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Intravascular ultrasound-guided drug-coated balloon angioplasty for femoropopliteal artery disease: a clinical trial

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Abstract

Background and Aims Drug-coated balloons (DCBs) have demonstrated favourable outcomes following endovascular therapy for femoropopliteal artery (FPA) disease. However, uncertainty remains whether the use of intravascular ultrasound (IVUS) can improve the outcomes of DCBs.

Methods This prospective, multicentre, randomized trial, conducted at seven centres in South Korea, compared the outcomes of IVUS-guided vs. angiography-guided angioplasty for treating FPA disease with DCBs. Patients were assigned to receive IVUS-guided ($n = 119$) or angiography-guided ($n = 118$) angioplasty using DCBs. The primary endpoint was 12-month primary patency.

Results Between May 2016 and August 2022, 237 patients were enrolled and 204 (86.0%) completed the trial (median follow-up; 363 days). The IVUS guidance group showed significantly higher primary patency [83.8% vs. 70.1%; cumulative difference 19.6% (95% confidence interval 6.8 to 32.3); $P = .01$] and increased freedom from clinically driven target lesion revascularization [92.4% vs. 83.0%; difference 11.6% (95% confidence interval 3.1 to 20.1); $P = .02$], sustained clinical improvement (89.1% vs. 76.3%, $P = .01$), and haemodynamic improvement (82.4% vs. 66.9%, $P = .01$) at 12 months compared with the angiography guidance group. The IVUS group utilized larger balloon diameters and pressures for pre-dilation, more frequent post-dilation, and higher pressures for post-dilation, resulting in a greater post-procedural minimum lumen diameter (3.90 ± 0.59 vs. 3.71 ± 0.73 mm, $P = .03$).

Conclusions Intravascular ultrasound guidance significantly improved the outcomes of DCBs for FPA disease in terms of primary patency, freedom from clinically driven target lesion revascularization, and sustained clinical and haemodynamic improvement at 12 months. These benefits may be attributed to IVUS-guided optimization of the lesion before and after DCB treatment.

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Structured Graphical Abstract

Key Question

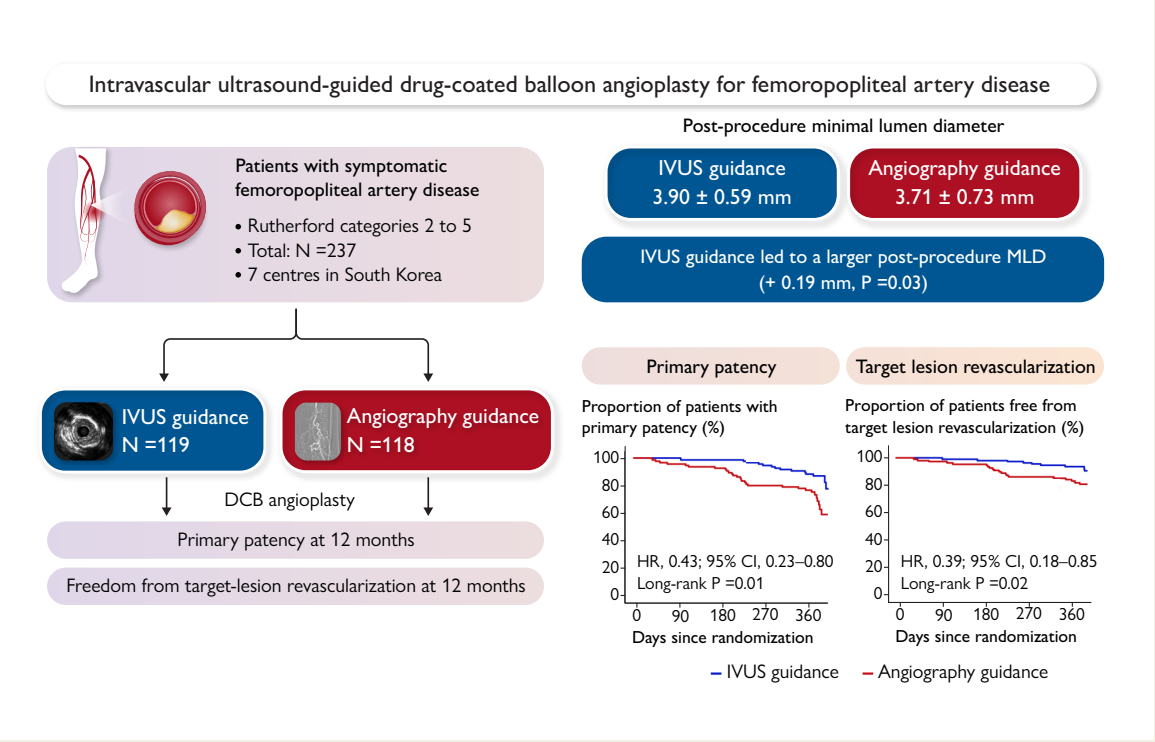
Does guidance by intravascular ultrasound (IVUS) improve primary patency and clinical outcomes after endovascular therapy (EVT) for femoropopliteal artery (FPA) disease using drug-coated balloons (DCBs), compared with angiography guidance?

