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CLINICAL TRIAL REPORT

Five-Year Outcomes of Post-Drug-Coated Balloon Angioplasty Dissection in Complex Femoropopliteal Artery Disease

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Objective: To evaluate the long-term outcomes after drug-coated balloon (DCB) angioplasty dissection in patients with complex femoropopliteal artery disease.

Methods: Two hundred patients with femoropopliteal peripheral artery disease were enrolled in the AcoArt I trial and randomly assigned to either the DCB or percutaneous transluminal angioplasty (PTA) group. A total of 86 patients with post-balloon angioplasty dissection were reanalyzed. The primary endpoint was clinically driven target lesion revascularization (CD-TLR) over five years. Kaplan–Meier curve estimates were used to evaluate the association between the treatment and CD-TLR. Interaction and stratified analyses were also performed.

Results: Over five years, patients treated with DCB angioplasty demonstrated an acceptable effect with a numerically higher but not statistically significant rate of freedom from CD-TLR compared with those treated by PTA (Kaplan–Meier estimate of 77.6% vs 64.4%; log-rank $P = 0.08$). Among the patients who underwent TLR, the mean time from intervention to TLR in the DCB group was significantly prolonged compared to the PTA group ($P < 0.001$). The stratified analysis showed that the Rutherford classification played an interactive role in the association between the DCB angioplasty and low CD-TLR rate at five years. No significant difference in the all-cause mortality was found in the patients with post-balloon angioplasty dissection between the two treatment groups.

Conclusion: The five-year follow-up outcomes of the post-balloon angioplasty dissection in the AcoArt I trial demonstrated that DCB angioplasty is more trustworthy than PTA, with a higher rate of freedom than CD-TLR and sustained improvement in clinical symptoms. However, the all-cause mortality rate in patients with femoropopliteal lesions is similar after both DCB angioplasty and PTA.

Clinical Trial Registration: http://www.clinicaltrials.gov.

Unique Identifier: NCT01850056.

Keywords: balloon angioplasty, dissection, femoropopliteal artery disease, long-term outcomes, drug-coated balloon, percutaneous transluminal angioplasty

Introduction

The development of the drug-coated balloon (DCB) introduced the potential to decrease the incidence of restenosis by directly and effectively delivering an antiproliferative agent (paclitaxel) to the vessel wall of the target lesion without the need for permanent implants in patients with peripheral arterial disease. The THUNDER trial was the first multicenter clinical study comparing patients with

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femoropopliteal artery reconstruction treated by DCB angioplasty versus percutaneous transluminal angioplasty (PTA). The study demonstrated the benefits of DCB angioplasty relative to traditional PTA in reducing late lumen loss and target lesion revascularization (TLR) at 6 months and maintaining the reduced TLR to 24 months.[1] Moreover, the subsequent interim results of several randomized controlled trials have demonstrated the advantages of DCB angioplasty over traditional PTA for peripheral arterial disease.[2–4]

Post-balloon angioplasty dissection is a difficult problem because the purpose of balloon angioplasty is to achieve lumen expansion by tearing the plaque of the target lesion off the vessel wall. As such, post-treatment dissection is unavoidable. A flow-limiting dissection requires a bailout stent, but complications such as in-stent restenosis and stent breakage can occur over time. Mid-term follow-up results have shown that patients with non-flow-limiting dissection treated with a paclitaxel-coated balloon have acceptable outcomes without the need for stent implantation.[5] Compared with PTA, DCB angioplasty exhibits durability of freedom from revascularization at the five-year follow-up.[6,7] We performed a subanalysis of patients with post-balloon angioplasty dissection in the AcoArt I trial, and the 2-year results were similar to those reported above. The results of the study showed that the TLR rate of dissection cases in the DCB group was lower than that in the PTA group. In addition, in the bailout stent for dissection cases, the TLR rate of the DCB group was lower than that of the PTA group.[8] However, the freedom from TLR after post-DCB dissection is better than PTA during long-term follow-up still needs to be confirmed.

Methods

Overview of the AcoArt I Trial: Design, Patients, and Follow-Up

The AcoArt I trial was a prospective, multicenter, randomized controlled study of the use of local paclitaxel to prevent femoropopliteal artery restenosis. It was registered on the National Institutes of Health website (ClinicalTrials.gov; identifier: NCT01850056). This study was conducted with approval from the Ethics Committee of Chinese PLA General Hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Two hundred patients were randomized in a 1:1 ratio to treatment with a DCB or PTA from April 2013 through June 2014. A single continuous lesion in the unilateral femoral or popliteal artery was the research object. The patients' mean age was 66 years, and 74% were male. The DCB and PTA groups had a mean lesion length of 147 ± 110 and 152 ± 109 mm ($P = 0.78$), a proportion of total occlusions of 57% and 52% ($P = 0.48$), and a bailout stent implantation rate of 19% and 21% ($P = 0.48$), respectively. At the 24-month follow-up, the primary patency rate in the DCB and PTA groups was 64.6% and 31.4%, respectively ($P < 0.001$). The rate of freedom from clinically driven TLR (CD-TLR) in the DCB and PTA groups was 86.5% and 58.9%, respectively ($P < 0.001$). At the five-year follow-up, the rate of freedom from all-cause death in the DCB and PTA groups was 82.7% and 73.2%, respectively ($P = 0.26$), while the rate of freedom from CD-TLR was 77.5% and 59.1%, respectively ($P < 0.001$). A more detailed description of the results has been published in previous articles.[9–11]

