Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Safety and Efficacy of Drug-Coated Balloon in the Treatment of Below-the-Knee Artery: A Meta-analysis

Hui Cai, DD,[a] *Jian Dong, DD,*[a] *Yuanpeng Ye, DD,*[a] *Qiang Song, MD,*[b] *and Shaoying Lu, DD*[a,*]

[a] *Department of Vascular Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China*
[b] *Department of Structural Heart Disease, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China*

ARTICLE INFO

Article history:
Received 17 August 2021
Received in revised form
19 February 2022
Accepted 19 April 2022
Available online 1 June 2022

Keywords:
Below-the-knee artery disease
Drug-coated balloon
Meta-analysis
Paclitaxel
Safety

ABSTRACT

Introduction: Chronic limb threat ischemia is associated with cardiovascular events, resulting in high amputation, morbidity and mortality rates. This study aims to accomplish a comprehensive summary of randomized controlled trials and single-center trials related to drug-coated balloons (DCBs) in the treatment of below-the-knee (BTK) artery disease, and to provide a recommendation for the application of DCBs in BTK artery disease.

Methods: Five electronic databases were used to retrieve relevant articles on the safety and effectiveness of DCBs in the treatment of BTK artery disease. A random-effects model was applied to calculate the standard mean deviation, odds ratio (OR) and their 95% of confidence interval (CI).

Results: As of April 8, 2021, a total of 241 articles were retrieved, but only 13 articles were finally included for meta-analysis. The 12 mo follow-up study found that major adverse events , all-cause mortality, major amputation ,and target lesion revascularization had no statistically significant difference between the DCBs group and the control group (target lesion revascularization: OR = 0.68, 95% CI: 0.36, 1.31; all-cause mortality: OR = 1.30, 95% CI: 0.69, 2.46; major amputation: OR = 1.34, 95% CI: 0.64, 2.79; target lesion revascularization: OR = 0.72, 95% CI: 0.35, 1.45).

Conclusions: The meta-analysis results of randomized controlled trials focusing on comparing DCBs and other treatments suggest that DCBs do not have significant advantages in the treatment of BTK artery disease when compare with percutaneous transluminal angioplasty (PTA), but better than control intervention except PTA in both safety and efficacy end points. However, the results of meta-analysis of single-arm trial reported DCBs in treating BTK artery lesions are significantly improved compared with the meta-analysis concentrating on PTA.

* *Corresponding author*. Department of Vascular Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, 277 W. Yanta Road, Xi'an, Shaanxi 710061, China. Tel.: +86 1899123201.
E-mail address: robertlu@xjtu.edu.cn (S. Lu).

0022-4804/$ – see front matter © 2022 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jss.2022.04.055

Introduction

Peripheral arterial occlusive disease affects more than 200 million patients worldwide.[1] Chronic limb threating ischemia (CLTI) represents the end-stage of Peripheral arterial occlusive disease or diabetic foot syndrome and is associated with cardiovascular events, leading to high amputation, morbidity and mortality rates.[2,3] The CLTI of the below-the-knee (BTK) is usually caused by severe atherosclerosis.[4] Currently, the main treatment for high-risk CLTI patients in the lower knee is endovascular revascularization. However, the incidence of restenosis and occlusion caused by neointimal hyperplasia in BTK lesions is very high, and the clinical results of either bare metal stents or percutaneous transluminal angioplasty (PTA) are still unsatisfactory.[5] Drug-coated balloons (DCBs) based on the anti-proliferative effect of paclitaxel on the proliferation of endothelial cells and vascular smooth muscle have developed to treat popliteal artery disease and have shown better clinical efficacy than conventional balloon angioplasty.[6-8] In response to the many alternative treatment options, it is important to compare the safety and efficacy of different treatment comprehensively which could help physicians make better treatment for patients in time.

However, the role of DCBs in revascularization of occluded BTK artery has been a controversial issue. Randomized trials evaluating the efficacy of DCBs and uncoated balloons in BTK vessels have yielded inconsistent results.[9-12] One single-center study of 104 patients reported the use of paclitaxel-coated balloon catheters in the treatment of BTK, the 1 y target lesion revascularization (TLR) rate was 17.3%, and the limb salvage rate was 95.6%.[12] In addition, results from the DEBATE BTK single-center trial showed superiority of DCBs over conventional balloons in tibial arteries. Bilateral restenosis was significantly reduced in the DCB group (27%) compared with the PTA group.[9] However, results from a randomized controlled trial of IN. Pact Amphirion DCB have shown a trend toward increased amputation and mortality among chronic limb ischemia (CLI) patients at 12 mo.[13]

Based on this background, we conducted this systematic review and meta-analysis to evaluate the results of randomized controlled trials and single-center trials related to DCBs in the treatment of BTK artery disease and compare the safety and efficacy among DCBs and other treatments in BTK revascularizations.

Methods

The methodology of the Cochrane Handbook for Systematic Reviews of Interventions version 6.0 was applied in this study.[14] Also, our description was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement.[15]

Search strategy

Five electronic databases up to April 8, 2021, PubMed, Cochrane, Web of Science, China National Knowledge Infrastructure and WANFANG DATA, were used to systematically search articles related to the safety and effectiveness of DCBs in the treatment of BTK artery disease. The search terms were as follow ([Drug-coated balloon] OR [Drug-eluting balloon]) AND ([artery] OR [artery{MeSH Terms}]) AND ([infrapopliteal] OR [descending] OR [genicular] OR [below-the-knee]). Moreover, the references of the articles initially included in the systematic search were searched to collect any relevant article for analysis, and to provide a comprehensive report on the randomized controlled trials and single-center trials of DCBs in the treatment of BTK artery disease.

Inclusion and exclusion criteria

According to the inclusion and exclusion criteria, researchers (Dong J, Ye YP and Song Q) who had been worked in vascular surgery department for nearly 10 y including more than 250 cases of lower limb arterioplasty per year and about 50 cases of simple BTK artery lesion assessed the titles and abstracts of the articles obtained from the preliminary search to determine whether the articles were included in the full-text evaluation, as well as the subsequent research analysis. When there was disagreement among the researchers, they could have a discussion, and researcher (Cai H) who has similar experience in conducting vascular surgery with the three researchers mentioned above would independently make the final decision based on their opinions.

