Journal on Surgery
www.journalonsurgery.org

Research Article

Open Access, Volume 2

Excimer Laser Assisted Therapy and Combined with Drug Coated Balloon in the Treatment of Femoropopliteal In-Stent Restenosis: A Systematic Review and Meta-Analysis

Dan Mei; Jie Wu; Xuesong Zhang; Liang Zhang; Kuiyang Wang; Lei Song*

The Second Affiliated Hospital of Dalian Medical University, China.

Abstract

Objective: The purpose of this article was to assess the efficiency of Excimer laser assisted therapy and combined with drug coated balloon in the treatment of stent stenosis femoropopliteal in-stent restenosis.

Methods: Pubmed, OVID, Scopus, Embase, and Cochrane were searched systematically. The endpoints were patency at 12 months, target lesion revascularization at 12 months, TLR of femoropopliteal In-Stent restenosis and Tosaka class III at 12 months, reocclusion of femoropopliteal In-Stent restenosis and Tosaka class III at 12 months, bail-out stenting, and ankle brachial index at 6 months.

Results: 12 studies with 1093 participants were included. Compared with drug-coated balloons (DCB), combine laser atherectomy with drug-coated balloon (LA+DCB) significantly increased the rate of patency (12 months:OR=2.87,95% CI 1.26 to 6.55, P=0.01<0.05) and excimer laser atherectomy was used to improve the patency rate in 12-month (OR=0.40, 95% CI 0.30 to 0.50, P<0.05). The rate of Target Lesion Revascularization (TLR) in the combine excimer laser atherectomy with percutaneous transluminal angioplasty (LA+PTA) group was significantly lower than that in the PTA (NOT LA: Excimer laser therapy was not used) group (OR=0.34, 95% CI 0.19 to 0.61, P=0.0003<0.05). Compared with combine excimer laser atherectomy with balloon angioplasty (LA+BA), LA+DCB significantly decreased the rate of TLR (12-month: OR=2.87,95% CI 1.26 to 6.55, P=0.01<0.05). LA+DCB for femoropopliteal arteries in-stent restenosis of Tosaka III lesions was associated with a numerically lower target lesion revascularization compared with LA+BA (OR=0.36, 95% CI 0.21 to 0.62, P=0.0002<0.05). Compared with LA+BA, LA+DCB significantly lower the rate of femoropopliteal arteries in-stent restenosis Tosaka III lesion reocclusion rate (12-month: OR=0.25, 95% CI 0.11 to 0.60, P=0.02<0.05). The rate of bail-out stenting in the LA+DCB group was significantly lower than that in the LA+BA group (OR=0.41, 95% CI 0.26 to 0.66, P=0.0002<0.05).

Conclusion: We came to the conclusion, excimer laser adjuvant therapy and excimer laser combined with DCB in the treatment of FP-ISR had significant clinical effects.

Keywords: Femoropopliteal in-stent restenosis; Excimer laser; Drug-coated balloon; Angioplasty.

Manuscript Information: *Received: Apr 15, 2022; Accepted: May 30, 2022; Published: Jun 07, 2022*

Correspondance: *Lei Song, The Second Affiliated Hospital of Dalian Medical University, China. Email: songlei_1975@126.com*

Citation: *Mei D, Wu J, Zhang X, Zhang L, Song L. Excimer Laser Assisted Therapy and Combined with Drug Coated Balloon in the Treatment of Femoropopliteal In-Stent Restenosis: A Systematic Review and Meta-Analysis. J Surgery. 2022; 2(1): 1024.*

Introduction

Femoropopliteal (FP) segment is the most common endovascular treatment segment. Self expanding bare metal stent has become a standard instrument for arterial occlusive diseases of FP segment. Although the continuous progress of stent technology, In-Stent Restenosis (ISR) is still a common clinical problem. After angioplasty and stent implantation, the inherent vascular system will produce inflammatory reaction, leading to neointimal hyperplasia and tissue growth, leading to ISR [1]. The incidence of In-Stent Stenosis (ISR) ranged from 15% to 32% [2].

Several treatments for stent stenosis have been proposed in the United States, including plain old balloon angioplasty (POBA), cutting balloon angioplasty, angioplasty with drug-eluting balloons (DEBs), repeat stenting, excimer laser, Viabahn covered stents, Drug-coated balloons (DCBs) and self-expanding nitinol stents [3,4]. Studies have shown that DCB has advantages over POBA in patency rate and revascularization rate [5,6]. The 1-year revascularization rate and 1-year patency rate of TASC C and D lesions treated with Nitinol stent were 31.8% and 64.8% respectively [7]. The development of self-expanding nitinol stents improved rates of restenosis yet they remain as high as 40%-65% [8]. In recent years, debulking devices have been widely used in vascular diseases. Debulkingof FP lesions in stent restenosis is an attempt to reduce the burden of restenosis tissue and theoretically delay or reduce the rate of revascularization [9]. Excimer laser is one of the debulking devices. Excimer laser can inhibit platelet aggregation, potentially reducing the chance of platelet-mediated thrombus reocclusion [10]. Excimer laser was first used in coronary artery disease in 1983. Excimer laser coronary resection has been used to treat a variety of complex diseases, including thrombosis, stent stenosis, chronic complete occlusion, etc [11]. Gradually it applied to lower limb artery disease. The incidence of in-stent stenosis is as high as 10% in clinical practice, which is challenging for the treatment of in-stent restenosis. The optimal treatment regimen is still unclear and there is no guidance [12]. At present, studies have shown that drug-coated balloon combined with excimer laser atherectomy for the treatment of femoropopliteal in-stent stenosis (FP-ISR).

In this study, we evaluated the prognostic significance of excimer laser-assisted and combined drug - coated balloon therapy for FP-ISR. Therefore, the aim of the current study was to conduct a meta analysis of all eligible published studies to quantify the prognostic value of treatment of in-stent stenosis.

Materials and methods

Literature search: Pubmed, OVID, Scopus, Embase, and Cochrane databases were searched according to the guidelines of the Cochrane Handbook, without language restrictions. Our meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and meta-analyses (PRISMA) recommendations. The following keywords: “Laser Atherectomy” were used, “Critical limb ischemia”, “Peripheral vascular disease”, “In-Stent restenosis”, “Combined laser atherectomy and drug-eluting ballon” et al. The full text of the literature is not available in the database, so we directly contact the corresponding authors by mail. All results were imported into Endnote X9 (Thomson Reuters, New York, USA) for the exclusion of duplicates, and subsequently, we screened the titles, abstracts, and full texts of eligible trials. Initial screening was conducted on the basis of titles and abstracts, followed by reading of the full text.