Study Design, Patients, and Post Hoc Analysis of Dissection

This study was designed to investigate the long-term durability of post-balloon angioplasty dissection using a DCB compared with PTA after femoropopliteal arterial intervention. In total, 86 patients with dissection were enrolled in the DCB (n = 41) and PTA groups (n = 45) after excluding those with in-stent restenosis, bailout stent implantation, and non-dissection; the details are shown in the flow diagram in Figure 1. At two years, a trained doctor at each center performed ultrasound follow-up examinations of the evaluable patients, primary patency was recorded. The five-year follow-up was completed by a specialized contact person at each center by telephone assessment and, finally, summarized at the PLA General Hospital Vascular Surgery Center. Two physicians identified and recorded the dissections, and, in the event of inconsistency, consensus was reached by a third party. The data analysis was performed by professional data analysts. Both the physicians who read the images and the data analysts were blinded to the treatment group categories.

Endpoints

The primary endpoints throughout the five-year follow-up were CD-TLR and all-cause death and primary patency,

wherein CD-TLR was defined as reintervention at the target lesion for symptom treatment, and primary patency is defined as freedom from CD-TLR and restenosis as determined by Doppler ultrasound peak systolic velocity ratio ≥2.4 of the target lesion. The secondary endpoints were the time to first CD-TLR and the average time of CD-TLR; both were counted in days and assessed with the Rutherford classification.

Statistical Analysis

The continuous variables were displayed as the mean ± standard deviation or median (quartile range), and the categorical variables were displayed as numbers and proportions. The Mann–Whitney test and chi-square test were used to identify significant differences between the means and proportions of the two groups. Freedom from CD-TLR and all-cause death was assessed as the time-to-event outcome with Kaplan–Meier curves, and the Log rank test was used to compare the differences between the groups. Stratified analysis and interaction tests were performed based on the patients' baseline characteristics and treatments.

Multivariable Cox proportional hazards models were used to identify the associations between the treatment and CD-TLR or all-cause death. Both unadjusted and multivariate-adjusted models were used, and the results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). A two-tailed *P*-value of <0.05 was considered statistically significant in all analyses. All analyses were performed with the statistical software packages R (http://www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria) and Empower Stats (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, U.S.A.).

Results

Baseline Demographic and Lesion Characteristics in the DCB and PTA Groups

With the exception of the reference vessel diameter, the demographic data and baseline lesion characteristics of dissection were not significantly different between the DCB and PTA groups (Table 1). At the two-year follow-up, the numbers of evaluable patients were 40 and 42 in the DCB and PTA groups, respectively. A total of 38 patients in the DCB group and 37 in the PTA group were eligible for the five-year follow-up (Figure 1).

Clinical Efficacy Results Over Five Years

Until the two-year follow-up, TLR was performed in 16 of 45 patients (35.6%) in the PTA group and 6 of 41 patients (14.6%) in the DCB group ($P = 0.03$). Between the two- and five-year follow-ups, there was no increase in the number of TLR procedures in the PTA group. In the DCB group, three TLR procedures were necessary to increase performance in 38 patients. At the five-year follow-up, 16 of 45 patients (35.6%) in the PTA group and 9 of 41 patients (22.0%) in the DCB group required TLR ($P = 0.17$). Data throughout the study indicated that the DCB group had the advantage of a reduced cumulative number of patients requiring TLR, although the difference was not statistically significant. Among the patients who underwent TLR, the mean time from the intervention to TLR was 768.22 ± 622.99 days in the DCB group and 172.88 ± 98.11 days in the PTA group ($P < 0.001$), and the mean time from the intervention to the termination of follow-up for all patients (with or without TLR) was 1565.54 ± 560.92 days in the DCB group and 1092.16 ± 789.17 days in the PTA group ($P = 0.002$) (Table 2). The Kaplan–Meier curve estimate of freedom from CD-TLR between the two groups at five years is shown in Figure 2A.

The multivariable Cox regression analysis revealed an association between DCB angioplasty and a low CD-TLR rate (HR = 0.49; 95% CI, 0.22–1.11; $P = 0.09$). The rate of freedom from CD-TLR showed a significant downward trend in adjusted Models I and II. Model I reduced the CD-TLR rate by 61% (HR = 0.39; 95% CI, 0.16–0.91; $P = 0.03$), while Model II reduced the CD-TLR rate by 74% (HR = 0.26; 95% CI, 0.10–0.67; $P = 0.006$). The specific adjustment variables in Models I and II are shown in Table 3.

