was no significant difference between the IC and CLI groups (0.97 ± 0.13 vs. 0.94 ± 0.18, p = 0.285).

Lesion characteristics of treated limbs

Table 2 shows comparisons of lesion characteristics of the treated limbs between groups. The level of ABI after excluding non-compressible arteries was lower in the treated limbs in the CLI group compared to the IC group (0.48 ± 0.15 vs. 0.57 ± 0.15, p < 0.001). We found more complex lesions in the CLI group regarding poor runoff (p = 0.001), severe vessel calcification (p = 0.002), concomitant BTK intervention (p = 0.020) and number of atherectomy devices used (p = 0.014). The mean LL was similar between the two groups (224 ± 114 vs. 206 ± 117 mm, p = 0.292), as well as proportions of lesion type, bailout stent, use of intravascular ultrasound and length of the DCB. The RVD, final MLD, lumen gain of superficial femoral and popliteal arteries and final balloon diameters were also similar between the two groups. However, the IC group had a higher proportion of lower-risk patients as stratified by FeDCLIP score compared to the CLI group (52% vs. 18%, p < 0.001). The median time to DCB restenosis and follow-up index were not significantly different between the IC and CLI groups (433 vs. 413 days, p = 0.664 and 0.96 ± 0.17 vs. 0.95 ± 0.17, p = 0.685, respectively).

Follow-up outcomes

Over a maximum 60-month follow-up period (median 883 days), 33 (4 IC and 29 CLI) patients died, and 3 (1 IC and 2 CLI) patients underwent major amputations. Accordingly, the 3-year AFS in the CLI group was significantly lower than that in the IC group (73% vs. 91%, p = 0.001) (Figure 2). Sixty-six treated limbs developed restenosis after treatment with DCBs. Of them, 45 under-

Table 1. Baseline patient and lesion characteristics

	Claudicants	Critical limb ischemia	p value
No. of patients	71	103	
Age (years)	69 ± 12	73 ± 11	0.022
Gender (male)	42 (59%)	56 (54%)	0.532
Diabetes mellitus	58 (82%)	79 (77%)	0.429
Hypertension	63 (89%)	87 (85%)	0.422
CAD	38 (54%)	55 (53%)	0.987
CVD	7 (10%)	22 (21%)	0.045
CKD	26 (37%)	38 (37%)	0.971
Dialysis	16 (23%)	39 (38%)	0.033
CHF	10 (14%)	23 (22%)	0.173
Atrial fibrillation	5 (7%)	17 (17%)	0.065
Smoking	32 (45%)	39 (38%)	0.342
Hyperlipidemia	56 (79%)	51 (50%)	< 0.001
BMI (kg/m^2)	24.0 ± 2.89	23.1 ± 3.29	0.047
Hematocrit (%)	36.7 (32.7, 41.2)	33.7 (29.4, 37.5)	< 0.001
WBC ($10^3/\mu l$)	6.98 (5.52, 8.70)	7.99 (6.35, 10.0)	0.004
Platelet count ($10^3/\mu l$)	205 (156, 249)	253 (186, 301)	< 0.001
NLR	2.60 (2.02, 3.92)	3.99 (2.63, 5.21)	< 0.001
PLR	112 (83, 177)	161 (119, 244)	< 0.001
CRP (mg/dL)	0.24 (0.12, 0.72)	1.17 (0.39, 5.52)	< 0.001
HbA1C (%)	7.45 ± 1.77	7.19 ± 1.93	0.372
LDL-C (mg/dL)	98 ± 30	98 ± 36	0.964
Albumin (mg/dL)	3.55 ± 0.50	2.98 ± 0.65	< 0.001
Medication			
No of antiplatelet drugs	2.3 ± 0.6	2.2 ± 0.6	0.193
Aspirin	44 (62%)	59 (58%)	0.586
Clopidogrel	66 (93%)	88 (86%)	0.167
Cilostazol	46 (65%)	63 (62%)	0.685
Warfarin or NOAC	4 (6%)	6 (6%)	0.513
ACEI or ARB	39 (55%)	45 (44%)	0.162
Statin	42 (59%)	42 (41%)	0.020*
Beta-blocker	41 (58%)	45 (44%)	0.078
Calcium channel blocker	33 (49%)	34 (37%)	0.128
Follow-up duration (days)	944 ± 447	916 ± 501	0.708
Follow-up index	0.97 ± 0.13	0.94 ± 0.18	0.216

Values are mean ± SD or n (%).