Inclusion and exclusion criteria: Studies were included if they met the following criteria: The study was published in English; the patients were treated by debulking devices (laser or mechanical); the study included at least 20 patients; femoropopliteal. In-Stent restenosis and; angiographic evidence of significant ISR > 70% by visual assessment within the stent; Rutherford category 2 to 6; reported at least one of the end points (primary patency, freedom from TLR, reocclusion, ankle brachial index, bail-out Stenting). Case reports were excluded (patient enrollment <20). Duplicate reports were excluded; only the most recent one was included.

Endpoints and data extraction: The endpoints were patency at 12 months, target lesion revascularization at 12 months, TLR of femoropopliteal. In-Stent restenosis and Tosaka class III at 12 months, reocclusion of femoropopliteal In-Stent restenosis and Tosaka class III at 12 months, bail-out stenting, and ankle brachial index at 6 months. Data included publication date, name of first author, study type, patient characteristics (mean age, number of patients, sex ratio, primary disease), inclusion criteria, exclusion criteria, and ISR lesion characteristics (Rutherford class, Tosaka class, TASC class). The endpoints were extracted from the eligible studies using standard data extraction.

Data synthesis and statistical analysis: Odds ratio (OR) with 95% Confidence intervals (CIs) and mean difference (SMD) with 95% CIs were used for the expression of dichotomous and continuous variables, respectively. A P value <0.05 was considered as statistically significant. The heterogeneity among trials was assessed with the Cochran’s Q-statistic test and the I^2 test. If I^2 was more than 50% or P value (Q-test) was less than 0.05, we thought high heterogeneity existed and a random-effects model was adopted. Otherwise, a fixed effects model was used. The statistical analysis was conducted using RevMan software (version 5.4; Cochrane Collaboration, Copenhagen, Denmark).

Quality assessment: Two authors independently assessed the following seven categories of risk of bias according to the Cochrane guidelines and the following three categories of risk of bias according to the Newcastle-Ottawa Scale, and lack of consensus was resolved in group discussions. The Cochrane guidelines was classifiied in the following seven categories: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, (7) other sources of bias. Each category can be graded into three levels: low risk, unclear risk, or high risk. The Newcastle-Ottawa Scale was applied to assess nonrandomized studies in three categories: selection, comparability, and exposure. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Result

Study selection 810 articles were identified initially. Finally, a total of 12 studies with 1093 participants were included in this meta-analysis. The detailed process of literature search is summarized in (Figure 1).

Table 1: Characteristics of included trials (a).

		n	Age, y	Male gander	Hyperlipidemia	Hypertension	CAD	CLI	Lesion Length, mm	Rutherford class	Tosaka class	TASC class	ABI
Roberto Gandini[13]	2013	LA+DEB 24	74.1 ± 7.2	(18) 75%	(21) 87%	(21) 87%	(9) 37%	NA	224±94	NA	Class 3:100%	NA	NA
		DEB 24	70.1 ± 11.6	(21) 87%	(18) 75%	(18) 75%	(6) 25%		259±87				
SenYang[14]	2021	LA+DCB 34	68.5 ± 6.9	(29) 82.9%	(15) 42.9%	(24) 68.6%	(14) 40.0%	NA	132 ± 83	Class4:(12)34.3% /(13) 29.5%;Class 5 : (21)60.0%/ (27)61.4% ; Class6:(2)5.7%/ (4)9.1%	NA	NA	0.35 ± 0.27
		DCB 42	68.3 ± 6.0	(34) 77.3%	(18)40.9%	(37) 84.1%	(24) 54.5%		113 ± 91				0.3 ± 0.3
Eric J. Dippel[15]	2015	LA+PTA=169	68.5 ± 9.8	(106) 62.7%	(163)96.4%	(162)95.8%	(109)64.3%	(27)16%/	196±120	NA	NA	C/D 59.9%	0.6 ± 0.2
		PTA=81	67.8 ± 10.3	(50) 61.7%	(77)95%	(76)93.8%	(56)68.8%	(10)12.3%	193±119			C/D 56.9%	0.7 ± 0.2
EhrinJ. Armstrong[16]	2015	LA+PTA 54	73 ± 11	(35) 65%	NA	(52) 96%	(29) 54%	(26) 49%	222±118	Class 1--3: (35) 65%/(44) 54% Class 4--6:(19) 35%/(37) 46%	Class1:(5)10%/(32) 40%; Class2:(12)22%/(32) 40%;Class3:(37) 69%/(17) 20%	C/D (37) 69%/(25) 35%	0.7 ± 0.22
		PTA 82	69 ± 11	(41) 51%		(74) 91%	(40) 50%	(47) 58%	114±106				0.65 ± 0.18
Damianos G.Kokkinidis[17]	2017	LA+DCB 62	68.5 ± 10	(51) 82.3%	(51) 83.6%	(54) 88.5%	(28) 45.9%	(22)36.1%	256±123	NA	Class2:16(25.8%)/13 (26.0%); lass3:46(74.2%)/37 (74.0%);	C/D:56(93.3%)/ 36(78.3%)	0.5 ± 0.3
		LA+BA) 50	72.± 10.8	(35) 70%	(25) 75.8%	(48) 96.0%	(28) 56.0%	(15)30.0%	240.6±107				0.69 ± 0.3
Damianos G.Kokkinidis[18]	2019	LA+DCB 66	68 ± 10	(55) 83%	(56) 85%	(58) 88%	(31) 47%	(18) 27%	263±126	NA	Class 3:49 (74%)/36 (71%)	C/D:61(84%)/37 (79%)	NA
		LA+BA 51	73 ± 11	(35) 69%	(25) 74%	(49) 96%	(28) 55%	(12) 24%	237±107				
Stefanos Giannopoulos[19]	2019	LA+DCB 27	67.4 ± 4.8	(27) 100%	(26) 96.3%	(24) 88.8%	(14) 52.6%	(11) 40.7%	132.8±80	NA	Class2:11.1%/29.4% Class3:88.8%/70.6%	A :0%/8.5% B: 7.4%/14.9% C: 7.4%/29.8% D:85.2%/46.8%	0.52
		LA+BA 51	72.5 ± 10.7	(35) 68.6%	(25) 73.5%	(49) 96.1%	(28) 54.9%	(14) 29.8%	106.8±60				0.69
Andrej Schmidt[20]	2014	LA+BA 90	69.5 ± 9.3	(65) 73.9%	(64) 71.1%	(80) 88.9%	NA	NA	123±96	Class 2:(19) 21.6%; Class 3:(63) 71.6%; Class 4: (3) 3.4%; Class 5: (3) 3.4%	Class 1:(24) 26.7%; Class 2:(35) 38.9%; class 3:(31) 34.4%	NA	0.61 ± 0.23
John R. Laird, Jr.[21]	2012	LA+BA+HC-SG 27	70 ± 10.5	(17) 63%	(24) 88.9%	(25) 92.6%	NA	NA	207±103	Class 2: (7) 25.9%; Class 3: (18) 66.7%; Class 4: (18) 66.7% Class 5: 0%	NA	A :(1) 3.7% B :(4) 14.8% C :(13) 48.1% D :(9) 33.3%	0.58 ± 0.24
Ming-Yuan Liu[22]	2021	LA+DCB 59	71 ± 11.2	(39) 66.1%	(35) 59.3%	(40) 67.8%	(17) 28.8%	(49) 83.1%	184 ± 78	Class 0-1:0 Class 2-3:(11) 18.6% Class 4-6: (48) 81.4%	NA	A :(4) 6.8% B :(8) 13.6% C :(16) 27.1% D :(31) 52.5%	0.38 ± 0.10
Matthew Allan[23]	2018	RA+DCB 26	68 (51-76)	(21) 80%	(24) 92%	(22) 85%	NA	NA	117±34	NA	Class 1: 15% Class 2:26% Class 3:0% Class 4:2%	NA	NA
Artur Milnerowicz[24]	2019	RA+DCB 74	66.7 ± 9.7	(49) 62%	NA	(45) 57%	(42) 53%	NA	220±150	Class 2:(13) 16.5% Class 3:(24) 30.4% Class 4 :(30) 38% Class 5 :(7) 8.9%	NA	B:(10) 12.7% C :(30) 38% D:(34) 43%	NA