Clinical Results of Safety Over Five Years

The final report from the AcoArt I trial showed that none of the deaths were adjudicated as device- or procedure-related.[11] Over the five-year follow-up of patients with post-balloon angioplasty dissection after intervention, there was no significant difference in mortality between the DCB group (3 of 41 patients, 7.3%) and PTA group (8 of 45 patients, 17.8%, $P = 0.15$). The mean time from the intervention to death was 1070.33 ± 793.95 days in the DCB group and 1226.62 ± 498.98 days in the PTA group ($P = 0.70$) (Table 2). The Kaplan–Meier estimates showed that the five-year rate of freedom from all-cause death in

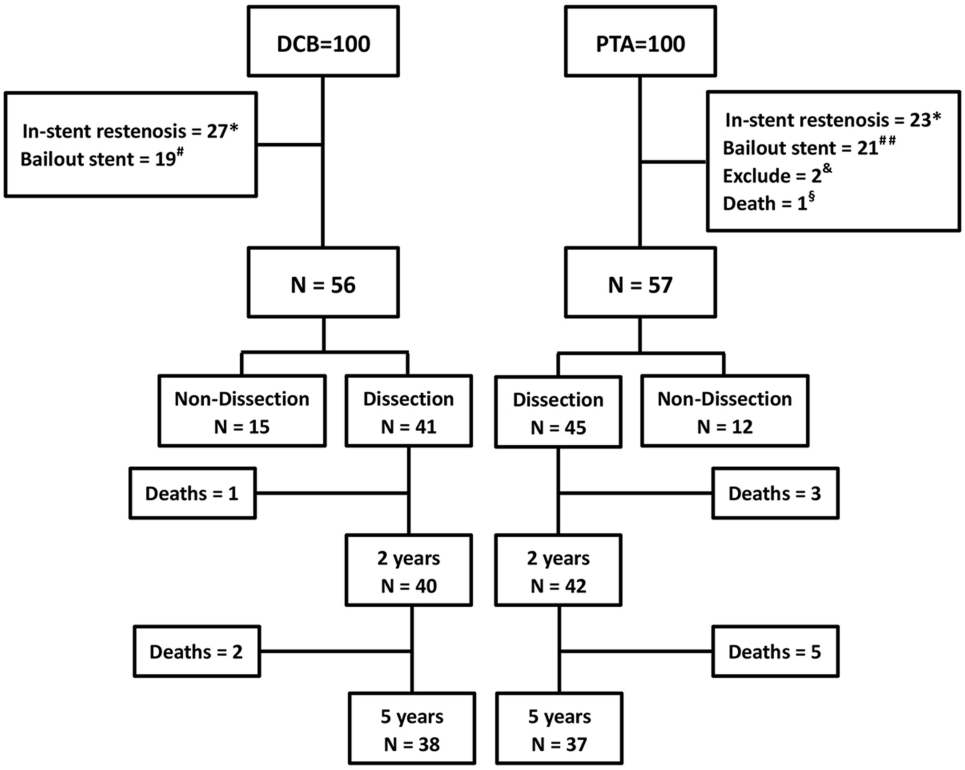

Figure 1 Flow diagram of patients with dissection in the AcoArt I trial throughout the five-year follow-up. *One death occurred before the six-month follow-up. # Two patients were treated for in-stent restenosis. ##Four patients were treated for in-stent restenosis. &Two patients were excluded due to use of a non-assigned uncoated balloon. §One death occurred shortly after the six-month follow-up.

the DCB group was 92.6% compared with 75.3% in the PTA group (log-rank P = 0.15) (Figure 2B). The Cox regression analysis indicated that the all-cause mortality in the DCB group was numerically lower than that in the PTA group (HR = 0.39; 95% CI, 0.10–1.47; P = 0.17). This trend did not change in adjusted Models I and II, and no significant differences were found (Table 4). The overall five-year rate of major amputation in the AcoArt I trial was 2.2% (2/89) in the DCB group and 4.4% (4/91) in the PTA group (P = 0.42). In the present study, since the number of patients was too small, the amputation rates were not compared between the groups.

Stratified Analysis of Freedom from CD-TLR

A post hoc analysis of the subgroups defined by the baseline demographic or clinical characteristics is presented in a forest plot comparing the freedom from CD-TLR in Figure 3A. Throughout the five-year follow-up, in some clinical and anatomical subgroups, the DCB group had a greater advantage of freedom from CD-TLR than the PTA group, including higher proportions of male patients, non-diabetic patients, non-hypertensive patients, and patients with Rutherford classifications 2 and 3. The interaction analysis showed that the Rutherford classification played an interactive role in the association between DCB and a low CD-TLR rate, ie, patients with a low Rutherford classification had a lower CD-TLR rate than those with a high Rutherford classification (P-value for interaction = 0.03). The stratified analysis results of freedom from CD-TLR at two years are shown in Figure 3B.