Inclusion criteria[1]: Research types: Randomized controlled trials that met ethical requirements, single-arm prospective and retrospective trials, published in English or Chinese.[2] Research subjects meeting criteria of age ≥18 y; diagnosed with BTK artery occlusion or stenosis presenting CLTI (Rutherford 3-6); postoperative follow-up time ≥6 mo.[3] Intervention measures: subjects were randomly divided into the DCB group and the control group for the treatment of BTK artery lesions, in addition to scheduled surgical procedures, other human factors were avoided.[4] Result indicators including 1) Safety indicators: major adverse events (MAEs, defined as composite of all-cause mortality, major amputation and TLR), all-cause mortality, major amputation and TLR; 2) Effective indicators: minimal luminal diameter (MLD), late lumen loss (LLL), ankle brachial index (ABI), primary patency rate, limb salvage rate.

Exclusion criteria: those meeting any of the following conditions were excluded[1]: Duplicate publication[2]; The report data was incomplete and relevant data could not be obtained[3]; There were serious flaws in the study design or severe bias in the results.

Data extraction and quality assessment

Researchers (Dong J, Ye YP and Song Q) independently extracted the following data provided by each included research into the extraction table: study title, first author, publication year, the number of subjects, grouping, gender, age, inclusion and exclusion criteria, baseline characteristics of lesions, surgical methods, outcome indicators, and research design related indicators (mainly including research plan and quality control). After the data extraction was completed, researcher (Cai H) would conduct a consistency check on the extracted data to confirm the data is correct.

The studies that met the inclusion criteria were evaluated in accordance with the quality assessment of the Cochrane handbook for systematic reviews of interventions 6.0.[14] It mainly included[1]: selection bias: random sequence generation[2]; implementation bias: whether the investigators and subjects were blinded[3]; measurement bias: whether the blind method of evaluation study results was described in detail[4]; follow-up bias: whether the result data were complete or not[5]; reporting bias: whether the research results were selectively reported[6]; other related biases: baseline, funding. If the results of the quality assessment of the three researchers were inconsistent, the fourth researcher should participate in the discussion and based on the opinions of the first three researchers to make the final judgment on the high or low risk of bias. According to the guidelines of the Cochrane Handbook, we determined whether the final quality of the included studies was low risk, medium risk, or high risk based on the conclusions of the overall quality assessment.

Statistical analysis

Results were merged across studies with STATA version 15.1 (Stata Corp MP., College Station, TX).[16,17] Considering the differences in DCBs treatment between included studies, it would be impractical to accurately calculate the effect value of DCBs in the treatment of the BTK artery disease for clinical practice guideline and to compare it with uncoated balloon therapy, so we merged the results using a random-effects model. Also, the differences in treatment program among studies may lead to high heterogeneity, and the source of the heterogeneity should be explored, which could be a significant guide for discussing the safety and effectiveness of DCBs in the treatment of BTK arteries. For binary variables, odds ratio (OR) and its 95% confidence interval (CI) were used to compare the effectiveness of DCBs and the control in treating BTK artery. Continuous variables were represented by standard mean difference (SMD) and 95% CI. In addition, for the single-arm trial, we combined the results, so as to compare with other single-arm trials for the other treatment protocol without DCBs of BTK artery disease, and evaluate whether the efficacy of DCBs in the treatment of BTK artery disease is superior to other methods. Moreover, the method of calculating the combined standard deviation of the study was referred to the Cochrane handbook.[14] Q test and I^2 statistics were used to assess the study heterogeneity. When the I^2 value was 0%-39%, 40%-59%, 60%-90%, the heterogeneity between studies would be low, medium, and high, respectively.[14] If the number of studies evaluating the safety and effectiveness of DCBs in the treatment of BTK artery disease was $\geq$5, the results would be displayed in the forest plot, otherwise the results would be displayed in the table. If the number of studies was $\geq$5, the Egger's test would be used to assess the publication bias of the results, and the Duval and Tweedie's trim and fill method were used to assess the sensitivity of the results.[18,19] Unless $P < 0.001$, we would give an accurate P-value. In addition to $P < 0.10$ in Egger's test, which was considered statistically significant, other $P < 0.05$ could be considered statistically significant.

Results

Literature search, study characteristics and quality assessment

A total of 195 and 46 articles were obtained by systematic database retrieval and manual retrieval, respectively. Thirty-three repeated articles were eliminated. Also, after screening the titles and abstracts of the retrieved articles, 189 articles that did not meet the inclusion criteria were excluded (not related to below-the-knee arteries disease $n = 103$; review or *in vitro*/animal studies or letter or editorial or conference paper $n = 37$; not related to DCB angioplasty $n = 27$; not related to therapeutic effect or safety effect $n = 5$). Moreover, four studies evaluated in full text were excluded as they could not provide or be translated into data that could be used effectively. Finally, a total of 13 studies were included in the meta-analysis (Fig. 1). This review included a total of 4911 patients with occlusive peripheral arterial disease who received DCBs for BTK artery disease and 3447 patients who received conventional plain old balloon angioplasty. The basic characteristics of the 13 studies included in meta-analysis were shown in Supplemental Table 1 and the baseline characterization of patients had been showed in Table 1(9-13, 20-27). Besides, the detail of which vessels were included in included studies were listed in Supplemental Table 2 to facilitate readers to understand the overall features of the included articles.

According to the quality assessment of the Cochrane handbook, the 13 included studies were systematically evaluated, such as selection bias, detection bias, incomplete reporting bias and publication bias. In general, the included studies were less biased. Three retrospective single-arm studies failed to follow random allocation, and the remaining 10 studies described the generation of random sequences in detail (Fig. 2). In addition, patients in some studies received an open trial, which may cause some implementation bias. Before the start of the included study, all the studies excluded patients with events that might cause adverse reactions to the subjects during follow-up and patients with a life expectancy of less than 1 y. Therefore, there were no significant data missing in all the studies (defined as the rate of lost to follow-up less than 10%), which would not have a significant impact on the test effectiveness and both biases were rated as low-risk. Furthermore, as noticed in Figure 2, outcomes assessment in each included study was totally blinded for researchers which considering low biases in commercial. In general, the overall evaluation of the research included in this meta-analysis considered low-risk of bias, and the research quality was good, also, the results were highly-reliable (Fig. 2A and B).

Outcomes

Comparison between DCBs and control of safety end-points and effective end-points in patients with BTK artery disease

Safety endpoints: MAEs, all-cause mortality, major amputation, TLR.