* $p < 0.05$ indicates a significant difference between groups.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; CKD, chronic kidney disease; CHF, congestive heart failure; CRP, C-reactive protein; HbA1C, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil-lymphocyte ratio; NOAC, non-vitamin K antagonist oral anticoagulant; PLR, platelet-lymphocyte ratio; WBC, white cell count.

went repeat EVT due to symptom recurrence. The restenosis pattern based on the index of treated length classification[19] was not different between the IC and CLI groups (focal restenosis 57% vs. 55%, p = 0.879). Moreover, there were no significant differences in the 3-year rates of freedom from binary restenosis (57% vs. 59%, p = 0.781) and MALE (77% vs. 67%, p = 0.507) between the two groups (Figures 3 and 4). However, the 3-year MALE-free rates among the patients with low, moderate and high-risk FeDCLIP scores were significantly different (83% vs. 68% vs. 58%, respectively, p = 0.04).

Multivariate analysis

A Cox proportional hazard model was used to identify independent predictors of binary restenosis, MALEs, and AFS. Detailed information on the univariate and multivariate analyses is shown in Supplementary Table 1-3. The multivariate analysis showed that the signifi-

Table 2. Lesion characteristics of treated limbs

Group	Claudicants	Critical limb ischemia	p value
No. of affected limbs	N = 83	N = 117	
Target-limb ABI	0.60 ± 0.23	0.58 ± 0.40	0.628
Target-limb ABI excluding the stiff artery	0.57 ± 0.15	0.48 ± 0.15	< 0.001*
Intermittent claudication	83 (100%)	0 (0%)	< 0.001*
Rest pain	0 (0%)	25 (21%)	
Non-healing ulcer	0 (0%)	72 (62%)	
Gangrene	0 (0%)	20 (17%)	
Concomitant intervention			
Iliac intervention	9 (11%)	7 (6%)	0.212
BTK intervention	52 (63%)	91 (78%)	0.020*
Poor BTK runoff	40 (48%)	81 (69%)	0.001*
PA involvement	39 (47%)	70 (60%)	0.072
Severe calcification	14 (17%)	43 (37%)	0.002*
Occlusion	37 (45%)	56 (48%)	0.646
Lesion type			
Denovo Lesions	54 (65%)	74 (63%)	0.527
Restenotic lesions	11 (13%)	22 (19%)	
In-stent lesions	18 (22%)	21 (18%)	
Mean lesion length (mm)	224 ± 114	206 ± 117	0.292
Bailout stent	36 (43%)	42 (36%)	0.285
Stent length (mm)	121.3 ± 65.5	134.3 ± 91.0	0.479
Numbers of DCB	2.1 ± 1.1	1.8 ± 1.0	0.070
Length of DCB (mm)	264 ± 123	230 ± 120	0.055
IVUS	22 (27%)	30 (26%)	0.891
Atherectomy	7 (8%)	25 (21%)	0.014*
RVD at SFA	5.35 ± 0.76	5.44 ± 0.74	0.392
RVD at PA	4.75 ± 0.80	4.75 ± 0.79	0.964
Final balloon size (mm)	5.7 ± 0.7	5.6 ± 0.8	0.210
Final MLD at SFA (mm)	4.31 ± 0.79	4.47 ± 0.73	0.191
Lumen gain at SFA (mm)	3.45 ± 0.91	3.57 ± 1.00	0.426
Final MLD at PA (mm)	3.84 ± 0.84	3.80 ± 0.84	0.815
Lumen gain at PA (mm)	3.00 ± 1.03	2.98 ± 1.03	0.916
FeDCLIP risk group			
Low-risk	43 (52%)	21 (18%)	< 0.001*
Moderate-risk	35 (42%)	60 (51%)	
High-risk	5 (6%)	36 (31%)	
Median time to DCB restenosis (days)	433 (216, 523)	413 (210, 655)	0.664
Follow-up index	0.96 ± 0.17	0.95 ± 0.17	0.685

Values are mean ± SD or n (%).