Key Finding

In this randomized clinical trial of 237 patients with FPA disease, IVUS-guided DCB angioplasty resulted in better primary patency (86.6% vs. 74.6%) and freedom from clinically-driven target lesion revascularisation (92.4% vs. 83.0%), sustained clinical improvement (89.1% vs. 76.3), and haemodynamic improvement (82.4% vs. 66.9%) at 12 months, compared with angiography-guided DCB angioplasty.

Take Home Message

IVUS-guided lesion optimisation before and after DCB treatment leads to improved vascular patency and clinical outcomes following DCB angioplasty for FPA disease.



In this prospective, multicentre, randomized trial conducted at seven centres in South Korea, intravascular ultrasound-guided drug-coated balloon treatment for femoropopliteal artery disease resulted in a greater minimal lumen diameter than angiography-guided drug-coated balloon treatment. Furthermore, intravascular ultrasound guidance led to favourable primary patency and freedom from target lesion revascularization. HR, hazard ratio; CI, confidence interval.

Keywords Peripheral arterial disease • Endovascular procedures • Ultrasonography • Interventional

Introduction

Femoropopliteal artery (FPA) lesions pose a challenge in endovascular therapy (EVT) due to the dynamic exposure of the FPA to various external forces from lower extremity movements. Moreover, stent-based EVT has been associated with a higher risk of restenosis, particularly in long lesions or near joints.[1] As a result, the 'leave nothing behind' EVT strategy using drug-coated balloons (DCBs) has emerged as an attractive option for treating FPA disease.[2] Various clinical studies, including randomized controlled trials and registry studies, have demonstrated that DCBs yield favourable outcomes in treating FPA lesions.[1,3] However, challenges such as vessel recoil, residual stenosis, and arterial dissection post-DCB treatment remain significant limitations. Thus, improved vessel preparation and post-DCB optimization, which may involve additional ballooning or stent implantation, are needed to enhance EVT outcomes. Intravascular ultrasound (IVUS), a catheter-based imaging modality, provides detailed insights into vessel dimensions and plaque characteristics.[2] Although IVUS use in percutaneous coronary interventions has been shown to improve clinical outcomes,[4] its role in EVT for peripheral artery disease (PAD) is less clear due to limited data. This study aimed to compare the outcomes of IVUS-guided DCB angioplasty with those of angiography-guided DCB angioplasty in the treatment of FPA disease.

Methods

Study design and participants

The current IVUS-DCB trial is an investigator-initiated, multicentre, randomized, single-blinded, superiority trial conducted across seven centres in Korea. The study protocol received approval from the institutional review board at each participating centre, and all participants provided written informed consent. Study coordination and data and site management services were carried out at the Cardiovascular Research Center, Seoul, Korea. A data and safety monitoring board oversaw the trial, and all clinical events were evaluated by an independent clinical event adjudication committee, whose members were masked to the trial group assignments. Supplementary data online provide details regarding the participating centres and study personnel. The funders, Medtronic Inc. (Santa Rosa, CA, USA) and Korea United Pharm (Seoul, Korea), had no involvement in the trial design; data collection, analysis, or interpretation; or writing of the manuscript. This trial was conducted in accordance with the principles of the Declaration of Helsinki.

Study population

Patients ≥19 years of age who were undergoing EVT for symptomatic FPA disease (Rutherford Categories 2–5) were eligible for enrolment. The key exclusion criteria included acute limb ischaemia and severe limb ischaemia (Rutherford Category 6). The comprehensive inclusion and exclusion criteria are detailed in Supplementary data online, *Table S1*.

Randomization and study procedures

Eligible patients who provided informed consent were randomly assigned in a 1:1 ratio to receive either IVUS-guided ($n = 119$) or angiography-guided ($n = 118$) EVT using an IN.PACT Admiral DCB (Medtronic Inc.). The randomization occurred after successful guidewire passage through the target lesion. Web response permuted block randomization (with mixed blocks of four or six) was employed at each site, with stratification based on the enrolling site and lesion length with a cut-off of 150 mm. For patients who were not at high risk of bleeding from triple antiplatelet therapy or cilostazol intolerance, an optional secondary randomization assigned them to either triple or dual antiplatelet therapy. Those in the triple therapy group received cilostazol (Cilostan® CR 200 mg once daily, Korea United Pharm) in addition to aspirin and clopidogrel for 1 year. The EVT for the FPA lesions involved standard techniques, including lesion preparation through balloon dilation with or without atherectomy before DCB applications, at the operator's discretion. Generally, all target lesions were predilated using a plain balloon catheter 1 mm smaller in diameter than the anticipated DCB size. Both intraluminal and subintimal wiring approaches were permitted for total occlusions. Atherectomy was allowed before DCB deployment for severely calcified lesions, and pre-dilation was not mandatory if atherectomy was used. Self-expanding nitinol stent implantation was permitted in cases of residual stenosis >50% or major flow-limiting dissections post-DCB, as evidenced by angiography or IVUS findings. All IVUS-guided DCB angioplasty procedures were conducted using a Volcano s5 IVUS system (Philips Healthcare, Andover, MA, USA) or a Boston Scientific iLab2 IVUS system (Boston Scientific, Marlborough, MA, USA). All operators were experienced in IVUS use and interpretation. The diameters of the proximal and distal reference vessels (external elastic membrane) were measured at the most normal-appearing segments adjacent to the target lesion. Post-DCB IVUS evaluations were performed to measure the minimum lumen area and to detect the presence of vessel dissection or thrombus, and additional treatment was left to the operator's discretion. If a patient was not on aspirin or clopidogrel at the time of EVT, loading doses of aspirin (300 mg) and clopidogrel (300 mg) were administered, and dual antiplatelet therapy was required for at least 90 days post-procedure. Clinical follow-up was conducted at 1, 3, 6, and 12 months post-procedure as well as upon any aggravation of the patient's symptoms. It included assessments of medical conditions, functional status, Rutherford category, adverse events, and medication compliance. At 12 months, the primary patency of the target lesion was evaluated using duplex ultrasound (DUS), computed tomography angiography (CTA), or digital subtraction angiography (DSA).