MAEs. Six studies revealed that patients with BTK artery disease treated with DCBs had a lower incidence of MAEs at

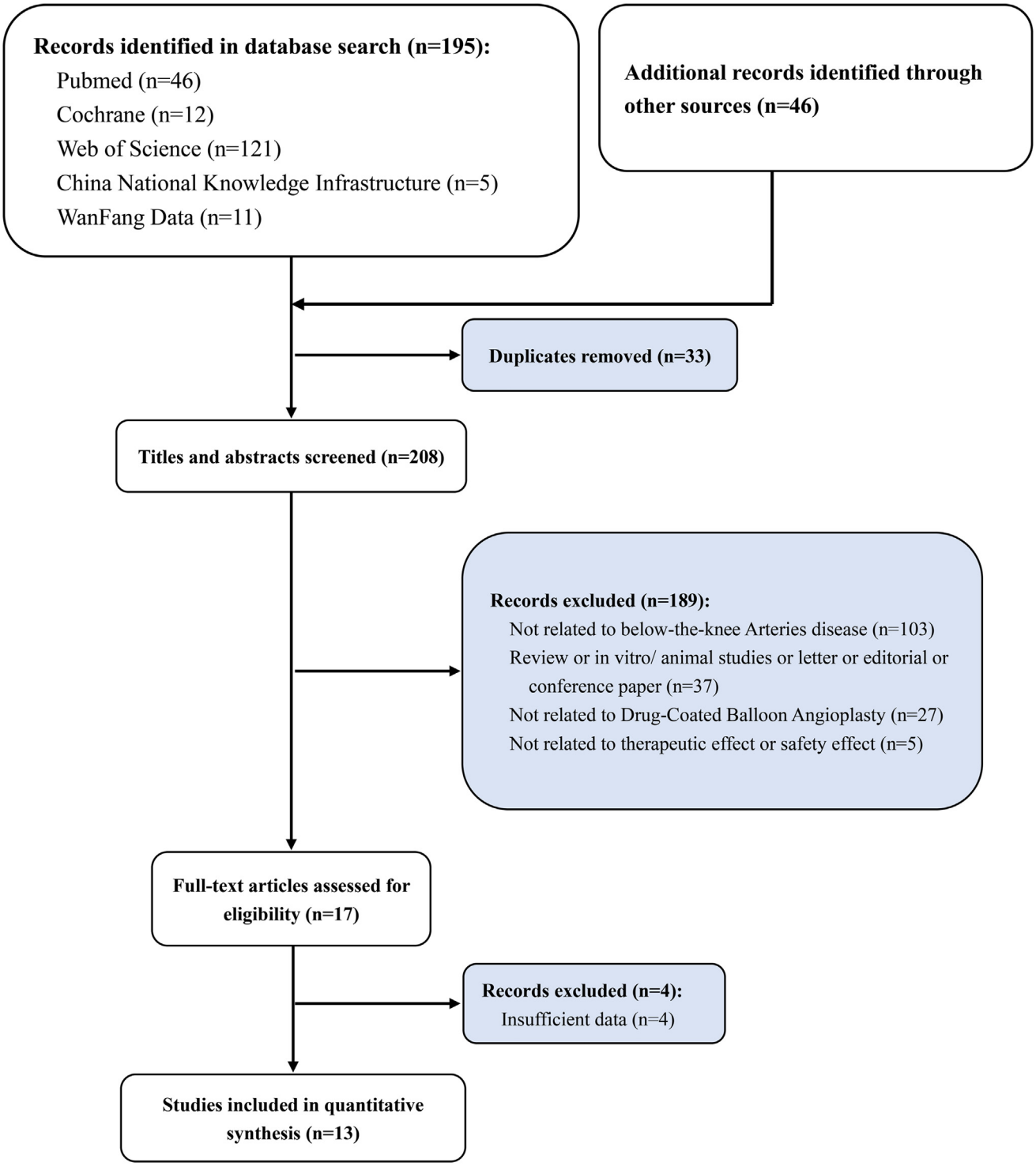


Fig. 1 – Study selection flowchart, systematic review and meta-analysis of safety and efficacy of drug-coated balloon in the treatment of below-the-knee artery.

6 mo and 12 mo compared with patients treated in the control group, but the difference was not statistically significant. However, at 60 mo, the incidence of MAEs in the DCBs group was higher than those in the control group, and the difference was not statistically significant. (6 mo: OR = 0.62, 95% CI: 0.20, 1.90; 12 mo: OR = 0.68, 95% CI: 0.36, 1.31; 60 mo: OR = 1.13, 95% CI: 0.73, 1.76; Fig. 3A, Table 2).

All-cause mortality. Five studies reported on the all-cause mortality of BTK artery disease after treatment. Patients treated with DCBs had higher mortality at 6 mo and 12 mo follow-up than the control, and the difference was not statistically significant. However, patients treated with DCBs had lower all-cause mortality at 60 mo than the control, and the difference was statistically significant. (6 mo: OR = 2.06, 95%

Table 1 – Baseline characteristics of patients of included studies for meta-analysis.