Discussion

In previous studies, after five years of follow-up, the rate of freedom from CD-TLR was higher in the DCB group than in the PTA group, while the all-cause mortality was not significantly different between the groups.[6,7,11] These results support the hypothesis that short-term exposure to paclitaxel in the vessel wall can inhibit neointimal hyperplasia and effectively reduce the need for TLR for up to five years. In addition, the use of a DCB did not increase the mortality compared with an uncoated balloon. Post-balloon angioplasty dissection inevitably occurs after DCB intervention, and mid-term follow-up results suggest that

Table 1 Demographic Data and Baseline Lesion Characteristics of Patients with Dissection in the DCB and PTA Groups

Characteristics	Overall n=86	DCB Group n=41	PTA Group n=45	P-value
Male	66 (76.7)	31 (75.6)	35 (77.8)	0.81
Age, yr	63.37 ± 9.12	64.02 ± 9.17	62.78 ± 9.14	0.53
BMI, kg/m2	23.27 ± 2.98	22.88 ± 3.01	23.62 ± 2.95	0.25
Smoking	44 (51.2)	22 (53.7)	22 (48.9)	0.66
Diabetes mellitus	44 (51.2)	18 (43.9)	26 (57.8)	0.20
Hypertension	51 (59.3)	23 (56.1)	28 (62.2)	0.56
Hyperlipidemia	21 (24.4)	10 (24.4)	11 (24.4)	1.00
CAD	15 (17.4)	5 (12.2)	10 (22.2)	0.22
Rutherford class				0.10
Grade 2	10 (11.6)	7 (17.1)	3 (6.7)	
Grade 3	42 (48.8)	22 (53.7)	20 (44.4)	
Grade 4	20 (23.3)	9 (22.0)	11 (24.4)	
Grade 5	14 (16.3)	3 (7.3)	11 (24.4)	
ABI	0.49 ± 0.27	0.54 ± 0.23	0.43 ± 0.29	0.06
Length of target lesion, mm	126.09 ± 93.60	120.85 ± 96.53	130.86 ± 91.68	0.62
RVD, mm	3.50 ± 0.60	3.64 ± 0.58	3.38 ± 0.60	0.04
MLD, mm	0.51 ± 0.71	0.54 ± 0.81	0.48 ± 0.62	0.71
Total occlusions	49 (57.0)	23 (56.1)	26 (57.8)	0.88
Degree of stenosis,%	81.49 ± 21.69	83.63 ± 21.79	85.07 ± 19.69	0.75
Residual stenosis, %	37.09 ± 12.11	36.75 ± 12.67	38.43 ± 11.91	0.53
Follow-up time, days	1689.33 ± 399.23	1745.98 ± 349.04	1637.71 ± 437.53	0.21

Note: Values are presented as mean ± standard deviation or n (%).
Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CAD, coronary artery disease; DCB, drug-coated balloon; MLD, minimal luminal diameter; PTA, percutaneous transluminal angioplasty (uncoated balloon); RVD, reference vessel diameter.

patients with dissection following treatment with a paclitaxel-coated balloon have superior outcomes of freedom from CD-TLR.[5,8] However, further research should be performed to assess the long-term outcomes of post-balloon angioplasty dissection to determine whether treatment with a DCB has a particularly positive effect and whether the all-cause death outcomes are worse than those after PTA.

Effectiveness

The main findings regarding the treatment effectiveness in this study are as follows: Five years after the intervention, post-DCB dissection required fewer vascular reconstructions than post-PTA dissection, this is consistent with the overall results of the AcoArt I trial for 5 years. In all patient follow-ups, CD-TLR was necessary for fewer patients in the DCB group (21 of 91 patients; 23%) than in the PTA group (40 of 92 patients; 43%) (P=0.003),[11] and the lack of statistical significance in this study might have been due to the small sample sizes. Therefore, combined with the results of the 2-year follow-up,[8] This study also further confirms the long-term stability of femoropopliteal artery disease after treatment with DCB, even in the presence of dissection. However, the evaluation of the time from the intervention to TLR and the mean time from the intervention to the termination of follow-up for all patients (with or without TLR) showed that the time to reintervention was significantly longer in the DCB group than in the PTA group (Table 2). This was also similar to the five-year outcomes of the AcoArt I trial.[11] Thus, compared with PTA, post-balloon angioplasty dissection with a DCB reduced the CD-TLR rate by at least 51% during the five-year follow-up period (Table 3).

In the subgroup analysis of the THUNDER trial,[5] 56% of patients in both groups developed dissection after the intervention, and TLR was performed in 56% of patients in the PTA group compared with 10% of patients in the DCB group throughout the two-year follow-up (P = 0.002). However, at the two-year follow-up of this study, the TLR was 35.6% in the PTA group compared with 14.6% in the DCB group (P = 0.03).[8] Moreover, the incidence of dissection in the IN.PACT trial was 63.8% in the DCB group and 61.1% in the PTA group (P = 0.36).[2] Unfortunately, for that large multicenter, randomized controlled trial, no follow-up study of dissection has been published. Therefore, we can only determine the effectiveness of the DCB treatment for femoropopliteal

Table 2 Comparison of Effectiveness and Safety Results During Follow-Up Between DCB and PTA Groups

