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

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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 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.
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. Debunking of 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 balloon” 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 Reuter, 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 I² test. If I² 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 classified 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>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age, y</th>
<th>Male gender</th>
<th>Hyperlipidemia</th>
<th>Hypertension</th>
<th>CAD</th>
<th>CLI</th>
<th>Lesion Length, mm</th>
<th>Rutherford class</th>
<th>Tosaka class</th>
<th>TASC class</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberto Gandini[13]</td>
<td>2013</td>
<td>LA+DEB</td>
<td>74.1 ± 7.2</td>
<td>18 (75%)</td>
<td>18 (87%)</td>
<td>9  (37%)</td>
<td>NA</td>
<td>224 ± 94</td>
<td>NA</td>
<td>Class 3:100%</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td></td>
<td>DEB</td>
<td>70.1 ± 11.6</td>
<td>21 (87%)</td>
<td>18 (75%)</td>
<td>6  (25%)</td>
<td>NA</td>
<td>259 ± 87</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>SenYang[14]</td>
<td>2021</td>
<td>LA+DCB</td>
<td>68.5 ± 6.9</td>
<td>29 (82.9%)</td>
<td>24 (68.6%)</td>
<td>14 (40.0%)</td>
<td>NA</td>
<td>132 ± 83</td>
<td>Class 4:1(34.3%)/13 29.5%; Class 5:2(160.0%)/(27)61.4%; Class 6:2(15.7%)/(4)9.1%</td>
<td>NA</td>
<td>NA</td>
<td>0.35 ± 0.27</td>
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<td></td>
<td></td>
<td>DCB</td>
<td>68.3 ± 6.0</td>
<td>34 (77.3%)</td>
<td>38 (84.1%)</td>
<td>24 (54.5%)</td>
<td>NA</td>
<td>113 ± 91</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.3 ± 0.3</td>
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<tr>
<td>Eric J. Dippe[15]</td>
<td>2015</td>
<td>LA+PTA</td>
<td>68.5 ± 9.8</td>
<td>106 (62.7%)</td>
<td>162 (95.8%)</td>
<td>109 (64.3%)</td>
<td>27 (16%)</td>
<td>196 ± 120</td>
<td>NA</td>
<td>NA</td>
<td>C/D 59.9%</td>
<td>0.6 ± 0.2</td>
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<td></td>
<td></td>
<td>PTA</td>
<td>67.8 ± 13.0</td>
<td>50 (61.7%)</td>
<td>76 (93.8%)</td>
<td>56 (68.8%)</td>
<td>10 (12.3%)</td>
<td>193 ± 119</td>
<td>NA</td>
<td>C/D 56.9%</td>
<td>0.7 ± 0.2</td>
<td></td>
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<tr>
<td>Ehrin J. Armstrong[16]</td>
<td>2015</td>
<td>LA+PTA</td>
<td>73 ± 11</td>
<td>35 (65%)</td>
<td>NA</td>
<td>74 (91%)</td>
<td>NA</td>
<td>222 ± 118</td>
<td>Class 1–3: 3565%/44 54% Class 4–6: 1935%/37 46%</td>
<td>Class 1:15%/32 40%; Class 2:12%/32 40%; Class 3: 17 69%/17 20%</td>
<td>Class 1:15%/32 40%; Class 2:15%/32 40%; Class 3: 17/17</td>
<td>C/D (37)69%/125 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTA</td>
<td>69 ± 11</td>
<td>41 (51%)</td>
<td>40 (50%)</td>
<td>47 (58%)</td>
<td>114 ± 106</td>
<td>NA</td>
<td>C/D (37)69%/125 35%</td>
<td>0.7 ± 0.22</td>
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<tr>
<td>Damianos G.Kokkinidis[17]</td>
<td>2017</td>
<td>LA+DCB</td>
<td>68.5 ± 10</td>
<td>51 (82.3%)</td>
<td>28 (45.9%)</td>
<td>22 (36.1%)</td>
<td>256 ± 123</td>
<td>NA</td>
<td>Class 2:1625.8%/13 (26.0%); class 3:4674%/37 (74.0%);</td>
<td>C/D 56/93.3%/3678.3%</td>
<td>0.5 ± 0.3</td>
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<tr>
<td></td>
<td></td>
<td>LA+BA</td>
<td>72 ± 10.8</td>
<td>35 (70%)</td>
<td>53 (60.6%)</td>
<td>28 (36.1%)</td>
<td>240 ± 107</td>
<td>NA</td>
<td>C/D 56/93.3%/3678.3%</td>
<td>0.69 ± 0.3</td>
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<tr>
<td>Damianos G.Kokkinidis[18]</td>
<td>2019</td>
<td>LA+DCB</td>
<td>68 ± 10</td>
<td>55 (83%)</td>
<td>31 (47%)</td>
<td>18 (27%)</td>
<td>263 ± 126</td>
<td>NA</td>
<td>Class 3:4074%/36 71%</td>
<td>Class 2:15%/32 40%; Class 3: 25%/32 40%; Class 4: 17/17</td>
<td>C/D 61/84%/37 79%</td>
<td>NA</td>