Table 2: Characteristics of included trials (b).

	Design	year	Inclusion criteria	Exclusion criteria	Results	Follow-up month
Roberto Gandini 2013	Prospective, Single-center, Randomized controlled trial	2009.10-2011.03	In-Stent Restenosis;superficial femoral artery (SFA) ;stent occlusion	NA	The good patency and clinical results, with 92% limb salvage at 12 months in patients treated with the LD+DEB angioplasty, indicate a benefit to completely and efficiently treating CLI patients with SFA stent occlusion	12
Sen Yang2021	Single-center, Retrospective	2018.09-2019.02	infrapopliteal arte- rial disease in diabetic foot patients with CLI in Rutherford grades 4 to 6	NA	LA+ DCB can better improve clinical symptoms and patency than DCB alone, significantly reduce the rate of major amputation at 24-month	12
Eric J. Dippe l2015	Prospective, Multi-central, Randomized controlled trial	2011.06-2014.02	Femoropopliteal in-Stent restenosis; significant ISR >50% diameter stenosis (DS)	NA	LA + PTA is safer and more effective than PTA alone	6 and 12
Ehrin J. Armstrong, 2015	Single-center	2006-2013	Femoropopliteal In-Stent Restenosis	NA	LA + PTA which treatment of class I / II FP-IRS can reduce the rate of revascularization , restenosis and reocclusion.	12
Damianos G. Kokkinidis,2017	Retrospective, Double-centers	NA	Tosaka II and Tosaka III ;FP-ISR	NA	LA + DCB is more effective in the treatment of complex FP-ISR The rate of bail-out stenting is reduced, and the revascularization are improved at 12-month	12
Damianos G. Kokkinidis,2019	Retrospective, Double-centers, Cohort study	NA	Tosaka II and Tosaka III ;FP-ISR	NA	Compared with LA + DCB and LA + BA,LA+DCB reduced the rate of bail-out stenting and improved revascularization and restenosis.	12
Stefanos Giannopoulos 2019	Retrospective, Double-centers, Cohort study	2015-2017	Tosaka II and Tosaka III;FP-ISR	NA	Compared with LA + DCB and LA + BA,LA+DCB reduced the rate of bail-out stenting and improved revascularization and restenosis	12
Andrej Schmidt 2014	Prospective, Multi-central, Single-arm study	NA	cri- teria were treated with excimer laser and adjunctive balloon angioplasty if indicated;ISR	3 months prior to study enrollment;aneu-rysm within the target lesion; grade 4/5 stent fracture affecting the target stent ; proximal to the target stent.		12
John R. Laird, Jr. 2012	Prospective, Multi-central, Single-arm study	NA	Femoropopliteal Artery In-Stent Restenosis (angiographic evidence of significant restenosis (defined as =50% by visual estimate) within a previously deployed femoropopliteal nitinol stent)	if there was Grade 4 or 5 stent fracture in the restenotic stent		6 and 12
Ming-Yuan Liu 2021	Single-center, Single-arm study	2016.06-2018.05	angiographic evidence of significant ISR > 70% by visual assessment within the stent; Rutherford category 2 to 6	stent fracture;planned amputation of the target limb; expected follow-up time < 2 years.	LA + DCB is safe, minimally invasive and effective in the treatment of FP-ISR.	12
Matthew Allan2018	Retrospective, Single-center, Single-arm study, Cohort study	2010.12-2016.04	ISR (in-stent restenosis)	NA	La + DCB treatment is effective and a feasible treatment option for selected cases of in-stent restenosis	12

Artur ilnerowicz2019	Retrospective, Single-center, Single-arm study, Cohort study	2014.04-2017.06	Total In-Stent Occlusions in Iliac and Infrainguinal Arteries	NA	RA + DCB can effectively treat complete intravascular occlusion and reduce the restenosis rate for 1 year	12

Study characteristics: 2 studies compared the treatment method of LA+PTA and PTA (NOT LA: excimer laser therapy was not used), 2 compared LA+DCB and DCB (NOT LA), 3 compared LA+DCB and LA+BA; In addition, 5 studies were single arm studies including 3 studies were treatment method of LA+BA/DCB,2 studies were RA+DCB. The 12 articles also included 2 randomized controlled trials. Patients included these studies were elderly, and most of them had disease of Hyperlipidemia and Hypertension. The clinical and angiographic characteristics of patients between groups in each study were comparable. More details are summarized in (Table 1,2).

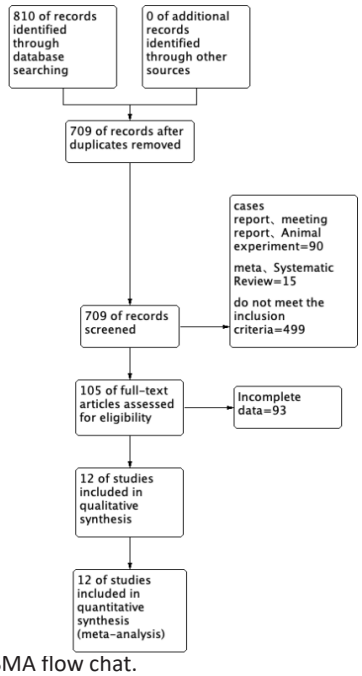


Figure 1: PRISMA flow chat.