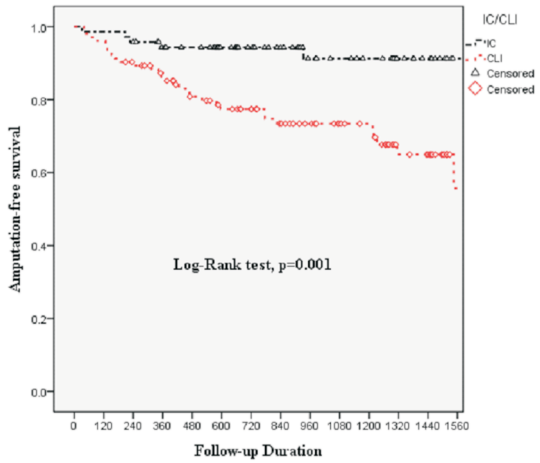
* p < 0.05 indicates a significant difference between groups.

ABI, ankle brachial index; BTK, below-the-knee; DCB, drug-coated balloon; IVUS, intravascular ultrasound; MLD, minimal lumen diameter; PA, popliteal artery; RVD, reference vessel diameter; SFA, superficial femoral artery; FeDCLIP, female, dialysis, critical limb ischemia, lesion length, poor runoff.

cant predictors were LL [hazard ratio (HR), 1.041, 95% confidence interval (CI), 1.006-1.076, p = 0.021] and severe vessel calcification (HR, 2.189; 95% CI, 1.032-4.646, p = 0.041) for binary restenosis. Meanwhile, restenotic lesions (HR, 2.515; 95% CI, 1.149-5.504, p = 0.021) independently predicted MALEs. In addition, AFS was associated with age (HR, 1.069; 95% CI, 1.020-1.120, p = 0.005), congestive heart failure (HR, 4.212; 95% CI, 1.536-12.55, p = 0.005), and dialysis dependence (HR, 5.770; 95% CI, 2.387-13.94, p < 0.001) (Table 3).

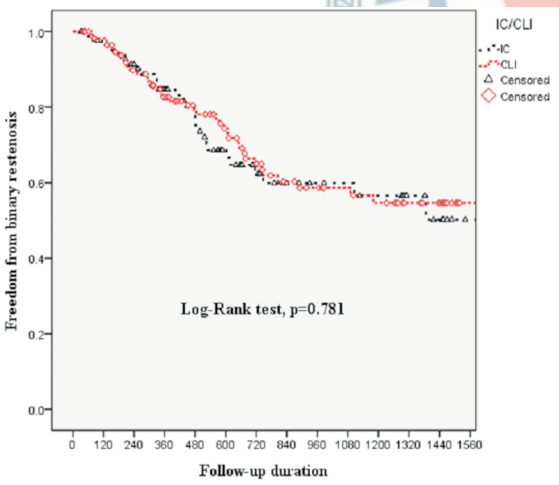
DISCUSSION

This study demonstrated that local drug delivery using a paclitaxel-coated balloon led to similar mid-term



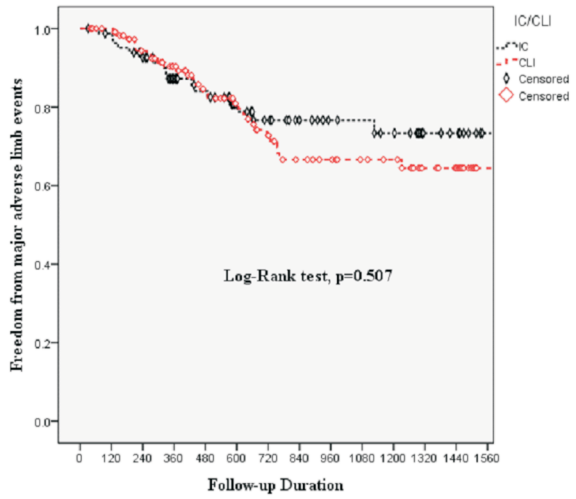
Follow-up period (days)	0	360	720	1080	1440
Claudication Number at risk Rate & SE	71 100±0	63 94.3±2.8	43 94.3±2.8	30 91.2±4.0	11 91.2±4.0
Critical limb ischemia Numbers at risk Rate & SE (%)	103 100±0	83 86.2±3.4	62 77.4±4.3	42 73.4±4.6	22 64.9±5.8

Figure 2. *Kaplan-Meier curves for amputation-free survival. The 3-year amputation-free survival was significantly different between intermittent claudication (IC) and critical limb ischemia (CLI) patients (73% vs. 91, p = 0.001). The black line indicates IC patients and the red line indicates CLI patients. SE means standard error.*



Follow-up period (days)	0	360	720	1080	1440
Claudication Number at risk Rate & SE	83 100±0	63 84.1±4.7	27 62.4±6.2	17 56.6±6.9	8 50.3±8.5
Critical limb ischemia Numbers at risk Rate & SE (%)	117 100±0	79 82.7±3.7	46 65.0±5.1	35 58.6±5.5	17 54.7±5.8