</tr>
<tr>
<td>Stefanos Giannopoulos[19]</td>
<td>2019</td>
<td>LA+DCB</td>
<td>67.4 ± 4.8</td>
<td>27 (100%)</td>
<td>24 (88.8%)</td>
<td>14 (52.6%)</td>
<td>132 ± 880</td>
<td>NA</td>
<td>Class 2:11.1%/29.4% Class 3:88.8%/70.6%</td>
<td>A: 0%/8.5%; B: 7.4%/14.9%; C: 7.4%/29.8%; D: 85.2%/46.8%</td>
<td>0.52</td>
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<td></td>
<td></td>
<td>LA+BA</td>
<td>72.5 ± 10.7</td>
<td>35 (68.6%)</td>
<td>25 (73.5%)</td>
<td>28 (54.9%)</td>
<td>106 ± 680</td>
<td>Class 1:24 26.7%; Class 2:35 38.5%; Class 3:31 34.4%</td>
<td>NA</td>
<td>0.61 ± 0.23</td>
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<tr>
<td>Andrej Schmidt[20]</td>
<td>2014</td>
<td>LA+BA</td>
<td>69.5 ± 9.3</td>
<td>65 (73.9%)</td>
<td>80 (88.9%)</td>
<td>NA</td>
<td>NA</td>
<td>123 ± 96</td>
<td>Class 2:19 21.6%; Class 3:63 71.6%; Class 4: 3 3.4%; Class 5: 3 3.4%</td>
<td>Class 1:24 26.7%; Class 2:35 38.5%; Class 3:31 34.4%</td>
<td>NA</td>
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<tr>
<td>John R. Laird, Jr.[21]</td>
<td>2012</td>
<td>LA+BA+HC</td>
<td>70 ± 10.5</td>
<td>17 (63%)</td>
<td>24 (88.9%)</td>
<td>25 (92.6%)</td>
<td>NA</td>
<td>207 ± 103</td>
<td>Class 2: 7 25.9%; Class 3: 18 66.7%; Class 4: 18 66.7%</td>
<td>Class 5: 0%</td>
<td>NA</td>
<td>0.58 ± 0.24</td>
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<tr>
<td>Ming-Yuan Liu[22]</td>
<td>2021</td>
<td>LA+DCB</td>
<td>71 ± 11.2</td>
<td>39 (66.1%)</td>
<td>40 (67.8%)</td>
<td>17 (28.8%)</td>
<td>184 ± 78</td>
<td>NA</td>
<td>Class 0-1:10 Class 2-3:11 18.5% Class 4-6: (48) 81.4%</td>
<td>Class 0-1:10 Class 2-3:11 18.5% Class 4-6: (48) 81.4%</td>
<td>NA</td>
<td>0.38 ± 0.10</td>
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<tr>
<td>Matthew Allan[23]</td>
<td>2018</td>
<td>RA+DCB</td>
<td>68 (51-76)</td>
<td>21 (80%)</td>
<td>24 (92%)</td>
<td>22 (85%)</td>
<td>NA</td>
<td>117 ± 34</td>
<td>Class 1: 15% Class 2:26% Class 3:0% Class 4: 2%</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Artur Milnerowicz[24]</td>
<td>2019</td>
<td>RA+DCB</td>
<td>66.7 ± 9.7</td>
<td>49 (62%)</td>
<td>45 (57%)</td>
<td>42 (53%)</td>
<td>NA</td>
<td>220 ± 150</td>
<td>Class 2:13 16.5% Class 3:24 30.4% Class 4:30 38% Class 5: 7 8.9%</td>
<td>NA</td>
<td>B:10 12.7%; C:30 38%; D:34 43%</td>
<td>NA</td>
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<tr>
<td>Design</td>
<td>year</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
<td>Follow-up month</td>
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<tr>
<td>Roberto Gandini 2013</td>
<td>Prospective, Single-center, Randomized controlled trial 2009.10-2011.03</td>
<td>In-Stent Restenosis; superficial femoral artery (SFA) ; stent occlusion</td>
<td>NA</td>
<td>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</td>
<td>12</td>
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<tr>
<td>Sen Yang 2021</td>
<td>Single-center, Retrospective 2018.09-2019.02</td>
<td>infrapopliteal arterial disease in diabetic foot patients with CLI in Rutherford grades 4 to 6</td>
<td>NA</td>
<td>LA+ DCB can better improve clinical symptoms and patency than DCB alone, significantly reduce the rate of major amputation at 24-month</td>
<td>12</td>
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<tr>
<td>Eric J. Dippe 2015</td>
<td>Prospective, Multi-center, Randomized controlled trial 2011.06-2014.02</td>
<td>Femoropopliteal In-Stent Restenosis; significant ISR &gt;50% diameter stenosis (DS)</td>
<td>NA</td>
<td>LA + PTA is safer and more effective than PTA alone</td>
<td>6 and 12</td>
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<tr>
<td>Ehrin J. Armstrong, 2015</td>
<td>Single-center 2006-2013</td>
<td>Femoropopliteal In-Stent Restenosis</td>
<td>NA</td>
<td>LA + PTA which treatment of class I / II FP-ISR can reduce the rate of recanalization, restenosis and reocclusion.</td>
<td>12</td>
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<tr>
<td>Damianos G. Kokkinidis, 2017</td>
<td>Retrospective, Double-centers NA</td>