Clinical outcomes

Primary parency: Five studies reported patency at 12-month follow-up. The rate of patency in the LA+DCB group was significantly higher than that in the DCB group (OR=2.87,95% CI 1.26 to 6.55, P=0.01<0.05) using a fixed effects model (I^2=0%, P=0.74) (Figure 3a). Three of the single-arm studies concluded that excimer laser atherectomy was used to improve the patency rate in 12-month (OR=0.40,95% CI 0.30 to 0.50, P<0.05). Three single-arm studies reported that excimer laser-assisted therapy was effective at 12-month follow-up(RD=0.40, 95% CI 0.30 to 0.50, P<0.05) using a random effects model (I^2=0%,P=0.40) (Figure 3b).

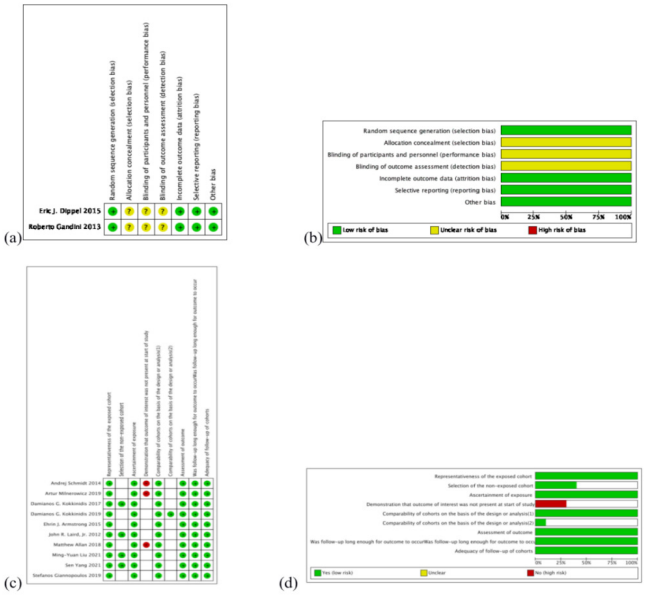


Figure 2: Risk and Bias Summry **(a,b)**: risk and bias assessed by the cochrane collaboration's tool; **(c,d)** Quality assessment of included nonrandomized studies-Newcastle-Ottawa Scale (NOS).

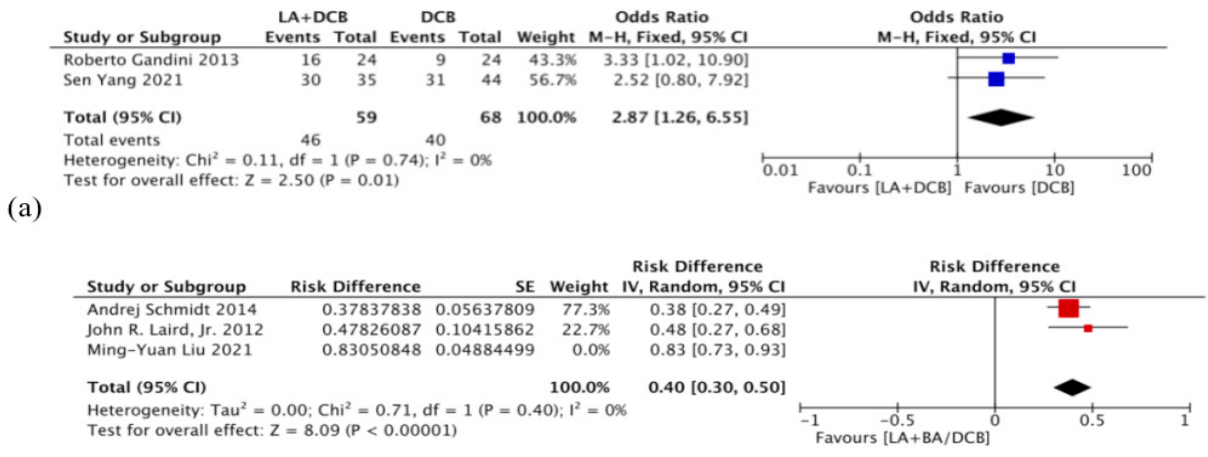


Figure 3: Primary parency at 12-month. **(a)** LA+DCB; **(b)** LA+DCB.LA+DCB: Combine excimer laser atherectomy with drug-coated balloons (DCB).

Target Lesion Revascularization (TLR): Nine studies reported TLR at 12-month follow-up.

The rate of TLR in the LA+PTA group was significantly lower than that in the PTA (NOT LA) group (OR=0.34, 95% CI 0.19 to 0.61, P=0.0003<0.05) using a fixed model (I^2=0%, P=0.39) (Figure 4a). Data from three trails were combined for LA+DCB for femoropopliteal arteries in-stent restenosis in terms of TLR at 12-month, all of which showed a statistically significantly benefit of LA+DCB compared with LA+BA (OR=0.33, 95% CI 0.20 to 0.56,P<0.05) using a fixed model(I^2=0%, P=0.38) (Figure 4b).

Three studies identified that the group using LA+DCB for femoropopliteal arteries in-stent restenosis of Tosaka III lesions was associated with a numerically lower target lesion revascularization compared with LA+BA (OR=0.36,95% CI 0.21 to 0.62, P=0.0002<0.05) using a fixed model (I^2=0%, P=0.39), with a summary estimate of 0.35 (95% CI 0.24 to 0.50, P<0.05) using a fixed model (I^2=0%, P=0.57) (Figure 4b).

Four single-arm studies reported combined for LA+BA/DCB for femoropopliteal arteries in-stent restenosis in terms of TLR at 12-month, all of which showed a statistically significantly benefit (RD=0.09, 95% CI 0.03 to 0.15, P=0.004<0.05) (Figure 4c) using a random model (I^2=39%, P=0.19) (Figure 4c).