Figure 3. *Kaplan-Meier curves for freedom from binary restenosis. No significant differences were noted between groups about the 3-year binary restenosis-free rate (57% vs. 59%, p = 0.781). The black line indicates IC patients and the red line indicates CLI patients.*



Follow-up period (days)	0	360	720	1080	1440
Claudication Number at risk Rate & SE	83 100±0	65 87.2±3.8	36 76.7±5.3	23 76.7±5.3	9 73.3±6.0
Critical limb ischemia Numbers at risk Rate & SE (%)	117 100±0	87 90.3±2.9	51 72.8±4.9	34 66.6±5.3	19 64.5±5.6

Figure 4. *Kaplan-Meier curves for freedom from major adverse limb events (MALE). No difference was observed between groups about MALE-free rate (77% vs. 67%, p = 0.507) at three years. The black line indicates IC patients, and the red line indicates CLI patients.*

vessel patency and MALE-free rate between patients with claudication and CLI. However, general comorbidities, advanced limb ischemia, and tissue loss led to a worse AFS in the CLI patients compared to the claudicants.

Amputation-free survival

CLI is an end-stage form of PAD with poor outcomes, with 1-year and 5-year mortality rates estimated to be 25% and 50%, respectively.[4] A recent analysis conducted in Japan demonstrated a 2-year mortality rate in CLI patients of 41%, with 47% of deaths being from cardiovascular causes.[20] A current registry reported a 3-year AFS rate of only 55%.[21] The antiproliferative effect of DCBs on AFS remains unclear. In the current study, we found that the mid-term AFS remained worse in the CLI patients despite the effectiveness of paclitaxel on vessel patency. The CLI patients were fragile and characterized by tissue inflammation, anatomical complexity and medical comorbidities, which is consistent with previous reports.[20-22] Meanwhile, 14% of the CLI patients died without above-the-ankle amputations in the first year, which may have been associated with the lower rate of major amputations in both groups. The independent

Table 3. Independently factors associated with binary restenosis, amputation-free survival and major adverse limb events

	Univariate		Multi-variate	
	HR (95% CI)	p value	HR (95% CI)	p value
Binary restenosis				
Severe calcification	1.492 (0.910-2.447)	0.113	2.189 (1.032-4.646)	0.041
Lesion length	1.047 (1.024-1.071)	< 0.001	1.041 (1.006-1.076)	0.021
Amputation-free survival				
Age	1.056 (1.022-1.092)	0.001	1.069 (1.020-1.120)	0.005
Dialysis	2.410 (1.252-4.683)	0.003	5.770 (2.387-13.94)	< 0.001
CHF	4.784 (1.677-13.65)	0.003	4.212 (1.536-12.55)	0.005
Major adverse limb events				
Restenotic vs. Denovo lesions	2.715 (1.397-5.297)	0.003	2.515 (1.149-5.504)	0.021

CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio.

predictors for AFS were age, dialysis, and congestive heart failure, which are commonly encountered in real-world CLI patients and is similar to previous studies.[20,21,23]

Vessel patency

A meta-analysis of balloon angioplasty and stenting in femoropopliteal arterial disease for patients with CLI reported 3-year patency rates of 43% and 30% for stenosis and occlusions, respectively. In addition, the patients with claudication fared better, with 3-year patency rates of 61% for those with stenosis and 48% for those with occlusions.[24] Promising results using drug eluting devices to treat shorter lesions have been reported previously,[11-14,25-28] however the long-term results of DCBs for long femoropopliteal lesions are scarce. The Lutonix global superficial femoral artery real-world registry reported favorable 2-year results with a 75.6% primary patency rate and 89.3% freedom from target lesion restenosis in long lesions up to 500 mm.[29] The 2-year primary patency (64%) and CD-TLR-free rates (77%) in our study were lower than those in the Lutonix global registry. This discrepancy may have been related to the larger number of CLI and dialyzed patients in this study. In addition, we determined vessel patency using DS > 50% on follow-up angiography or peak systolic velocity ratio ≥ 2.4 by duplex ultrasound rather than clinical recurrence and ABI, which will over-estimate vessel patency. Our results are close to outcomes of real-world registries.[30,31] We previously reported that a LL > 15 cm could independently predict the 1-year binary restenosis in high-risk patients.[15] In the current study, LL remained an independent factor for binary restenosis at 3 years, which is consistent with other reports.[32,33] Potential mechanisms for a higher restenosis rate in longer lesions may be associated with sizeable atherosclerotic burden, poorer lesion preparation, and uneven drug distribution with the use of multiple DCBs. The DEBATE-SFA trial included many CLI patients, of whom 74% had resting pain or tissue loss. They reported a 1-year binary restenosis rate of 17% in the group treated with DCBs followed by BMSs.[11] The 1-year result (16%) in our CLI patients was similar.