	DCB Group n=41	PTA Group n=45	P-value
Findings at 2 years			
CD-TLR	6 (14.6%)	16 (35.6%)	0.03
Time to first CD-TLR, days	400.83 ± 311.02	172.88 ± 98.11	0.01
Primary patency	17 (47.22%)	12 (30.00%)	0.12
Rutherford stage improvement			0.02
No	6 (16.7%)	17 (43.6%)	
Yes	30 (83.3%)	21 (53.8%)	
Worse	0 (0.0%)	1 (2.6%)	
Rutherford class	1.72 ± 0.81	2.54 ± 0.88	<0.001
ABI	0.84 ± 0.20	0.60 ± 0.28	0.002
Improvement in ABI	0.29 ± 0.30	0.18 ± 0.37	0.26
Death	1 (2.4%)	3 (6.7%)	0.35
Time of death, days	164	805.67 ± 110.89	0.04
Findings at 5 years			
CD-TLR	9 (22.0%)	16 (35.6%)	0.17
Time to first CD-TLR, days	768.22 ± 622.99	172.88 ± 98.11	<0.001
Average time of CD-TLR, days	1565.54 ± 560.92	1092.16 ± 789.17	0.002
Rutherford stage improvement			0.80
No	6 (19.4)	8 (24.2)	
Yes	22 (71.0)	23 (69.7)	
Worse	3 (9.7)	2 (6.1)	
Rutherford class	1.81 ± 1.11	2.48 ± 1.56	0.05
Death	3 (7.3%)	8 (17.8%)	0.15
Time of death, days	1070.33 ± 793.95	1226.62 ± 498.98	0.70

Note: Values are presented as mean ± standard deviation or n (%).
Abbreviations: ABI, ankle-brachial index; CD-TLR, clinically driven target lesion revascularization; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty (uncoated balloon).

lesions based on the overall outcomes. The patients in the DCB group maintained lower CD-TLR rates than the patients in the PTA group (25.5% vs 35.6%, respectively; $P = 0.08$). Furthermore, the Kaplan–Meier estimate of freedom from CD-TLR was significantly higher with DCB angioplasty than PTA (74.5% vs 65.3%,

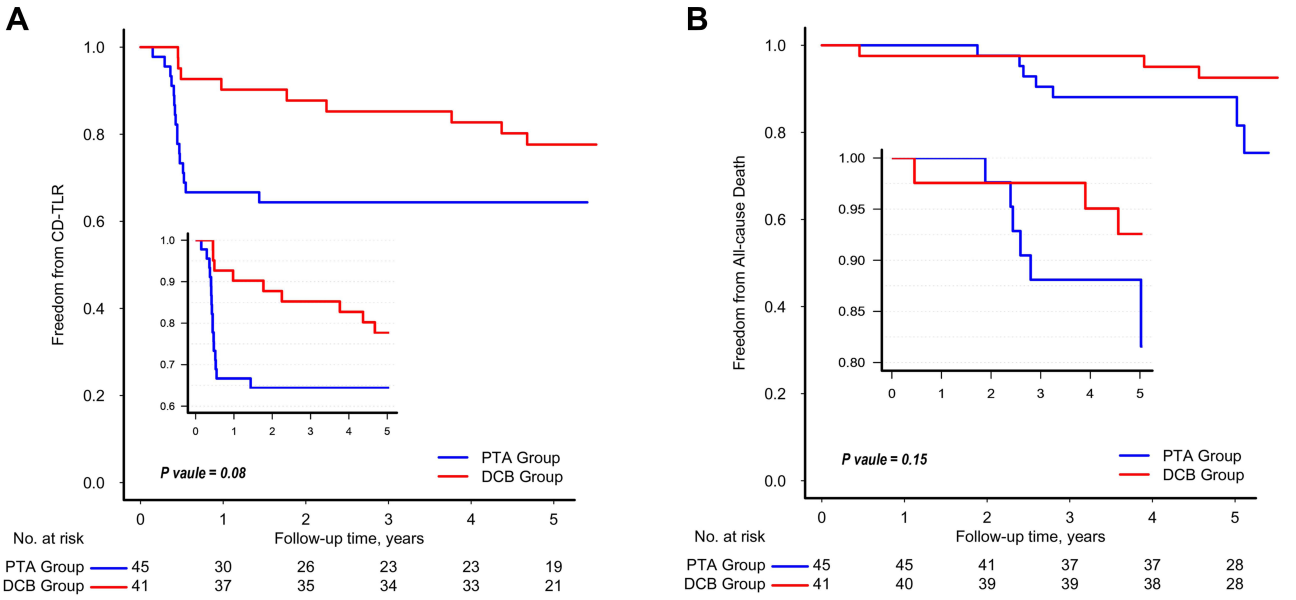

Figure 2 (**A**) Kaplan–Meier curve estimate of freedom from CD-TLR at five years. (**B**) Kaplan–Meier curve estimate of freedom from all-cause death at five years.