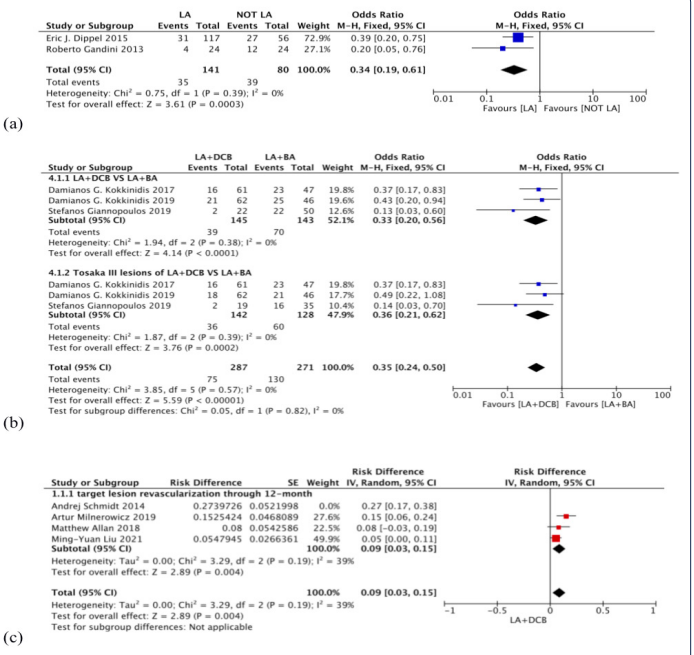


Figure 4: Target Revascularization (TLR) at 12-month. **(a)** LA+PTA vs PTA (NOT LA); **(b)** LS+DCB vs LA+BA; **(c)** LA+BA/DCB. BA: Balloon Angioplasty.

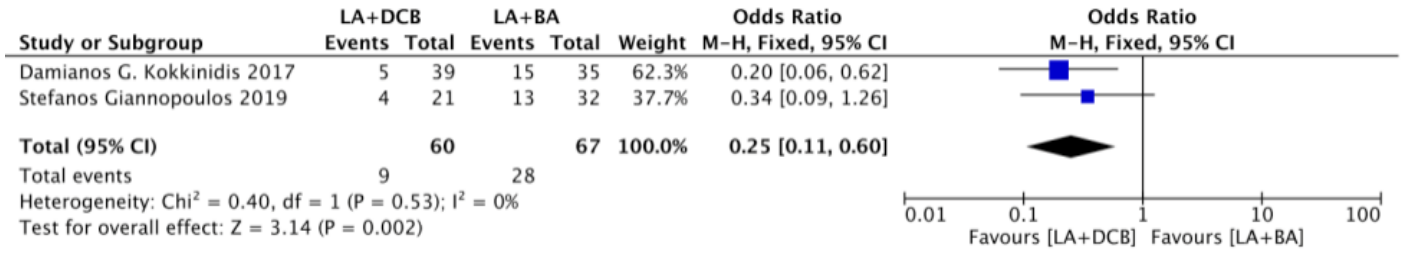


Figure 5: Reocclusion at 12-month: LA+DVB vs La+BA.

Reocclusion: Two studies reported femoropopliteal arteries in-stent restenosis Tosaka III lesion reocclusion rate at 12-month follow-up, all of which showed a statistically significantly benefit of LA+DCB compared with LA+BA (OR=0.25, 95% CI 0.11 to 0.60, P=0.02<0.05) using a fixed model(I^2=0%, P=0.53) (Figure 5).

Bail-out Stenting: The rate of bail-out stenting in the LA+DCB group was significantly lower than that in the LA+BA group (OR=0.41, 95% CI 0.26 to 0.66, P=0.0002<0.05) using a fixed model (I^2=0%, P=0.43) (Figure 6).

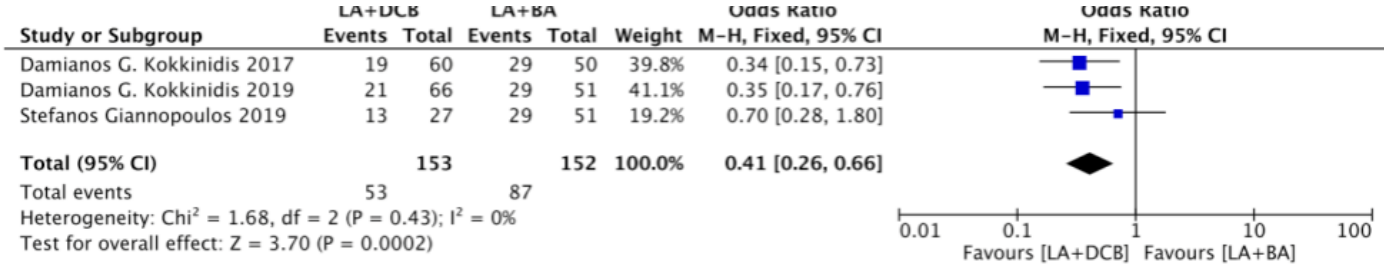
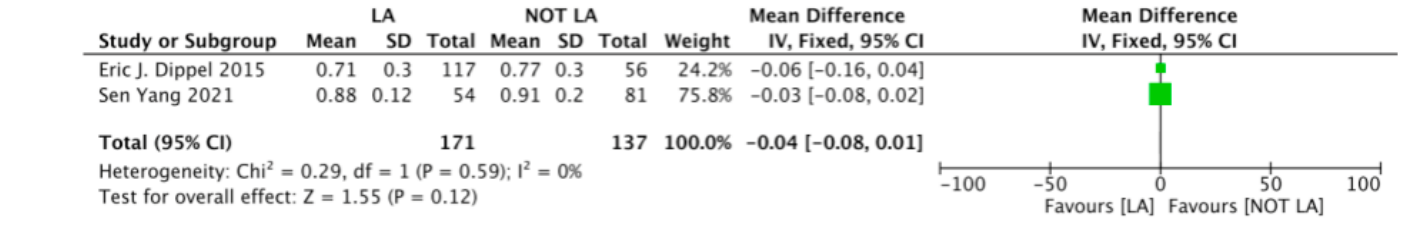
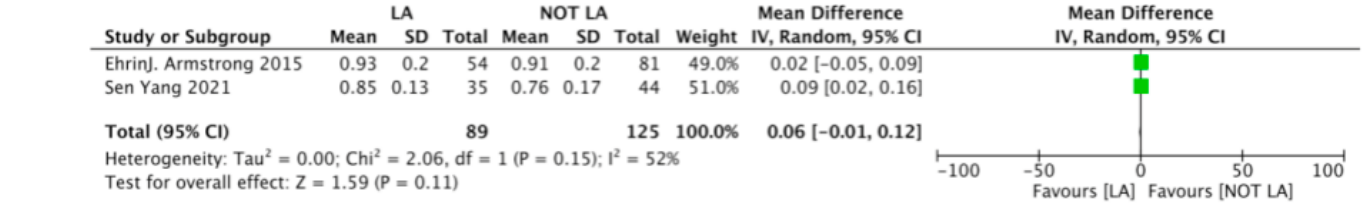


Figure 6: Bail-out Stenting; LA+DCB vs LA+BA.