The impact of vessel calcification on the efficacy of DCB is unclear. Fanelli et al. conducted a study to assess the circumferential distribution of calcium on axial computed tomography, and found that the DCB effect was lower in the patients with high calcium burden.[34] Schneider recently reported the 4-year results of the IN.PACT SFA trial, in which severe calcification independently predicted CD-TLR at 4 years.[33] Taken together, these findings suggest that combining atherectomy and DCB may be able to improve the DCB results in calcified lesions.[35,36] One-fifth of CLI patients with severe calcification were pretreated with debulking or plaque modification devices before the use of DCBs, however, multivariate analysis showed that severe vessel calcification remained an independent predictor of binary restenosis.

Major adverse limb events

We previously reported a similar 1-year CD-TLR-free rate among different FeDCLIP risk groups.[15] Although the 3-year MALE-free rate was similar between the claudicants and CLI patients, the antiproliferative effect of DCB continued to decrease over time after 1 year in the

patients with moderate to high-risk FeDCLIP scores. Lesion complexity and medical comorbidities in these patients will adversely impact the effectiveness of DCBs. Compared to the de novo lesions, the restenotic lesions had a significantly lower 3-year MALE-free rate (47% vs. 79%, p = 0.002) and continued to be an independent factor after adjustments. The different effect of DCBs on de novo versus restenotic lesions could be related to discrepancies in the paclitaxel distribution at the target cells. Several animal studies have demonstrated that paclitaxel reaches the smooth muscle cell (SMC) layer despite intimal plaque in de novo stenotic vessels.[37]

In contrast, the composition of extracellular matrix components changes from a provisional fibrin-rich to a permanent matrix in restenotic lesions. These changes are accompanied by reduced SMC density.[38] The noncellular material in the innermost vessel layer has been reported to contribute to restenosis and to prohibit the cytotoxic effect of paclitaxel from reaching the cellular layer of SMCs.[39] Removal of these inner layers can allow paclitaxel to reach the target cells, which may improve the antiproliferative effect and maintain sustained vessel patency.

Study limitations

This study has several limitations. First, this observational study is retrospective in design with a relatively small sample size, making robust conclusions impossible. In addition, the full use of DCBs for all patients with PAD in Taiwan is not possible due to the cost and reimbursement policy. Second, using data from only three-institutions may have caused bias towards particular patient demographics and practice patterns. However, these data represent the real-world application of DCBs in critically ill patients with femoropopliteal disease. Finally, no routine follow-up angiography was performed in cases of DCB restenosis without clinical symptoms. Thus details of late area and lumen loss were not available.

CONCLUSIONS

In conclusion, the 3-year rates of freedom from binary restenosis and MALEs were similar between the claudication and CLI patients after treatment with DCBs for femoropopliteal disease. Overall survival remained worse in the CLI patients. A longer lesion length and severe vessel calcification predicted binary restenosis. Furthermore, AFS and MALEs were correlated with underlying comorbidities and anatomical complexity.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENT

Supplementary Table 1. Summary of factors predicting the amputation-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.056 (1.022-1.092)	0.001*	1.069 (1.020-1.120)	0.005*
Female	1.144 (0.593-2.207)	0.687		
Atrial fibrillation	2.633 (1.205-5.866)	0.015		
Body mass index	0.905 (0.807-1.014)	0.085		
Diabetes mellitus	1.679 (0.807-3.494)	0.166		
CAD	1.767 (0.882-3.540)	0.109		
CHF	2.782 (1.387-5.582)	0.004*	4.212 (1.536-12.55)	0.005*
Dialysis	2.410 (1.252-4.683)	0.008*	5.770 (2.387-13.94)	< 0.001*
CLI	4.449 (1.729-11.45)	0.002*		
Lesion length	1.021 (0.092-1.051)	0.159		
Poor runoff	3.664 (1.523-8.812)	0.004*		
ABI level of affected leg	0.016 (0.002-0.156)	< 0.001*		
Hematocrit	0.249 (0.036-1.735)	0.160		
NLR	2.082 (1.404-3.087)	< 0.001*		
PLR	2.571 (1.566-4.222)	< 0.001*		
C-reactive protein	1.232 (1.022-1.486)	0.029*		
Albumin	0.439 (0.284-0.680)	< 0.001*		
Use of statin	0.442 (0.216-0.904)	0.025*		
Use of cilostazol	0.741 (0.355-1.543)	0.423		