Author	Grouping	Number of case (male)	Average age (y, DCB/Ctrl)	Inclusion period	Characteristics of lesions				No. of diseased vessels	Indicators
					Number	No. of occlusion	No. of calcification	Length (cm)		
Fanelli *et al.* 2012[20]	DCB	25 (19)	66.0 ± 6.0	Sep. 2010–Mar. 2011	31	15	19	7.6 ± 0.6	27	6 mo follow-up results of MLD, LLL, ABI, all-cause mortality, TLR, amputation, MAEs.
	AB	25 (18)	67.0 ± 6.0		28	12	22	7.8 ± 0.7	27	
Tepe *et al.* 2021[21]	DCB	151 (111)	72.3 ± 10.0	Oct. 2014–Jan. 2017	185	34	184	7.9 ± 7.2	185	6mo, 12 mo and 24 mo follow-up end point of TLR, amputation, primary patency, all-cause mortality and MAEs, respectively.
Zeller *et al.* 2014[11]	DCB	239 (182)	73.3 ± 8.2	Sep. 2009–Jul. 2012	350	135	48	10.2 ± 9.1	NA	12 mo follow-up results of TLR, LLL, all-cause mortality, MAEs, amputation.
	PTA	119 (84)	71.7 ± 9.9		181	83	19	12.9 ± 9.5	NA	
Liistro *et al.* 2013[9]	DCB	65 (54)	74.0 ± 9.4	Nov. 201–Oct. 2011	80	62	20	12.9 ± 8.3	NA	12 mo follow-up results of all-cause mortality, MAEs, ABI, amputation.
	PTA	67 (52)	75.0 ± 9.6		78	64	22	13.1 ± 7.9	NA	
Zeller *et al.* 2015[10]	DCB	36 (27)	72.9 ± 10.3	Jul. 201–Jun. 2013	50	NA	31	11.3 ± 8.8	50	6 mo and 12 mo follow-up end point of TLR, LLL, all-cause mortality, MAEs, amputation, MLD, primary patency, respectively.
	PTA	36 (30)	69.6 ± 8.9		54	NA	23	11.5 ± 8.7	54	
Jia *et al.* 2020[22]	DCB	61 (36)	70.7 ± 7.4	May. 201–Jun. 2018	65	48	56	16.9 ± 8.6	65	12 mo follow-up end point of TLR, LLL, all-cause mortality, MAEs, amputation; 6 mo follow-up results of TLR, LLL, amputation, MLD, primary patency.
	Uncoated balloon	59 (36)	70.8 ± 9.0		66	54	54	17.9 ± 8.1	66	
Palena *et al.* 2018[23]	DCB	21 (15)	67.0 ± 11.7	Aug. 2014–Aug. 2016	21	0	21	24.5 ± 14.9	21	12 mo follow-up result of limb salvage.
Teichgräber *et al.* 2019[24]	DCB	164 (109)	74.7 ± 9.2	Nov. 2015–Sep. 2017	248	105	83	7.1 7.6	273	6 mo follow-up results of TLR rate, amputation rate and primary patency rate; 12 mo follow-up results of TLR rate, amputation rate, primary patency rate, all-cause mortality rate and limb salvage.
Heidemann *et al.* 2020[25]	DCB	3284 (1755)	77.4 ± 9.8	Jan. 201–Dec. 2018	NA	NA	NA	NA	NA	60 mo follow-up results of all-cause mortality and amputation.
	PBA + BMS	3284 (1755)	77.3 ± 9.9		NA	NA	NA	NA	NA	
Steiner *et al.* 2016[26]	DCB	208 (138)	74.1 ± 9.7	May 201–Oct. 2014	220	140	NA	NA	220	6 mo follow-up results of TLR rate, amputation rate and all-cause mortality rate.

(*continued*)

Table 1 — (continued)

Author	Grouping	Number of case (male)	Average age (y, DCB/Ctrl)	Inclusion period	Characteristics of lesions				No. of diseased vessels	Indicators
					Number	No. of occlusion	No. of calcification	Length (cm)		
Schmidt *et al.* 2011[12]	DCB	104 (69)	73.6 ± 6.7	Jan. 200–Feb. 2010	109	79	NA	17.6 8.8	NA	12 mo follow-up result of limb salvage, TLR rate, amputation rate, all-cause mortality rate.
Zeller *et al.* 2020[13]	DCB	239 (182)	73.3 ± 8.2	Sep. 200–Jul. 2012	350	135	48	10.2 9.1	NA	60 mo follow-up results of TLR, MAEs and amputation.
	PTA	119 (84)	71.7 ± 9.9		181	83	19	12.9 9.5	NA	
Thieme *et al.* 2018[27]	DCB	314 (224)	73.5 ± 9.5	NA	305	NA	204	12.3 9.9	314	6 mo follow-up results of TLR rate, all-cause mortality rate.

DCBs = drug-coated balloons; Ctrl = control; AB = angioplasty balloon; PTA = percutaneous transluminal angioplasty; PBA = plain balloon angioplasty; BMS = bare metal stent; MAEs = major adverse events, TLR = target lesion revascularization, MLD = minimum lumen diameter, LLL = late lumen loss, ABI = ankle-brachial index.

CI: 0.18, 23.94; 12 mo: OR = 1.30, 95% CI: 0.69, 2.46; 60 mo: OR = 0.88, 95% CI: 0.80, 0.97; Fig. 3B, Table 2). It is worth mentioning that in the study of Fanelli *et al.*, no deaths were observed in the two groups at the end of follow-up.[20]

Major amputation. Seven studies investigated the major amputation rates of the DCBs group and the uncoated balloon group at 6 mo, 12 mo, and 60 mo after treatment of BTK artery disease. There was no statistically significant difference in the outcome indicators at 6 mo and 12 mo, but the major amputation rate showed an upward trend. At 60 mo, the major amputation rate of DCBs group was higher than those of the control group, and the difference was statistically significant (6 mo: OR = 0.97, 95% CI: 0.37, 2.53; 12 mo: OR = 1.34, 95% CI: 0.64, 2.79; 60 mo: OR = 1.21, 95% CI: 1.01, 1.46; Fig. 4A, Table 2).

TLR. Five studies showed that the TLR rate of the DCBs group increased with time compared with the control group, but the TLR rate of the DCBs group at 6 mo and 12 mo was lower than those of the control group, and the difference in the outcome indicators at 6 mo was statistically significant (6 mo: OR = 0.31, 95% CI: 0.11, 0.91; 12 mo: OR = 0.72, 95% CI: 0.35, 1.45; 60 mo: OR = 1.17, 95% CI: 0.67, 2.04; Fig. 4B, Table 2).

Effective endpoints: MLD, LLL, ABI, primary patency, limb salvage

MLD. Three studies reported MLD at the end of the 6-mo follow-up. The results suggested that patients treated with DCBs had higher MLD than patients treated with control therapy, and the difference was statistically significant (6 mo: SMD = 3.05, 95% CI: 0.63, 5.47; Table 2).

LLL. The meta-analysis results of four studies indicated that the DCBs group had lower LLL than the control group at 6 mo and 12 mo, but the difference was not statistically significant. (6 mo: SMD = -0.59, 95% CI: -1.21, 0.04; 12 mo: SMD = -0.01, 95% CI: -0.23, 0.21; Table 2).

Subgroup analysis of comparison among DCBs and different interventions of control group

The meta-analysis results of RCT focusing on comparing safety and efficacy end point between DCBs and PTA have showed that there are no significant advantages in DCB group (Table 3). They have similar follow-up results of all indicators we reported in this review (Table 3).