Ankle brachial index: Two studies reported ABI at 6-month and two studies reported ABI at 12-month. There is no statistical difference of ABI between LA group and NOT LA group (MD=-0.04, 95% CI -0.08 to 0.01, P=0.12>0.05) using a fixed model (I^2=0%, P=0.59) at 6-month (Figure 7a). There is statistical difference of ABI between LA group and NOT LA group (MD=0.06, 95% CI -0.01 to 0.12, P=0.11>0.05) using a random model (I^2=52%, P=0.15) at 12-month (Figure7b).



(a)



(b)

Figure 7: Ankle Brachial Index. **(a)** LA vs NOT LA at 6-month; **(b)** LA vs NOT LA at 12-month.

Sensitivity analysis and publication bias: Sensitivity analyses were performed to evaluate the stability of our results. There was heterogeneity in patency rates in the three single-arm studies at 1-year follow-up. We conducted sensitivity analysis and found that eliminating Ming-Yuan Liu this article can eliminate heterogeneity (using fixed model P<0.00001, I^2=95% before elimination vs P=0.04, I^2=0% after elimination using random model) (Figure 8). The revascularization rates of the four single arm studies were heterogeneous at 1-year follow-up (P=0.002, I^2=80%). For heterogeneity, we first performed subgroup analysis according to different surgical methods. The results showed that there was no heterogeneity in the subgroup of the three studies with the same surgical methods (P=0.19, I^2=39%). However, there is still heterogeneity between the results and the results of another summary. Therefore, we performed sensitivity analysis and deleted the Andrej Schmidt [20] study to eliminate heterogeneity (P=0.19, I^2=39%) (Figure 9). ABI was also heterogeneous at 1-year follow-up (P=0.15,I^2=52%).The reasons for their heterogeneity may be related to the insufficient number of included studies, different lesion length and different degree of stenosis.

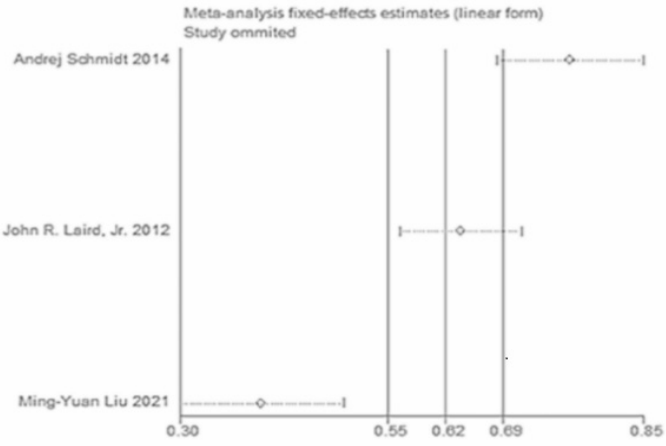


Figure 8: Sensitivity analysis of 1-year patency in the presence of heterogenecity.

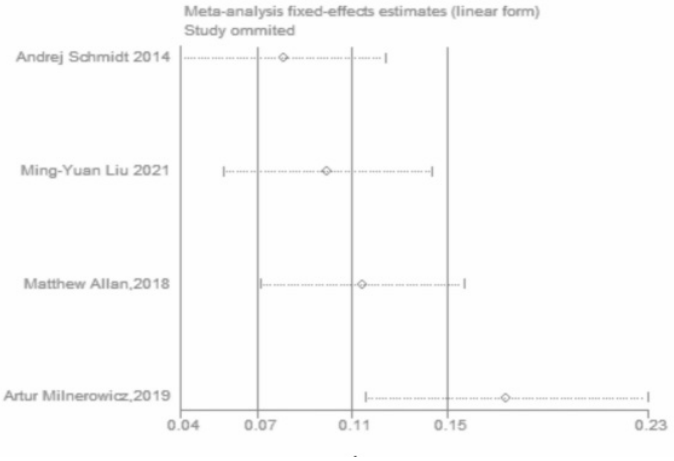


Figure 9: Sensitivity analysis of 1-year revascularization rate in the presencr of heterogeneity.

Discussion

Some studies have proved that excimer laser assisted treatment of lower extremity in-stent stenosis is effective. In addition, excimer laser combined with drug-coated balloon is superior to excimer laser combined with balloon angioplasty in the treatment of in-stent stenosis. At present, excimer laser combined with drug - coated balloon therapy for in-stent stenosis is rarely studied. Therefore, we reviewed published studies and performed a meta-analysis to obtain a more accurate assessment of the value of excimer laser atherectomy combined with drug-coated balloon in the treatment of in-stent stenosis.

Our meta-analysis combined the outcomes of 1093 patients with lower extremity arterial in-stent stenosis from 12 individual studies, indicating that patency at 12-month in the LA+DCB group was significantly higher than that in the DCB group (OR=2.87, 95% CI 1.26 to 6.55, P=0.01<0.05), excimer laser-assisted therapy was effective at 12-month follow-up at primary Patency. The rate of TLR in the LA+PTA group was significantly lower than that in the PTA (NOT LA) group (OR=0.34, 95% CI 0.19 to 0.61, P=0.0003<0.05), LA+DCB was superior to LA+BA, especially in femoropopliteal

arteries in-stent restenosis of Tosaka III lesions (OR=0.36, 95% CI 0.21 to 0.62, P=0.0002<0.05). Reocclusion rate at 12-month showed a statistically significantly benefit of LA+DCB compared with LA+BA (OR=0.25, 95% CI 0.11 to 0.60, P=0.02<0.05) at femoropopliteal arteries in-stent restenosis Tosaka III lesion. In addition, the rate of bail-out stenting in the LA+DCB group was significantly lower than that in the LA+BA group (OR=0.41, 95% CI 0.26 to 0.66, P=0.0002<0.05). However, ankle-brachial index did not improve significantly with or without excimer laser-assisted therapy, indicating that LA+DCB did not significantly increase the ABI and improve ischemic condition.