Outcomes

The primary endpoint of the study was the primary patency of the target lesion at 12 months, defined as the absence of clinically driven target lesion revascularization (CD TLR) or binary restenosis on DUS, CTA, or DSA. Binary restenosis was defined as a peak systolic velocity ratio of >2.4 on DUS or luminal narrowing of 50% or more on CTA or DSA.[1,5,6] The non-invasive imaging studies (DUS or CTA) were conducted by independent imaging specialists (imaging cardiologist or interventional radiologist) at each participating site who were unaware of the patients' clinical status and randomization group. All raw CTA image data were centrally collected and analysed by two interventional radiologists in a blinded manner. Follow-up DSA images were also centrally collected and analysed by an independent core laboratory in a blinded fashion, after initial assessment by the operator to determine the need for revascularization. The key secondary endpoints included freedom from CD TLR, major amputation, and sustained clinical improvement and haemodynamic improvement. Clinically driven target lesion revascularization was defined as reintervention due to significant target lesion stenosis of ≥50% within 5 mm proximal or distal to the original treatment segment, accompanied by recurrent symptoms or a decrease in the ankle–brachial index (ABI) of 0.15 or more.[1,5] Major amputation was defined as any amputation of the target limb above the ankle level.[7] Primary sustained clinical improvement was defined as an increase in Rutherford category from baseline and freedom from major amputation, or CD TLR.[8] Sustained haemodynamic improvement was defined as an increase in ABI by ≥0.15 from baseline and freedom from CD TLR.[9] Safety endpoints included all-cause death, cardiovascular death, and major bleeding according to the Thrombolysis in Myocardial Infarction criteria.[10] Technical success was defined as residual stenosis of <30% without flow compromise, and procedural success was defined as the achievement of technical success without any acute procedure-related complications.[7]

Statistical analysis

We estimated that a sample size of 240 patients with symptomatic FPA disease would provide the trial with at least 80% power to detect a between-group difference of 15% in primary patency at 12 months (90% in the IVUS guidance group vs. 75% in the angiography guidance group), with a two-sided alpha level of 0.05, assuming a 15% loss to follow-up. These estimates were based on 12-month data on the TLR rate from LEVANT 2 and the IN.PACT SFA trial as well as previous large cohort registry data demonstrating the benefit of IVUS-guided EVT over angiography-guided conventional EVT.[1,8,11] Primary patency was analysed on a modified intention-to-treat basis, where patients with missing data for binary restenosis throughout the close of the 12-month follow-up (window on Day 395) were excluded from the analysis.[1] Analyses for all other clinical outcomes were based on the intention-to-treat principle. Event rates between the two groups were compared using log-rank tests, with hazard ratios (HRs), and 95% confidence intervals (CIs) calculated by Cox regression analysis, adjusting for lesion length with a cut-off of 150 mm. The cumulative risk difference was calculated by comparing the estimated Kaplan–Meier estimates at 395 days after randomization. Sensitivity analyses were performed in (i) the per-protocol population, (ii) the best-case scenario, and (iii) the worst-case scenario. The per-protocol analysis excluded patients who underwent randomization but did not receive assigned treatment strategy (IVUS use in the angiography guidance group or no use of IVUS in the IVUS guidance group). The best-case scenario assumed that all participants lost to follow-up were free of binary restenosis at 395 days post-randomization. Conversely, the worst-case scenario assumed that all participants with missing data had developed binary restenosis at 395 days post-randomization.[12,13] A *post hoc* analysis was conducted utilizing mixed effects modelling to account for enrolment site effects, with the site being treated as a random effect. Two-sided 95% CIs were calculated to

compare the between-group differences in observed primary patency and other clinical events. Categorical variables are presented as numbers and percentages and were compared using a χ^2 test or Fisher's exact test, as appropriate. Continuous variables are reported as means ± standard deviations or medians and interquartile ranges, as appropriate, and were compared using a *t*-test or Mann–Whitney test. *Post hoc* univariate and multivariate Cox regression analyses were performed to determine the independent predictors of binary restenosis. Variables were selected based on their established clinical relevance and considered for inclusion in the multivariable model if the variable was significant in the univariate analysis ($P < .05$). The assumption of proportional hazards was assessed using a log-minus-log survival function. All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC, USA). *P*-values < .05 were considered statistically significant.