Meanwhile, DCBs group showed non-negligible better follow-up results in both safety and efficacy endpoints which including lower MAEs rate, major amputation rate, TLR rate and LLL parameter, and higher MLD parameter and ankle brachial index (ABI) parameter than control intervention except PTA (Table 3).

Moreover, the results of the ABI, primary patency, limb salvage indicators and single rate meta-analysis of safety endpoints for single-arm trials were listed in Table 2, to compare the results of other studies on the application of uncoated balloon therapy in the treatment of BTK artery lesions.

Publication bias assessment and sensitivity analysis

Egger's test was used for the analysis of publication bias. It suggested that TLR and primary patency had publication bias in the single rate meta-analysis, while no significant

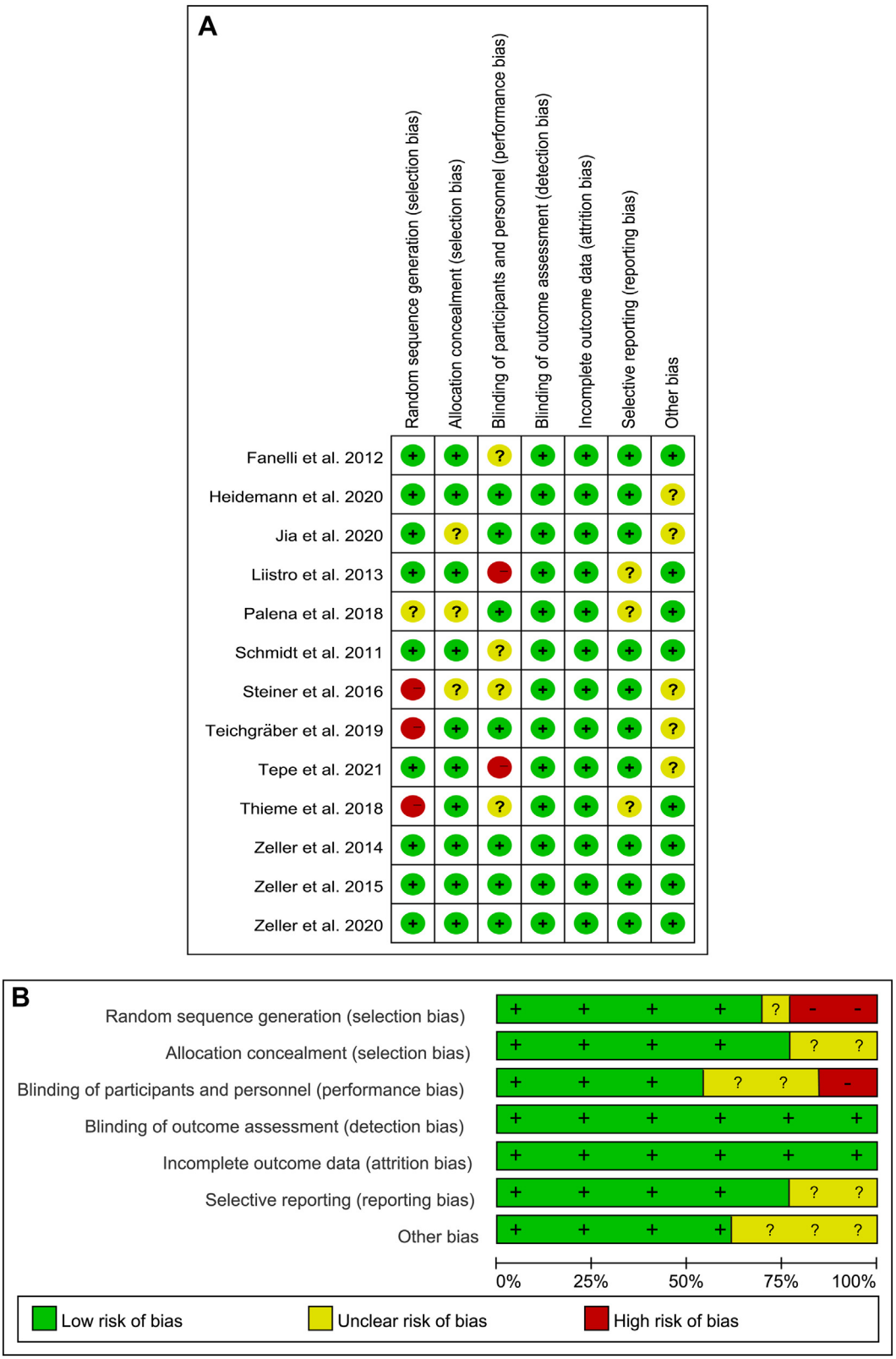


Fig. 2 – A, Risk of bias summary: Review authors' judgments about each risk of bias item for each included study; B, Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies; texture of "+", "-", "?" mean low risk of bias, high risk of bias and unclear risk of bias respectively.