Meta-analysis by Zhu Tong et al [25] analyzed the studies of Gandini (2013), Sixt (2013) and Kokkinidis, D.G (2017). The results showed that the LD+DCB group significantly improved the patency rate (12 months: 66.7% vs 37.5%, P = 0.01) and reduced the revascularization rate (12 months: 16.7% vs 50%, P = 0.01) compared with the DCB group alone, and the LD+DCB group also improved the patency rate (12-month 86.7% vs 56.9%, P < 0.01) and lower revascularization rates (72.5% vs 50.5%, P < 0:05) compared with the LA alone at 12-month, respectively. These results indicated that LA+DCB is superior in the treatment of in-stent stenosis. These results are consistent with the results of this meta-study. In our meta-analysis, the freedom from revascularization rate of FP-ISR Tosaka class III in the LA+DCB group was higher than that in the LA+BA group [17-19]. In the 12 studies included in our meta-analysis, the lesion length was all longer than 200 mm. These studies indicate that excimer laser-assisted therapy can achieve better therapeutic effect in complex lesions. In our meta-analysis, the rate of bail-out stenting in the LA+DCB group was significantly lower than LA+BA group (OR=0.41, 95% CI 0.26 to 0.66,P=0.0002<0.05). Eric J. Dippel et al. concluded that bail-out stenting in LA+PTA group was lower than that in PTA alone(4.1% vs 11.1%,P=0.05) [15]. This difference is important for FP disease, which is associated with a higher rate of stent thrombosis and stent stenosis. This is partly because most vascular lesions are longer and have a higher grade of stenosis [17,18]. In our meta-analysis, ABI did not change at 6 and 12 months of follow-up because of the surgical methods (6-month: P=0.12>0.05; 12-month: P=0.11>0.05). This result is consistent with the conclusion of Zhu Tong [25]. However, this result is inconsistent with the results of other clinical studies. This difference may be due to the insufficient number of studies included.

FP-ISR is a difficult problem, especially after long lesions and initial stenting. There is no uniform treatment guideline for stent stenosis. At present, the technologies applied to in stent stenosis include cutting balloon angioplasty, debulking strategies (excimer laser, exact atherecto) and DES. But they did not get good long-term treatment effect [26]. DES has been shown to be effective in the treatment of coronary in-stent stenosis, and can be gradually applied to femoropopliteal ISR [27]. ZILVER-PTX study showed that the revascularization rate of drug-eluting stent in PF ISR was low at 12 and 24 months of follow-up (22%, 31%, respectively) [28]. DCB has long been shown to be effective in the treatment of Femoropopliteal Disease. Drug coated balloons are mostly paclitaxel-coated balloons. More than 80% of the drug is retained when the balloon is delivered to the target lesion, and 10-15% of the initial dose is delivered to the vessel wall when it expands at 60 seconds [29]. The advantages of paclitaxel include anti proliferation, rapid absorption of smooth muscle cells [30], in addition exposure to paclitaxel in high concentration and uniform distribution can prevent restenosis for a long time [31]. At present, paclitaxel is the preferred drug for dcbs in peripheral arterial diseases. Because of its lipophilicity, paclitaxel can prevent adventitia erosion and prolong the duration of anti proliferative effect. It ensures that the local tissue concentration of the drug is high without additional side effects [26]. Excimer laser debulking may be beneficial to ISR patients, because this technology can effectively remove proliferative tissue and inhibit platelet aggregation, thus potentially reducing the chance of platelet mediated thrombus reocclusion. The combination of excimer laser and DCB can play a good clinical effect. Laser atherectomy can remove the neointimal tissue in the occluded stent, which is helpful to prevent the reverse regeneration of neointimal tissue after balloon angioplasty. Many restenosis lesions are complex and contain obvious thrombosis. Laser atherectomy can vaporize effectively. Laser atherectomy also changes plaque and produces endothelial micropores, so paclitaxel is easier to penetrate neointimal tissue [32]. The kinetic energy generated by each pulse and the laser-induced pressure wave can alter the plaques, providing more room for subsequent balloon angioplasty [33,34]. In our meta-analysis, the included study of LA combined with DCB in the treatment of in-stent stenosis showed remarkable clinical efficacy. In summary, laser atherectomy and DCB have a synergistic mechanism.

In the included studies, some results showed significant heterogeneity. Although sensitivity analysis was used, the source of heterogeneity could not be fully traced. The overall quality of the meta-analysis included studies are not very high. A total of 12 studies were included, including 2 randomized controlled trials, 5 single arm studies, and the rest were cohort studies. There are few studies on excimer laser assisted therapy and excimer laser combined with DCB in the treatment of FP-ISR, and more studies are needed in the future, so as to make the results more reliable. The current form of research is literature analysis, and the cause of potential publication bias may be partly attributed to the publication tendency of positive results. At the same time, relatively strict inclusion criteria may also help.

Conclusion

Our meta-analysis concluded that excimer laser adjuvant therapy and excimer laser combined with DCB in the treatment of FP-ISR had significant clinical effects in terms of patency rate and revascularization rate. Especially in the long lesions, severe stenosis of complex lesions also have significant therapeutic effect. More clinical studies of LA combined with DCB in the treatment of FP-ISR are needed in the future to further prove its effectiveness.

References

1. Özpak B, Çayır MÇ. Drug-eluting balloon treatment in femoropopliteal in-stent restenosis of different lengths[J]. Turk Gogus Kalp Dama 2020; 28: 460-466.
2. Rajkumar Doshi, Ashish Kumar, Devina Adalja, et al. Meta-analysis of Usefulness of Drug Coated Balloon versus Standard Balloon in the Treatment of Femoropopliteal In-stent-restenosis[J]. The American Journal of Cardiology, 2020.
3. Kayssi A, Al-Jundi W, Papia G,et al. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for the treatment of in-stent restenosis of the femoropopliteal arteries[J]. Cochrane Database of Systematic Reviews 2019.

4. Nicolas W. Shammas, MS EJD. Femoropopliteal In-Stent Restenosis: Gaining Ground With Excimer Laser and Drug-Coated Balloons[J]. Journal of Endovascular Therapy, 2017.

5. Kinstner CM, Lammer J, Willfort-Ehringer A, et al. Paclitaxel-eluting balloon versus standard balloon angioplasty in in-stent restenosis of the superficial femoral and proximal popliteal artery: 1-year results of the PACUBA trial[J]. JACC Cardiovasc Interv. 2016; 9: 1386-1392.

6. GT. Cotavance paclitaxel-coated balloon vs. Uncoated balloon angioplasty for treatment of in-stent restenosis in SFA and the popliteal arteries: 2-year results of the COPA CABANA trial[J]. Leipzig Interventional course. Leipzig, Germany; 2017.

7. Bosiers M, Deloose K, Callaert J, et al. Results of the Protege Ever-Flex 200-mm-long nitinol stent (ev3) in TASC C and D femoropopliteal lesions[J]. J Vasc Surg. 2011; 54: 1042-1050.

8. Cleveland T, KP Donas, A Schwindt, et al. Comment on: below-knee bare nitinol stent placement in high-risk patients with critical limb ischemia and unlimited supragenicular inflow as treatment of choice [J]. Eur J Vasc Endovasc Surg. 2009; 37: 694-695.