Results

Patients

A total of 243 patients were enrolled between May 2016 and August 2022. After excluding six patients who refused to provide consent, 119 patients were randomized to receive IVUS-guided DCB angioplasty, and 118 patients were randomized to receive angiography-guided DCB angioplasty (*Figure 1*). The assigned treatment strategy was performed in 234 patients. Of the remaining three patients, one assigned to the IVUS guidance group received angiography-guided DCB angioplasty and two assigned to the angiography guidance group received IVUS-guided DCB angioplasty. Out of the original 237 patients, 204 patients completed a 12-month follow-up visit. The remaining 33 included 16 patients who died, 8 who withdrew consent, and 9 who were lost to follow-up before 12 months after the index procedure. The baseline clinical characteristics were well balanced between the two treatment groups (*Table 1*). The mean age was 70 years, and 85% were men. Additionally, 63% had diabetes, 26% presented with critical limb-threatening ischaemia (Rutherford Category 4 or 5), and 48% had complex anatomical lesions (Trans-Atlantic Inter-Society Consensus [TASC] II Type D).

Procedural characteristics

Pre- and post-procedural IVUS findings for the IVUS guidance group are provided in Supplementary data online, *Table S2*. The angiographic features outlined in *Table 2* did not differ between groups. Overall, 62% showed total occlusions and 29% exhibited severe calcification (peripheral arterial calcium scoring system score 4). Although the procedural characteristics, such as the maximum and mean diameters of DCBs, showed no significant differences between the treatment groups, the IVUS guidance group had greater pre-balloon diameters (5.0 ± 0.9 vs. 4.5 ± 1.1 mm, $P < .001$), maximum pre-balloon pressures (11.8 ± 3.6 vs. 8.9 ± 2.7 mm Hg, $P < .001$), and maximum post-balloon pressures (13.7 ± 2.9 vs. 9.6 ± 4.0 mm Hg, $P = .001$) compared with the angiography guidance group. Adjuvant post-dilation was conducted more frequently in the IVUS guidance group (26.1% vs. 13.6%, $P = .03$), while the rates of bailout stenting were comparable between the groups (20.5% vs. 14.5%, $P = .30$). No significant differences were observed in subintimal wiring and atherectomy between the two groups. *Table 2* presents the immediate procedural outcomes. Post-procedural

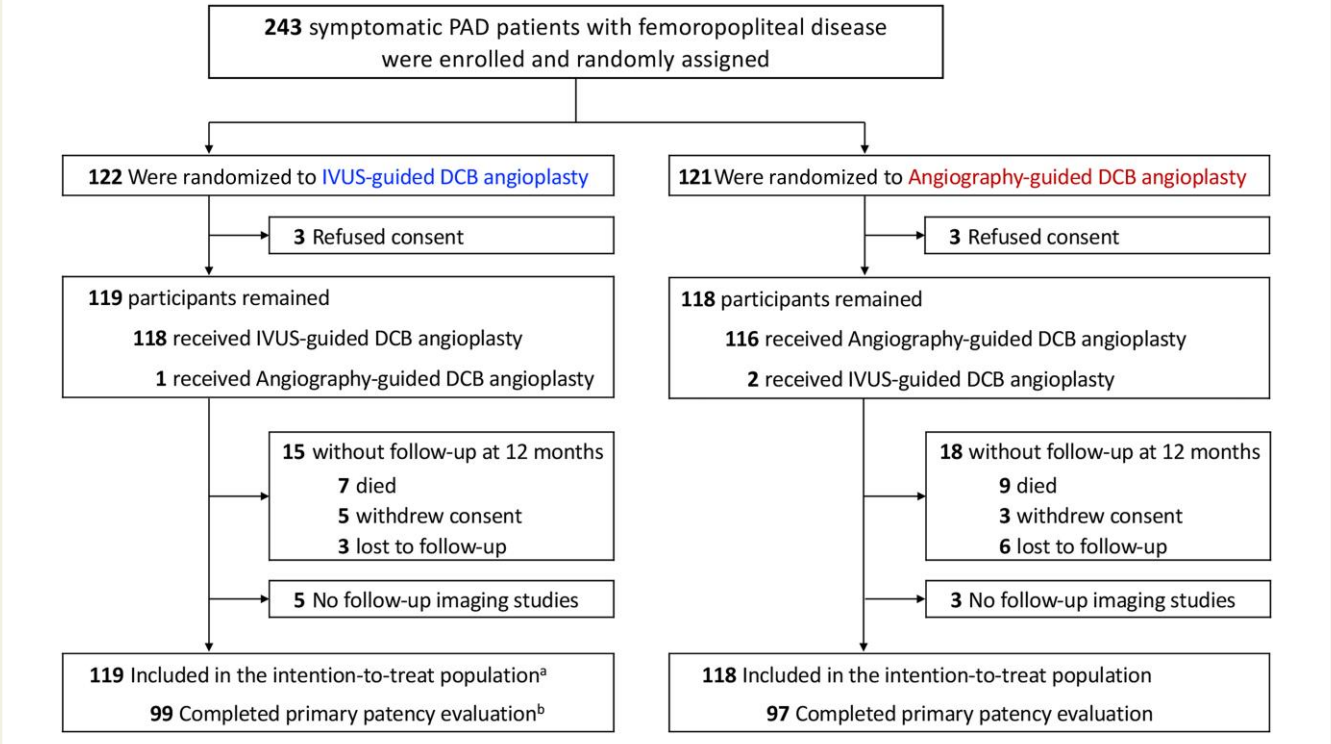


Figure 1 Patient flow diagram. [a]All randomized patients were included in the time-to-event analyses for clinical efficacy and safety endpoints throughout the study period, including those who withdrew consent or were lost to follow-up. [b]Patients with missing binary restenosis data were excluded from the primary patency analysis, which was conducted using a modified intention-to-treat approach. PAD, peripheral artery disease; IVUS, intravascular ultrasound; PTA, percutaneous transluminal angioplasty; DCB, drug-coated balloon