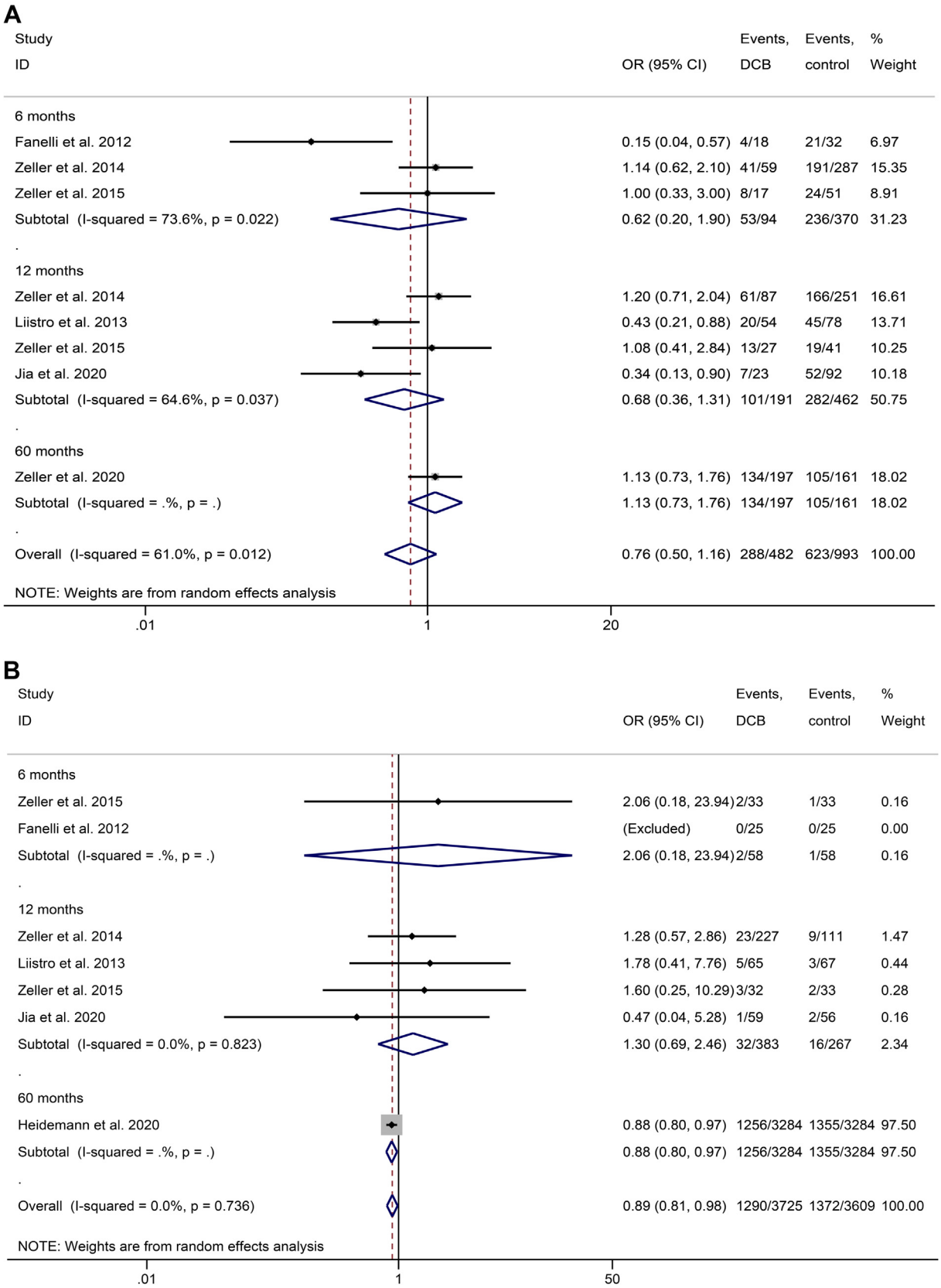
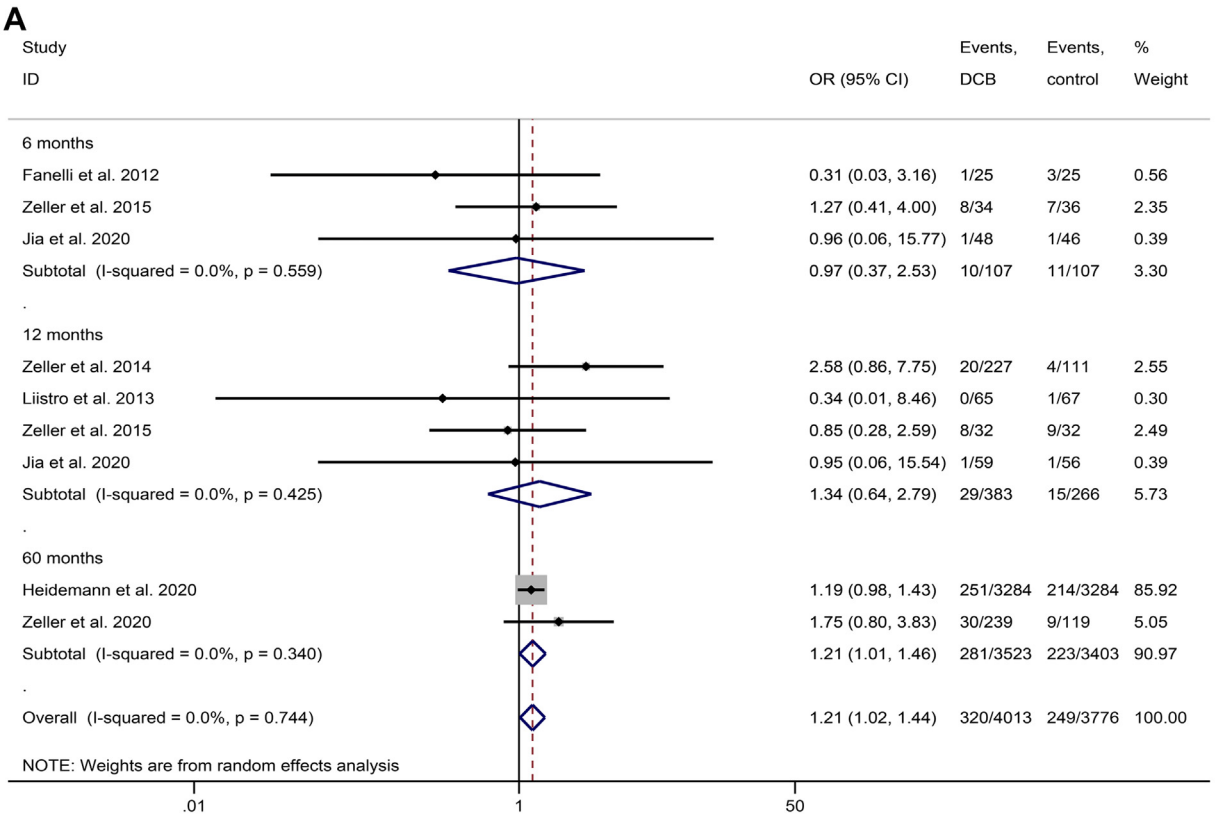


Fig. 3 – Forest plot of comparison between DCBs and control of safety endpoints and effective endpoints in patients with BTK artery disease: A, major adverse events; B, all-cause mortality.

Table 2 – Summarized results of included studies.