Table 3 Cox Regression Analysis of CD-TLR in Patients with Post-Balloon Angioplasty Dissection Between DCB and PTA Groups

Overall	Crude		Model I		Model II	
	HR, 95% CI	P-value	HR, 95% CI	P-value	HR, 95% CI	P-value
PTA group	Ref	–	Ref	–	Ref	–
DCB group						
2 years	0.34 (0.13, 0.86)	0.02	0.27 (0.10, 0.72)	0.01	0.18 (0.06, 0.53)	0.002
5 years	0.49 (0.22, 1.11)	0.09	0.39 (0.16, 0.91)	0.03	0.26 (0.10, 0.67)	0.006

Notes: Crude means were not adjusted. Model I was adjusted for age, hypertension, hyperlipidemia, coronary artery disease, and smoking. Model II was adjusted for age, hypertension, hyperlipidemia, coronary artery disease, smoking, Rutherford class at baseline, reference vessel diameter at baseline, and ankle brachial index at baseline.
Abbreviations: CD-TLR, clinically driven target lesion revascularization; CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; PTA, percutaneous transluminal angioplasty (uncoated balloon).

respectively; log-rank $P = 0.02$) throughout the five years.[7] In the AcoArt I trial, the incidence of dissection was 78.1% in the DCB group versus 81.1% in the PTA group, Undeniably, this correlates with the high complexity of the selected femoropopliteal artery lesions, such as the mean lesion length was 126 mm, and more than half (57%) were total occlusions; notably, however, patients with in-stent restenosis were excluded when calculating the incidence of dissection. In the present study, the cumulative rate of freedom from CD-TLR by the Kaplan–Meier estimate at two years was 85.4% for DCB and 64.4% for PTA (log-rank $P = 0.017$), while that at five years was 77.6% for DCB and 64.4% for PTA (log-rank $P = 0.08$). The lower CD-TLR rate in DCB group compared to PTA group indicated that DCB still has the advantage to maintain the clinical treatment effect during the five year follow-up. Notably, the effect of freedom from CD-TLR was better maintained after DCB angioplasty in patients with Rutherford classifications 2 and 3 than Rutherford classifications 4 and 5 during the five-year follow-up. This was consistent with our real-world experience. The Rutherford classification represents the severity of limb ischemia. As the severity of limb ischemia increases, patients are more likely to require CD-TLR after intervention. We should also note that few TLR events occurred in the two groups after two years of intervention. However, we cannot be blindly optimistic about this. Considering the differences between the medical model in China and that in the United States or in European countries as well as patients' financial situations, some patients might be unwilling to seek revascularization because of limited finances or may lose confidence in the operation's effect. Additionally, some patients may die before requesting to undergo TLR and, therefore, be lost to follow-up. In addition, we should also be soberly aware that the effectiveness of DCB lies in delaying rather than preventing restenosis for femoropopliteal artery disease. With the disappearance of the antiproliferative effect of paclitaxel, the advantage of DCB over PTA will gradually decrease, which is consistent with the difference between Rutherford stage and freedom from

Table 4 Cox Regression Analysis of All-Cause Death During 5-Year Follow-Up Period in Patients with Post-Balloon Angioplasty Dissection Between DCB and PTA Groups

Overall	Crude		Model I		Model II	
	HR, 95% CI	P-value	HR, 95% CI	P-value	HR, 95% CI	P-value
PTA group	Ref	–	Ref	–	Ref	–
DCB group						
2 years	0.35 (0.04, 3.40)	0.37	0.19 (0.02, 1.91)	0.16	0.11 (0.00, 3.48)	0.21
5 years	0.39 (0.10, 1.47)	0.17	0.32 (0.07, 1.34)	0.12	0.21 (0.04, 1.25)	0.09

Notes: Crude means were not adjusted. Model I was adjusted for sex, age, hypertension, hyperlipidemia, coronary artery disease, and smoking. Model II was adjusted for sex, age, hypertension, hyperlipidemia, coronary artery disease, smoking, Rutherford class at baseline, reference vessel diameter at baseline, and ankle brachial index at baseline.
Abbreviations: CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; PTA, percutaneous transluminal angioplasty (uncoated balloon).