Table 1 Baseline characteristics

Characteristics	IVUS guidance ($n = 119$)	Angiography guidance ($n = 118$)
Age, mean (SD), *y*	69.0 (9.1)	70.2 (8.6)
Men	102 (85.7)	100 (84.7)
Body mass index, mean (SD), kg/m^2	23.8 (3.4)	23.4 (3.1)
Hypertension	94 (78.0)	99 (83.8)
Diabetes mellitus	71 (59.7)	79 (67.5)
Diabetes mellitus on insulin	12 (10.1)	15 (12.7)
Chronic kidney disease[a]	29 (24.4)	19 (16.1)
End-stage kidney disease on dialysis	14 (11.8)	8 (6.8)
Dyslipidaemia	84 (70.6)	86 (72.9)
Current smoker	37 (31.1)	41 (34.7)
Prior peripheral revascularization	18 (15.1)	18 (15.3)
Prior limb amputation	5 (4.2)	4 (3.4)
Coronary artery disease	45 (37.8)	31 (26.3)
Prior myocardial infarction	6 (5.0)	10 (8.5)
Prior percutaneous coronary intervention	24 (20.2)	17 (14.4)
Prior stroke	14 (11.8)	14 (11.9)
Rutherford category		
2	3 (2.5)	6 (5.1)
3	86 (72.3)	80 (67.8)
4	10 (8.4)	12 (10.2)
5	20 (16.8)	20 (16.9)
Pre-procedural ABI, mean (SD)	0.64 (0.21)	0.63 (0.21)
Medication at discharge		
Aspirin	112 (94.1)	111 (94.9)
Clopidogrel	115 (96.6)	113 (96.6)
Cilostazol	48 (40.3)	49 (41.9)
Statin	105 (88.2)	104 (88.1)

IVUS, intravascular ultrasound; ABI, ankle–brachial index.
[a]Estimated glomerular filtration rate of <60 mL/min/1.73 m of body surface area.

angiography revealed that the target lesions treated in the IVUS guidance group had a larger minimum lumen diameter (3.90 ± 0.59 vs. 3.71 ± 0.73 mm) and a lower residual diameter stenosis (21.5 ± 12.0% vs. 25.4 ± 13.3%) compared with the angiography guidance group. Procedure-related complications did not differ between the two groups. Changes in Rutherford category from baseline during the study period are shown in Supplementary data online, *Figure S1*.

Primary and secondary endpoints

The primary and secondary endpoints are summarized in *Table 3*, and Kaplan–Meier curves for primary patency and CD TLR are presented in *Figure 2*. Primary patency was assessed for 196 patients (83%) who had completed 12 months of follow-up using predefined imaging modalities (see Supplementary data online, *Table S3*). The baseline clinical, demographic, angiographic, and procedural characteristics of the patients who completed the 12-month imaging follow-up are provided in Supplementary data online, *Tables S4* and *S5*. The 12-month primary patency rate was 83.8% in the IVUS guidance group and 70.1% in the angiography guidance group [cumulative difference 19.6% (95% CI 6.8–32.3); HR 0.43 (95% CI 0.23–0.80); $P = .01$; *Figure 2A*]. Clinically driven target lesion revascularization occurred in 9 of 119 patients (7.6%) in the IVUS guidance group and 20 of 118 patients (16.9%) in the angiography guidance group, resulting in a higher rate of freedom from CD TLR in the IVUS guidance group [cumulative difference 11.6% (95% CI 3.1–20.1); HR 0.39 (95% CI 0.18–0.85); $P = .02$; *Figure 2B*]. Similarly, the IVUS guidance group demonstrated significantly better sustained clinical improvement [cumulative difference 15.1% (95% CI 4.4–25.8);