Indicators	No. of studies	Sample size	Effect size (95%CI)	Heterogeneity (%)	
				I^2	P
Comparison between DCBs and control of safety endpoints and effective endpoints in patients with BTK artery disease					
6 mo					
MAEs	3	464	0.62 (0.20, 1.90)	73.6	0.022
All-cause mortality	1	66	2.06 (0.18, 23.94)	-	-
Major amputation	3	214	0.97 (0.37, 2.53)	0.0	0.559
TLR	3	215	0.31 (0.11, 0.91)	42.2	0.178
MLD	3	206	3.05 (0.63, 5.47)	97.6	<0.001
LLL	3	206	-0.59 (-1.21, 0.04)	78.8	0.009
ABI	1	50	1.08 (0.48, 1.67)	-	-
Primary patency	2	185	2.14 (0.17, 26.39)	92.5	<0.001
12 mo					
MAEs	4	653	0.68 (0.36, 1.31)	64.6	0.037
All-cause mortality	4	650	1.30 (0.69, 2.46)	0.0	0.823
Major amputation	4	649	1.34 (0.64, 2.79)	0.0	0.425
TLR	3	514	0.72 (0.35, 1.45)	41.3	0.182
LLL	1	358	-0.01 (-0.23, 0.21)	-	-
ABI	1	132	1.23 (0.86, 1.60)	-	-
Primary patency	1	88	1.18 (0.51, 2.74)	-	-
Limb salvage	2	250	0.95 (0.93, 0.98)	0.0	0.942
60 mo					
MAEs	1	358	1.13 (0.73, 1.76)	-	-
All-cause mortality	1	6568	0.88 (0.80, 0.97)	-	-
Major amputation	2	6926	1.21 (1.01, 1.46)	0.0	0.340
TLR	1	358	1.17 (0.67, 2.04)	-	-
Single rate meta-analysis of safety endpoints for single-arm trials					
6 mo					
MAEs	4	414	0.17 (0.14, 0.21)	0.0	0.760
All-cause mortality	4	489	0.10 (0.07, 0.13)	18.3	0.299
Major amputation	6	502	0.07 (0.03, 0.12)	81.0	<0.001
TLR	7	696	0.09 (0.05, 0.13)	64.6	0.009
Primary patency	4	369	0.87 (0.81, 0.93)	59.4	0.061
12 mo					
MAEs	5	505	0.25 (0.17, 0.33)	73.0	0.005
All-cause mortality	8	753	0.08 (0.05, 0.12)	64.9	0.006
Major amputation	6	645	0.09 (0.04, 0.14)	83.7	<0.001
TLR	7	707	0.13 (0.09, 0.16)	40.1	0.124
Primary patency	3	326	0.68 (0.53, 0.83)	88.4	<0.001
60 mo					
MAEs	1	239	0.61 (0.55, 0.67)	-	-
All-cause mortality	1	3284	0.38 (0.37, 0.40)	-	-
Major amputation	2	3523	0.11 (0.04, 0.19)	90.7	0.001
TLR	1	239	0.29 (0.23, 0.35)	-	-

DCBs = drug-coated balloons, BTK = below-the-knee, MAEs = major adverse events, TLR = target lesion revascularization, MLD = minimum lumen diameter, LLL = late lumen loss, ABI = ankle-brachial index. For indicators (MAEs, All-cause mortality, Major amputation, TLR, primary patency) in Comparison between DCBs and control of safety endpoints and effective endpoints in patients with BTK artery disease, effect size is OR; for indicators (MLD, LLL, ABI) in Comparison between DCBs and control of safety endpoints and effective endpoints in patients with BTK artery disease, effect size is SMD; for indicators in single rate meta-analysis of safety endpoints for single-arm trials, effect size is rate.



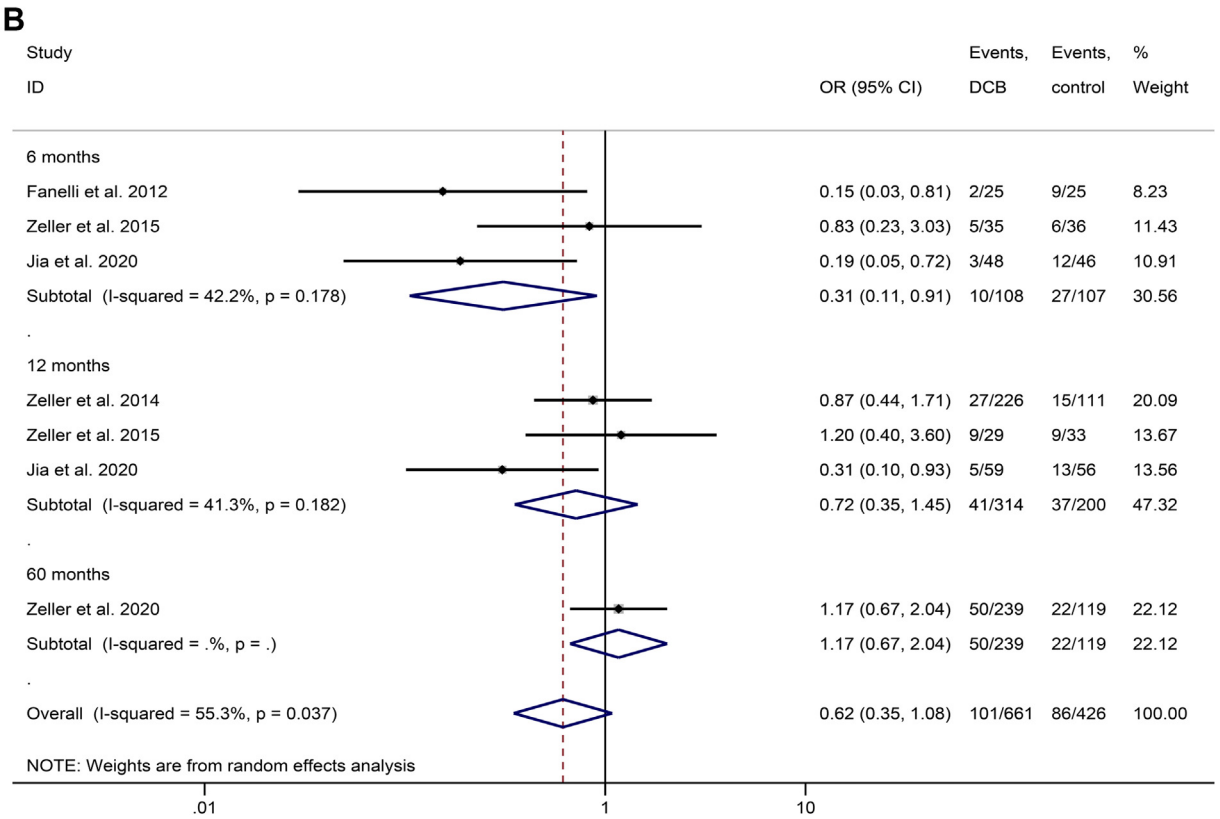


Fig. 4 – Forest plot of comparison between DCBs and control of safety endpoints and effective endpoints in patients with BTK artery disease: A, Major amputation; B, target lesion revascularization.