9. Nicolas W Shammas, Gail A Shammas, Alexander Hafez, et al. Safety and One-Year revascularization outcome of excimer laser ablation therapy in treating in-stent restenosis of femoropopliteal arteries: A retrospective review from a single center[J]. Cardiovascular Revascularization Medicine. 2012; 341-344.

10. Topaz O, Minisi AJ, Bernardo NL, et al. Alterations of platelet aggregation kinetics with ultraviolet laser emission: the "stunned platelet" phenomenon[J]. Thromb Haemost 2001; 86: 1087-93.

11. Takashi Shibui, Takaaki Tsuchiyama, Sho Nagamine, et al. Excimer laser coronary atherectomy prior to paclitaxel-coated balloon angioplasty for de novo coronary artery lesions[J]. Lasers in Medical Science. 2021; 36: 111-117.

12. Daniele Giacoppo, Giuseppe Gargiulo,et al. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients[J]. BMJ. 2015; 351: h6364.

13. Roberto Gandini, Costantino Del Giudice, Stefano Merolla, et al. Treatment of Chronic SFA In-Stent Occlusion With Combined Laser Atherectomy and Drug-Eluting Balloon Angioplasty in Patients With Critical Limb Ischemia: A Single-Center, Prospective, Randomized Study[J]. J ENDOVASC THER. 2013; 20: 805-814.

14. Sen Yang, Shengyu Li, Likun Hou, et al. Excimer laser atherectomy combined with drug-coated balloon versus drug-eluting balloon angioplasty for the treatment of infrapopliteal arterial revascularization in ischemic diabetic foot: 24-month outcomes[J]. Lasers in Medical Science, 2019.

15. Eric J Dippel, Prakash Makam, Y Richard Kovach. Randomized Controlled Study of Excimer Laser Atherectomy for Treatment of Femoropopliteal In-Stent Restenosis[J]. JACC:CARDIOVASCULARINTERVENTIONS,VOL.8,NO.1,2015

16. Ehrin J Armstrong, Thejasvi Thiruvoipati, Kundai Tanganyika, et al. Laser Atherectomy for Treatment of Femoropopliteal In-Stent Restenosis[J].Journal of Endovascular Therapy,2015.

17. Damianos G Kokkinidis, Prio Hossain, Omar Jawaid, et al. Laser Atherectomy Combined With Drug-Coated Balloon Angioplasty Is Associated With Improved 1-Year Outcomes for Treatment of Femoropopliteal In-Stent Restenosis[J].Journal of Endovascular Therapy, 2017.

18. Damianos G. Kokkinidis, Sean Behan, Omar Jawaid, et al. Laser atherectomy and drug-coated balloons for the treatment of femoropopliteal in-stent restenosis: 2-Year outcomes[J].Catheter Cardiovasc Interv. 2019; 1-8.

19. S Giannopoulos, DG Kokkinidis, O Jawaid, et al. Turbopower™ laser Atherectomy combined with drug-coated balloon angioplasty is associated with improved one-year outcomes for the treatment of Tosaka II and III Femoropopliteal in-stent restenosis[J]. Cardiovascular Revascularization Medicine, 2019.

20. Andrej Schmidt, Thomas Zeller, Horst Sievert, et al. Photoablation Using the Turbo-Booster and Excimer Laser for In-Stent Restenosis Treatment: Twelve-Month Results From the PATENT Study[J].J ENDOVASC THER. 2014; 21: 52-60.

21. John R Laird, Khung Keong Yeo, Krishna Rocha-Singh, et al. Excimer Laser with Adjunctive Balloon Angioplasty and Heparin-Coated Self-Expanding Stent Grafts for the Treatment of Femoropopliteal Artery In-Stent Restenosis: Twelve-Month Results From the SALVAGE Study[J].Catheterization and Cardiovascular Interventions, 2012.

22. Liu M-Y, Li W, Guo X, et al. Percutaneous Mechanical Atherectomy Plus Thrombectomy Using the Rotarex®S Device Followed by a Drug-Coated Balloon for the Treatment of Femoropopliteal Artery In-stent Restenosis: A Prospective Single-Center, Single-Arm Efficacy Trial (PERMIT-ISR Trial)[J]. Front. Surg. 8: 671849.

23. Matthew Allana, Dominic Vickersc, Mark Pitney, et al. Rotational atherectomy combined with drug coated balloons for in-stent restenosis[J].Cardiovascular Revascularization Medicine, 2018.

24. Artur Milnerowicz, Aleksandra Milnerowicz, Wiktor Kuliczkowski, et al. Rotational Atherectomy Plus Drug-Coated Balloon Angioplasty for the Treatment of Total In-Stent Occlusions in Iliac and Infrainguinal Arteries[J].Journal of Endovascular Therapy, 2 019.

25. Zhu Tong, Lianrui Guo, Lixing Qi, et al. Drug-Coated Balloon Angioplasty and Debulking for the Treatment of Femoropopliteal In-Stent Restenosis: A Systematic Review and Meta-Analysis[J]. BioMed Research International Volume, 2020.

26. Saurabh Mehrotra, Ganesh Paramasivam, Sundeep Mishra, et al. Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease[J]. Curr Cardiol Rep, 2017; 19: 10.

27. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, et al. Treatment of coronary in-stent restenosis with a paclitaxelcoated balloon catheter[J]. N Engl J Med. 2006; 355: 2113-24.

28. Dake, Ansel, Jaff, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve month Zilver PTX randomized study results[J]. Circulation Cardiovascular Interventions. 2011; 4(5): 495-504.

29. Schnorr B, Speck U, Scheller B. Review of clinical data with Paccocath-coated balloon catheters[J]. Minerva Cardioangiol, 2011; 59: 431-45.

30. Mori T, Kinoshita Y, Watanabe A, et al. Retention of paclitaxel in cancer cells for 1 week in vivo and in vitro. Cancer Chemother Pharmacol[J]. 2006; 58: 665-72.

31. Herdeg C, Oberhoff M, Baumbach A, et al. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo[J]. J Am Coll Cardiol. 2000; 35: 1969-76.

32. Armstrong EJ. Strategies for femoropopliteal in-stent restenosis[J]. Endovascular Today. 2014; 84-87.

33. Jayasuriya S, Ward C, Mena-Hurtado C. Role of laser atherectomy for the management of in-stent restenosis in the peripheral arteries[J]. J Cardiovasc Surg (Torino). 2014; 55: 339-345.

34. Inoue S, Koyama H, Miyata T, et al. Pathogenetic heterogeneity of in-stent lesion formation in human peripheral arterial disease[J]. J Vasc Surg. 2002; 35: 672-678.