Table 2 Angiographic and procedural characteristics for target lesions

Characteristics	IVUS guidance (*n* = 119)	Angiography guidance (*n* = 118)	*P* value
Angiographic characteristics			
Lesion length, mean (SD), mm	204.9 (103.1)	214.5 (102.9)	.48
Reference vessel diameter, mean (SD), mm	5.0 (0.7)	5.0 (0.7)	.79
Minimal lumen diameter, mean (SD), mm	0.36 (0.65)	0.47 (0.68)	.20
Total occlusion	78 (66.7)	68 (58.1)	.23
TASC type			
A–C	60 (50.4)	63 (53.4)	.69
D	59 (49.6)	55 (46.6)	
PACSS calcification score			
0–2	65 (54.6)	72 (61.0)	.52
3–4	54 (45.4)	46 (39.0)	
Popliteal involvement	11 (9.2)	10 (8.5)	>.99
Poor distal runoff vessels[a]	30 (25.2)	36 (30.5)	.44
Procedural characteristics			
Subintimal recanalization	31 (26.5)	31 (26.5)	>.99
Use of atherectomy device	41 (35.0)	38 (32.5)	.78
Pre-balloon diameter, mean (SD), mm	5.0 (0.9)	4.5 (1.1)	<.001
Pre-balloon length, mean (SD), mm	122.3 (57.5)	119.1 (62.8)	.69
Pre-balloon maximal pressure, mean (SD), mm Hg	11.8 (3.6)	8.9 (2.7)	<.001
Total DCB length (treated lesion length), mean (SD), mm	252.3 (117.9)	262.7 (117.4)	.50
Number of DCBs, total	2.0 (0.8)	2.0 (0.8)	.75
Maximal DCB diameter, mean (SD), mm	5.8 (0.7)	5.8 (0.7)	.95
Mean DCB diameter, mean (SD), mm	5.4 (0.6)	5.4 (0.6)	.92
Adjuvant post-dilatation	31 (26.1)	16 (13.6)	.03
Maximal post-balloon pressure, mean (SD), mm Hg	13.7 (2.9)	9.6 (4.0)	.001
Bailout stenting	24 (20.5)	17 (14.5)	.30
Post-procedural minimal lumen diameter, mean (SD), mm	3.90 (0.59)	3.71 (0.73)	.03
Post-procedural diameter stenosis, mean (SD), %	21.5 (12.0)	25.4 (13.3)	.02
Immediate procedural outcomes			
Technical success	91 (76.5)	72 (61.0)	.02
Procedural success	88 (73.9)	71 (60.2)	.03
Dissection type	70 (59.8)	68 (58.1)	.67
A	8 (10.7)	15 (20.3)	
B	35 (46.7)	29 (39.2)	
C	20 (26.7)	18 (24.3)	
D	5 (6.7)	5 (6.8)	
E	2 (2.7)	1 (1.4)	

Continued

Table 2 *Continued*

Characteristics	IVUS guidance ($n = 119$)	Angiography guidance ($n = 118$)	*P* value
Distal embolization	0	0	–
Target lesion perforation	1 (0.9)	1 (0.9)	>.99
Access site complications	2 (1.7)	2 (1.7)	>.99
Post-procedure ABI[b], mean (SD)	0.99 (0.13)	0.93 (0.15)	.001

IVUS, intravascular ultrasound; PACSS, peripheral arterial calcium scoring system; DCB, drug-coated balloon; TASC, Trans-Atlantic Inter-Society Consensus; ABI, ankle–brachial index.
[a]Indicates that the number of patent runoff vessels is either 0 or 1.
[b]Measured within 48 h after the index procedure.

Table 3 Clinical outcomes at 12 months after DCB angioplasty

Outcomes	Event no./total. no (%)		Risk difference[a] (95% CI)	Hazard ratio[b] (95% CI)	*P* value
	IVUS guidance ($n = 119$)	Angiography guidance ($n = 118$)			
Primary endpoint					
Primary patency[c]	83.8 (83/99)	70.1 (68/97)	19.6 (6.8–32.3)	0.43 (0.23–0.80)	.01
Secondary efficacy endpoints					
Freedom from CD TLR	92.4 (110/119)	83.0 (98/118)	11.6 (3.1–20.1)	0.39 (0.18–0.85)	.02
Sustained clinical improvement[d]	89.1 (106/119)	76.3 (90/118)	15.1 (4.4–25.8)	0.42 (0.22–0.82)	.01
Sustained haemodynamic improvement[e]	82.4 (98/119)	66.9 (79/118)	20.3 (10.3–30.3)	0.50 (0.29–0.85)	.01
Major amputation of target limb	0/119	0/118			
Secondary safety endpoints					
All-cause death	6.7 (8/119)	7.6 (9/118)	−1.1 (−9.0–6.8)	0.76 (0.29–1.98)	.58
Cardiovascular death	2.5 (3/119)	2.5 (3/118)	−0.6 (−5.1–4.0)	0.85 (0.17–4.20)	.84
Major bleeding	1.7 (2/119)	2.5 (3/118)	−1.0 (−4.6–2.6)	0.67 (0.11–4.02)	.66

IVUS, intravascular ultrasound; CI, confidence interval; DCB, drug-coated balloon; CD TLR, clinically driven target lesion revascularization.
[a]The risk difference presented was derived through a comparison of the estimated Kaplan–Meier estimates at 395 days post-randomization.
[b]Hazard ratios are for IVUS-guided DCB angioplasty vs. angiography-guided DCB angioplasty, calculated using the Cox proportional hazards model adjusted for lesion length with a cut-off of 150 mm.
[c]Primary patency was based on the number of subjects with available imaging studies (Doppler ultrasound, CT angiography, or digital subtraction angiography).
[d]Defined as an increase in Rutherford class from baseline and freedom from target limb amputation, or target lesion revascularization.
[e]Defined as an increase in the ankle–brachial index by ≥0.15 from baseline and freedom from target lesion revascularization.