<td>Tosaka II and Tosaka III ;FP-ISR</td>
<td>NA</td>
<td>LA + DCB is more effective in the treatment of complex FP-ISR The rate of bail-out stenting is reduced, and the recanalization are improved at 12-month</td>
<td>12</td>
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<tr>
<td>Damianos G. Kokkinidis, 2019</td>
<td>Retrospective, Double-centers, Cohort study NA</td>
<td>Tosaka II and Tosaka III ;FP-ISR</td>
<td>NA</td>
<td>Compared with LA + DCB and LA + BA,LA+DCB reduced the rate of bail-out stenting and improved recanalization and restenosis.</td>
<td>12</td>
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<tr>
<td>Stefanos Giannopoulos 2019</td>
<td>Retrospective, Double-centers, Cohort study 2015-2017</td>
<td>Tosaka II and Tosaka III;FP-ISR</td>
<td>NA</td>
<td>Compared with LA + DCB and LA + BA,LA+DCB reduced the rate of bail-out stenting and improved recanalization and restenosis</td>
<td>12</td>
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<tr>
<td>Andrej Schmidt 2014</td>
<td>Prospective, Multi-central, Single-arm study NA</td>
<td>cri- teria were treated with excimer laser and adjunctive balloon angioplasty if indicated;ISR</td>
<td>NA</td>
<td>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.</td>
<td>12</td>
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<tr>
<td>John R. Laird, Jr. 2012</td>
<td>Prospective, Multi-central, Single-arm study NA</td>
<td>Femoropopliteal Artery In-Stent Restenosis (angiographic evidence of significant restenosis (defined as &lt;50% by visual estimate) within a previously deployed femoropopliteal nitinol stent)</td>
<td>if there was Grade 4 or 5 stent fracture in the restenotic stent</td>
<td></td>
<td>6 and 12</td>
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<tr>
<td>Ming-Yuan Liu 2021</td>
<td>Single-center, Single-arm study 2016.06-2018.05</td>
<td>angiographic evidence of significant ISR &gt;70% by visual assessment within the stent; Rutherford category 2 to 6</td>
<td>stent fracture; planned amputation of the target limb; expected follow-up time &lt; 2 years.</td>
<td>LA + DCB is safe, minimally invasive and effective in the treatment of FP-ISR.</td>
<td>12</td>
<td></td>
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<tr>
<td>Matthew Allan 2018</td>
<td>Retrospective, Single-center, Single-arm study, Cohort study 2010.12-2016.04</td>
<td>ISR (in-stent restenosis)</td>
<td>NA</td>
<td>La + DCB treatment is effective and a feasible treatment option for selected cases of in-stent restenosis</td>
<td>12</td>
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</table>
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).

Clinical outcomes

Primary patency: 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 1: PRISMA flow chat.

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 patency 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 (I²=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 (I²=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 (I²=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 (I²=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 (I²=39%, P=0.19) (Figure 4c).

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 (I²=0%, P=0.39) (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 (I²=0%, P=0.43) (Figure 6).

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 (I²=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 (I²=52%, P=0.15) at 12-month (Figure 7b).
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.

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...
arrest 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 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. Dipple 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 atherectomy) 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 FP 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 recoulement. 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 microvessels, 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**