ABI, ankle-brachial pressure index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CLI, critial limb ischemia; CTO, chronic total occlusion; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; PA, popliteal artery; PLR, platelet-lymphocyte ratio; SFA, superficial femoral artery. * $p < 0.05$.

Supplementary Table 2. Summary of factors predicting the binary restenosis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.020 (1.000-1.042)	0.095		
Female	1.128 (0.696-1.831)	0.625		
Atrial fibrillation	1.262 (0.575-2.770)	0.562		
Body mass index	1.048 (0.967-1.135)	0.251		
Diabetes mellitus	1.085 (0.579-2.034)	0.799		
CAD	1.068 (0.653-1.745)	0.794		
CHF	1.070 (0.545-2.101)	0.844		
Dialysis	1.011 (0.602-1.697)	0.968		
CLI	1.072 (0.657-1.748)	0.781		
Lesion length	1.047 (1.024-1.071)	< 0.001*	1.041 (1.006-1.076)	0.021*
Poor runoff	1.104 (0.668-1.824)	0.700		
CTO	1.663 (1.022-2.707)	0.041*		
Lumen gain of SFA	0.819 (0.630-1.065)	0.137		
Lumen gain of PA	0.700 (0.511-0.959)	0.026*		
Severe calcification	1.492 (0.910-2.447)	0.113	2.189 (1.032-4.646)	0.041*
C-reactive protein	1.001 (0.864-1.160)	0.990		
Albumin	0.983 (0.668-1.444)	0.929		
Use of statin	0.872 (0.538-1.414)	0.580		
Use of cilostazol	0.980 (0.598-1.606)	0.935		
ABI of affected leg	0.130 (0.020-0.824)	0.030*		
Lesion type				
Restenosis vs. Denovo lesion	1.909 (1.042-3.497)	0.036*		
In-stent vs. Denovo lesion	2.005 (1.107-3.633)	0.022*		

ABI, ankle-brachial pressure index; CAD, coronary artery disease; CHF, congestive heart failure; CLI, critical limb ischemia; CTO, chronic total occlusion; PA, popliteal artery; SFA, superficial femoral artery. * p < 0.05.

Supplementary Table 3. Summary of factors predicting the major adverse limb events

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.020 (0.997-1.045)	0.092		
Female	1.028 (0.574-1.843)	0.926		
Atrial fibrillation	1.288 (0.507-3.273)	0.595		
Body mass index	1.042 (0.946-1.147)	0.407		
Diabetes mellitus	1.101 (0.531-2.285)	0.795		
CAD	1.106 (0.619-1.977)	0.734		
CHF	1.408 (0.556-3.570)	0.471		
Dialysis	1.505 (0.832-2.723)	0.177		
CLI	1.224 (0.673-2.229)	0.508		
Lesion length	1.029 (1.003-1.056)	0.030*		
Poor runoff	1.093 (0.601-1.991)	0.770		
CTO	1.608 (0.897-2.881)	0.111		
Lumen gain of SFA	0.746 (0.548-1.016)	0.064		
Lumen gain of PA	0.886 (0.629-1.247)	0.487		
Severe calcification	1.339 (0.735-2.439)	0.340		
C-reactive protein	1.032 (0.867-1.230)	0.722		
Albumin	0.868 (0.556-1.355)	0.533		
Use of statin	0.710 (0.396-1.272)	0.250		
Use of cilostazol	0.749 (0.404-1.387)	0.357		
ABI of affected leg	0.143 (0.016-1.279)	0.082		
Lesion type				
Restenosis vs. Denovo lesion	2.715 (1.397-5.297)	0.003*	2.515 (1.149-5.504)	0.021*
In-stent vs. Denovo lesion	1.549 (0.716-3.352)	0.266		

ABI, ankle-brachial pressure index; CAD, coronary artery disease; CHF, congestive heart failure; CLI, critical limb ischemia; CTO, chronic total occlusion; PA, popliteal artery; SFA, superficial femoral artery. * p < 0.05.