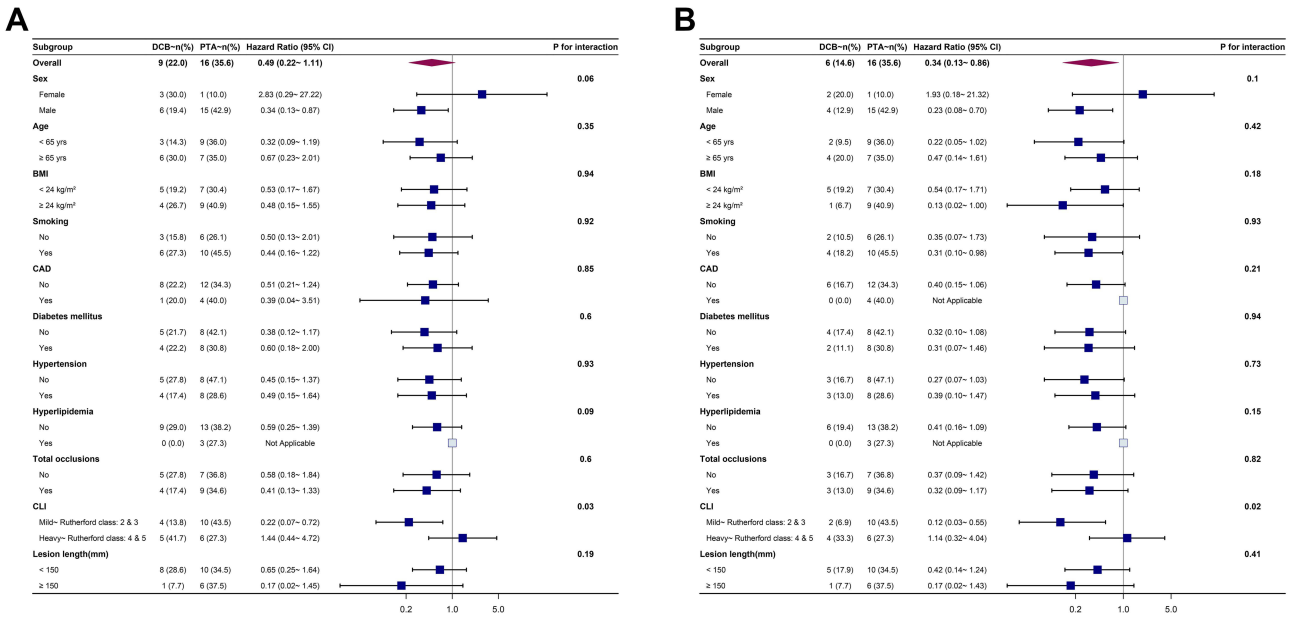

Figure 3 (**A**) Post hoc analysis of freedom from CD-TLR at five years. (**B**) Post hoc analysis of freedom from CD-TLR at two years.

CD-TLR in this study being less pronounced at the 5-year follow-up than at the 2-year follow-up. In any case, it must be acknowledged that after five years of follow-up, the amputation rate in the AcoArt I trial was indeed lower in the DCB group than in the PTA group (2.2% vs 4.4%, respectively; $P = 0.42$).[11]

Safety

Controversy has persisted over whether the use of paclitaxel-coated devices is associated with increased mortality. This argument was brought to the forefront after the publication of Katsanos et al's article,[12] in which a systematic review and meta-analysis of 28 randomized controlled trials investigating the femoral and/or popliteal arteries was performed. The authors reported an increased risk of death following the application of paclitaxel-coated devices in the femoropopliteal artery. For safety reasons, the US Food & Drug Administration has suspended several major ongoing randomized controlled trials in the field. The use of a DCB as a first-line treatment in intravascular revascularization of the femoropopliteal artery is generally prohibited and may be limited to patients with a particularly high risk of restenosis.[13]

However, Bonassi[14] questioned Katsanos et al's[12] meta-analysis, suggesting that the existence of selection bias led to doubt regarding the authenticity of the increase in the all-cause mortality of patients treated with paclitaxel-coated devices. The long-term follow-up outcomes from several clinical studies such as THUNDER, IN. PACT SFA, and LEVANT Series Research[6,7,15] as well as several meta-analyses[16,17] identified no differences in mortality between DCB angioplasty and PTA. Additionally, the authors indicated the lack of a dose–response relationship between paclitaxel and mortality.

The five-year all-cause mortality rate in the AcoArt I trial was 19.1% in the DCB group and 26.4% in the PTA group ($P = 0.26$),[11] while that in the present study was 7.3% in the DCB group and 17.8% in the PTA group ($P = 0.15$) (Table 2). It indicates that after long-term follow-up, the use of DCB did not increase overall mortality compared with PTA, and this trend did not change in patients with dissection. Furthermore, the all-cause mortality rate in the patients with dissection in the DCB group was 61% lower than that of the patients in the PTA group (Table 4). After adjusting for the relevant influencing factors, the trend did not change. Of course, this may also have been an artifact caused by the insufficient number of patients. Additionally, in the Kaplan–Meier curve estimate of freedom from all-cause death at the end of the follow-up, there was no significant difference between the two groups. Moreover, although coronary artery disease plays an interactive role in the association between dissection and death (Table 5), we found no increase in the mortality of the patients with dissection among those with coronary artery disease. However, coronary heart disease was associated with a higher risk of mortality in

Table 5 Comparison of All-Cause Death in Different Subgroups Between Patients with and without Dissection