HR 0.42 (95% CI 0.22–0.82); $P = .01$], and haemodynamic improvement [cumulative difference 20.3% (95% CI 10.3–30.3); HR 0.50 (95% CI 0.29–0.85); $P = .01$] compared with the angiography guidance group (see Supplementary data online, *Figure S2*). The incidence rates of other secondary endpoints, including all-cause death, cardiovascular death, and major bleeding, were similar in both groups (*Table 3*). These findings were consistent in the per-protocol population (see Supplementary data online, *Tables S6–S8*).

Additional analyses

The beneficial effect of IVUS guidance on primary patency was consistent in best-case and worst-case sensitivity analyses (see Supplementary data online, *Table S9*). The *post hoc* analysis adjusting for enrolment site effects showed consistent results with the primary analysis (see Supplementary data online, *Table S10*). As a *post hoc* analyses, independent predictors of 12-month binary restenosis, including (Model 1) and excluding (Model 2) IVUS use as a covariate, are presented in Supplementary data online, *Table S11*. In Model 1, after multivariable adjustment, IVUS guidance was significantly associated with a lower risk of restenosis at 12 months [HR 0.40 (95% CI 0.21–0.75), $P = .004$], whereas longer lesion length [≥200 mm; HR 2.36 (95% CI 1.14–4.91); $P = .02$] and subintimal recanalization [HR 1.91 (95% CI 1.02–3.06); $P = .04$] were significant predictors of restenosis. In Model 2, a decrease in post-procedural minimal lumen diameter was significantly associated with a higher risk of 12-month restenosis, along with longer lesion length [≥200 mm; HR 2.15 (95% CI 1.07–4.34); $P = .03$].

Discussion

In this randomized, multicentre trial, IVUS-guided DCB angioplasty for FPA lesions was associated with improved rates of technical and

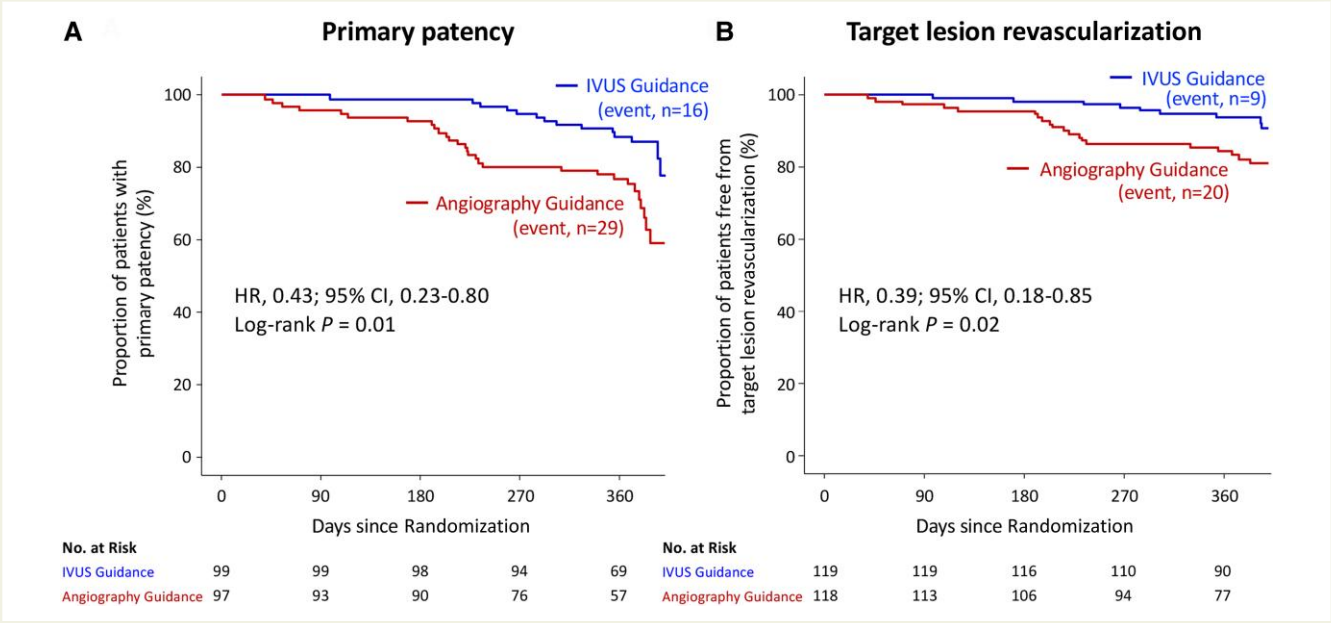


Figure 2 Kaplan–Meier survival curves for primary patency (*A*) and freedom from clinically driven target lesion revascularization (*B*). IVUS, intravascular ultrasound; DCB, drug-coated balloon; HR, hazard ratio, CI, confidence interval. Kaplan–Meier curves for the (A) primary patency and (B) target lesion revascularization. Patients were eligible for the primary patency analysis if they underwent predefined imaging evaluations for the target lesion within 395 days after the index procedure. Hazard ratios are for IVUS-guided DCB angioplasty vs. angiography-guided DCB angioplasty, calculated using the Cox proportional hazards model adjusted for lesion length with a cut-off of 150 mm

procedural success and higher post-procedural ABI compared with angiography guidance. The improved immediate procedural results included a larger post-procedural minimum lumen diameter and a lower incidence of residual stenosis (>30%). Furthermore, the IVUS guidance group exhibited higher primary patency of the target lesion, freedom from CD TLR (*Structured Graphical Abstract*), and sustained clinical and haemodynamic improvement at 12 months compared with the angiography guidance group. To the best of our knowledge, this trial is the first to demonstrate the clinical benefits of IVUS guidance for DCB angioplasty in FPA disease.

There have been several studies exploring the role of IVUS during EVT in PAD.[2,14] However, these studies have reported inconsistent clinical outcomes with IVUS-guided EVT. Iida *et al*. found that IVUS guidance was beneficial for achieving higher primary patency in TASC-II Types A–C lesions in a retrospective cohort treated with plain balloons or bare metal stents for FPA disease.[11] However, this benefit was less pronounced in TASC-II Type D lesions. Another cohort study of patients treated with DCBs for FPA disease found only a marginal association between IVUS use and reduced risk of restenosis.[15] In patients treated with drug-eluting stenting for FPA, IVUS guidance did not reduce the 1-year restenosis rate, although it appeared to produce more favourable outcomes in patients with chronic total occlusion.[16] Two large-scale retrospective studies from the United States and Japan showed that IVUS use significantly lowered the incidences of amputations and major adverse limb events in patients undergoing EVT for PAD.[17,18] Paradoxically, however, the Japanese cohort study also showed a positive association between the IVUS use and an increased risk of reintervention and readmission.[18] In a recent randomized clinical trial, Allan *et al*. demonstrated that IVUS-guided EVT improved 1-year freedom from binary restenosis in FPA lesions compared with the angiography-guided EVT group.[19] However, the rates of CD TLR remained similar between the two groups. In their trial, various devices, such as plain balloons, DCBs, bare metal stents, covered stents, and drug-eluting stents, were used for EVT, with DCBs used in approximately 50% of cases. No differences in the device size or restenosis rate for plain old balloon angioplasty or stent treatment were noted between the groups, but the IVUS group used larger DCB diameters, which may have contributed to the higher rate of freedom from restenosis in the IVUS group. The benefits of IVUS guidance compared with EVT without IVUS may be due to its better detection of calcification and dissections, more accurate vessel dimension measurements, and better identification of optimal landing zones. These IVUS findings could lead to improved vessel preparation or post-DCB lesion optimization. In our study, the IVUS guidance group demonstrated similar rates of atherectomy and provisional stenting compared with the angiography guidance group. However, the IVUS group exhibited a higher frequency of adjuvant post-dilation and post-DCB lesion optimization and used greater pre-dilation balloon diameters and post-dilation balloon pressures despite the similarity of the DCB diameters in both groups. This difference in pre- and post-dilation could have resulted in a greater post-procedural lumen diameter, a lower incidence of residual stenosis, and, subsequently, a higher post-procedure ABI in the IVUS guidance group. This pre- and post-DCB lesion optimization based on IVUS correlated with better 12-month clinical outcomes for DCB angioplasty. Our study is the first to demonstrate this causal relationship between IVUS use and improved EVT outcomes in FPA lesions. In addition to IVUS use, our study identified longer lesions (≥200 mm) and a subintimal approach as independent predictors of target lesion restenosis after DCB treatment (Model 1). Furthermore, in the second prediction model (Model 2), longer lesion length and a decreased post-procedural minimal lumen diameter were significant predictors of restenosis. This finding aligns with those of previous studies, which have shown that smaller post-procedural lumen areas and greater residual stenosis are associated with a higher risk of restenosis after DCB treatment.[15,20]

Limitations

The present study has several limitations. First, this trial was a single-blinded trial, and it was not possible for the operator to be unaware of the patient's assigned therapy group. However, an independent clinical endpoint committee blinded to the therapy assignments adjudicated all clinical outcomes and imaging analyses were performed by the independent core laboratory or imaging specialists in a blinded manner. Second, there are no established IVUS criteria for optimal EVT using DCB in the FPA. In this study, we did not set any specific IVUS goals, and decisions regarding additional pre- and post-DCB treatment or device size selection were left to the operator's discretion. Third, the methods for 12-month follow-up imaging included DUS, CTA, and DSA. Because CTA, unlike DUS, is reimbursed by the Korean national insurance system, the majority of the subjects underwent follow-up CT scans. Duplex ultrasound was primarily used in patients with decreased renal dysfunction. Finally, the generalizability of our findings requires further investigation because the current study was conducted exclusively in a Korean population whose baseline and lesion characteristics, including reference vessel diameters, may differ from those of other ethnic groups.

Conclusions

Intravascular ultrasound guidance significantly improved the outcomes of DCB angioplasty for FPA disease in terms of primary patency, freedom from CD TLR, and sustained clinical and haemodynamic improvement at 12 months. These improvements may be attributed to IVUS-guided optimization of the lesion before and after DCB treatment.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Y.-G.K. and D.C. received research grants from Medtronic, Korea United Pharm, Cook Medical, Boston Scientific, Otsuka Korea, Dong-A ST, Samjin Pharm, and Cordis.

Data Availability

The data sets generated and/or analysed during the current study are not publicly available to maintain patient confidentiality but are available from the corresponding author on reasonable request and after the agreement of all the co-authors.

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Ethical Approval

The study protocol was approved by the institutional review committee at each centre.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is ClinicalTrial.gov, NCT03517904.

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