Characteristic	Dissection Group		Non-Dissection Group		P	p for Interaction
	N	Death	n	Death		
Sex						0.49
Female	20	1 (5.0%)	8	1 (12.5%)	0.49	
Male	66	10 (15.2%)	19	2 (10.5%)	0.61	
Age						0.82
<65 yrs	46	4 (8.7%)	12	1 (8.3%)	0.97	
≥65 yrs	40	7 (17.5%)	15	2 (13.3%)	0.71	
BMI, kg/m^2						0.80
<24	49	7 (14.3%)	18	2 (11.1%)	0.74	
≥24	47	4 (10.8%)	9	1 (11.1%)	0.98	
Smoking						0.37
No	42	6 (14.3%)	14	1 (7.1%)	0.48	
Yes	44	5 (11.4%)	13	2 (15.4%)	0.70	
CAD						0.02
No	71	9 (12.7%)	17	0 (0.0%)	0.12	
Yes	15	2 (13.3%)	10	3 (30.0%)	0.31	
Diabetes mellitus						0.31
No	42	5 (11.9%)	11	2 (18.2%)	0.58	
Yes	44	6 (13.6%)	16	1 (6.2%)	0.43	
Hypertension						0.74
No	35	6 (17.1%)	9	1 (11.1%)	0.66	
Yes	51	5 (9.8%)	18	2 (11.1%)	0.88	
Hyperlipidemia						0.58
No	65	9 (13.8%)	20	2 (10.0%)	0.65	
Yes	21	2 (9.5%)	7	1 (14.3%)	0.72	
Total occlusions						0.14
No	37	5 (13.5%)	19	1 (5.3%)	0.35	
Yes	49	6 (12.2%)	8	2 (25.0%)	0.34	
CLI						0.38
Mild, Rutherford class: 2 and 3	52	7 (13.5%)	15	1 (6.7%)	0.48	
Heavy, Rutherford class: 4, 5	34	4 (11.8%)	12	2 (16.7%)	0.67	
Long lesions, ≥150mm						0.49
No	57	7 (12.3%)	25	3 (12.0%)	0.97	
Yes	29	4 (13.8%)	2	0 (0.0%)	0.57	
Group						0.62
DCB	41	3 (7.3%)	15	2 (13.3%)	0.48	
PTA	45	8 (17.8%)	12	1 (8.3%)	0.43	
Aspirin, ≥12mon						0.51
No	23	2 (8.70%)	6	1 (16.67%)	0.57	
Yes	63	9 (14.29%)	21	2 (9.52%)	0.58	
Clopidogrel, ≥12mon						0.62
No	33	5 (15.15%)	4	1 (25.00%)	0.61	
Yes	53	6 (11.32%)	23	2 (8.70%)	0.73	

Note: Values are presented as mean ± standard deviation or n (%).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CLI, critical limb ischemia; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty (uncoated balloon).

the DCB group during the 5-year follow-up period of AcoArt I trial (47.06% in patients who died versus 18.06% in survivors) (P=0.023), this predictor might indicate poor general and cardiovascular status.[11] Overall, this needs to be confirmed in further studies involving larger numbers of patients.

Summary

Undeniably, as the follow-up period increases, the number of available patients and the effect of antiproliferative drugs gradually decrease. However, the subgroup analysis of the AcoArt I trial showed that the long-term outcomes support the advantages of maintaining freedom from re-intervention with DCB angioplasty in patients with post-balloon angioplasty dissection in complex femoropopliteal lesions. Indeed, the mid-term results[8] seem congruent with the published literature.[5] Herein, the mean lesion length was 126 mm, and more than half (57%) of all lesions were chronic total occlusions. This suggests that the efficacy of DCB angioplasty may be suitable for extension to more complex lesions in real-world clinical settings. As mentioned earlier, this seems to be consistent with the profile of DCB use recommended by the US Food & Drug Administration. Therefore, our research on post-balloon angioplasty dissection in Chinese patients with complex femoropopliteal artery disease is a useful supplement to the worldwide study of DCB angioplasty, especially with respect to long-term follow-up.

Limitations

The AcoArt I trial was not prespecified in the initial study protocol at the five-year follow-up. Therefore, the five-year follow-up was limited to a telephone interview, and the efficacy endpoints of DCB angioplasty in reducing late restenosis after dissection are not available in this study. Another limitation of this study is that because of the limited number of cases, there is no study on the specific grade classification of dissections but only on whether a dissection was present or absent. Finally, the lack of statistical significance in some associations may have been caused by insufficient statistical power, and larger clinical studies are needed to address this issue.

Conclusions

The subgroup analysis of dissection in the AcoArt I trial showed that compared with PTA, DCB angioplasty in patients with complex femoropopliteal artery disease has a higher rate of freedom from CD-TLR at five years. No increase in the all-cause mortality was found in patients with post-balloon angioplasty dissection between DCB and PTA or between patients with and without dissection overall.

Abbreviations

CD-TLR, clinically driven target lesion revascularization; CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.

Data Sharing Statement

We are willing to share individual deidentified participant data. The raw data used for the tables and figures covered in this article can be shared. (Note: Parts of the original data are in Chinese. And the explanatory notes for the abbreviations of the original data are also in Chinese.) We can provide the protocol of AcoArt I trial (in Chinese). Additional information on the design of the trial and reports are available at ClinicalTrials.gov. (Identifier: NCT01850056). Readers may contact the corresponding author to obtain the data. Available from the publication of this article and valid for five years after the publication of the article.

Disclosure

The authors report no conflicts of interest in this work.

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