Table 3 – Summarized results of included studies by subgroup.

Indicators	No. of studies	Sample size	Effect size (95%CI)	Heterogeneity (%)	
				I^2	*P*
Comparison between DCBs and PTA of safety endpoints and effective endpoints in patients with BTK artery disease					
6 mo					
MAEs	2	414	1.11 (0.65, 1.89)	0.0	0.833
All-cause mortality	1	66	2.06 (0.18, 23.94)	-	-
Amputation	1	70	1.27 (0.41, 4.00)	-	-
TLR	1	71	0.83 (0.23, 3.03)	-	-
MLD	1	62	0.03 (−0.47, 0.52)	-	-
LLL	1	62	0.03 (−0.47, 0.53)	-	-
Primary patency	1	91	0.59 (0.21, 1.64)	-	-
12 mo					
MAEs	3	538	0.83 (0.42, 1.63)	62.6	0.069
All-cause mortality	3	535	1.41 (0.73, 2.72)	0.0	0.918
Amputation	3	534	1.32 (0.51, 3.42)	26.6	0.256
TLR	2	499	0.95 (0.53, 1.69)	0.0	0.623
LLL	1	358	−0.01 (−0.23, 0.21)	-	-
ABI	1	133	1.23 (0.86, 1.60)	-	-
Primary patency	1	88	1.18 (0.51, 2.74)	-	-
60 mo					
MAEs	1	358	1.13 (0.73, 1.76)	-	-
Amputation	1	358	1.75 (0.80, 3.83)	-	-
TLR	1	358	1.17 (0.67, 2.04)	-	-
Comparison between DCBs and control except from PTA of safety endpoints and effective endpoints in patients with BTK artery disease					
6 mo					
MAEs	1	50	0.15 (0.04, 0.57)	-	-
Amputation	2	144	0.68 (0.05, 9.34)	0.0	0.327
TLR	2	144	0.17 (0.09, 0.88)	0.0	0.878
MLD	2	144	3.87 (1.26, 7.54)	91.2	<0.001
LLL	1	94	-0.95 (-1.38, -0.53)	-	-
ABI	1	50	1.08 (0.48, 1.67)	-	-
Primary patency	1	94	7.62 (0.17, 26.39)	-	-
12 mo					
MAEs	1	115	0.34 (0.13, 0.90)	-	-
All-cause mortality	1	115	0.47 (0.04, 5.28)	-	-
Amputation	1	115	0.95 (0.06, 15.54)	-	-
TLR	1	115	0.31 (0.10, 0.93)	-	-
60 mo					
All-cause mortality	1	3284	0.38 (0.37, 0.40)	-	-

DCBs = drug-coated balloons, PTA = percutaneous transluminal angioplasty, BTK = below-the-knee, MAEs = major adverse events, TLR = target lesion revascularization, MLD = minimum lumen diameter, LLL = late lumen loss, ABI = ankle-brachial index. For indicators (MAEs, All-cause mortality, Amputation, TLR, primary patency) in Comparison between DCBs and PTA of safety endpoints and effective endpoints in patients with BTK artery disease, effect size is OR; for indicators (MLD, LLL, ABI) in Comparison between DCBs and PTA of safety endpoints and effective endpoints in patients with BTK artery disease, effect size is SMD.

publication bias was observed in the other indicators. The Duval and Tweedie's trim and fill test of TLR in the single rate meta-analysis found that after the small sample was filled, the TLR rate had significant change, proving that the effect size was not stable, and its guiding significance required further discussion (Table 4).

Discussion

In this meta-analysis, the safety and effectiveness of DCBs in the treatment of BTK artery disease is not better than those of the PTA group, and the results of 5 y follow-up also shows

Table 4 – Evaluation of publication bias and sensitivity analysis.

Index	Egger's regression		Duval and Tweedie's trim and fill		
	Intercept	P	Original effect size	Studies trimmed	Adjusted effect size
Comparison between DCBs and uncoated balloon of safety endpoints and effective endpoints in patients with below-the-knee artery disease					
MAEs	-1.769	0.179	0.98 (0.73, 1.22)	0	0.98 (0.73, 1.22)
All-cause mortality	0.686	0.167	0.89 (0.79, 0.98)	2	0.88 (0.79, 0.97)
Major amputation	0.159	0.753	1.32 (1.00, 1.65)	0	1.32 (1.00, 1.65)
TLR	-1.540	0.162	0.88 (0.54, 1.22)	0	0.88 (0.54, 1.22)
Single rate meta-analysis					
MAEs	0.977	0.979	0.27 (0.17, 0.36)	0	0.27 (0.17, 0.36)
All-cause mortality	2.041	0.570	0.11 (0.03, 0.19)	0	0.11 (0.03, 0.19)
Major amputation	1.110	0.281	0.09 (0.07, 0.12)	3	0.08 (0.05, 0.10)
TLR	4.009	<0.001	0.12 (0.08, 0.16)	9	0.05 (0.01, 0.09)
Primary patency	-5.246	0.034	0.78 (0.71, 0.86)	0	0.78 (0.71, 0.86)

MAEs = major adverse events, TLR = target lesion revascularization, DCBs = drug-coated balloons.

that the DCBs group has higher incidence of MAEs and major amputation.[13,25] Published data has demonstrated that PTA of the popliteal artery is an effective treatment for CLI patients.[28] However, the use of PTA has been limited by its complications and high restenosis rate. Therefore, DCB seems to be a good alternative to PTA and uncoated balloons for drug delivery. They are thought to reduce the incidence of restenosis, one of the major complications of PTA.[10] However, based on the results of this meta-analysis, we have not observed the superiority of DCBs over other treatment. The results at 6 mo and 12 mo do not show any significant differences between the DCBs group and the control group (mainly PTA), which are manifested as TLR, LLL, major amputation, all-cause mortality. The results of 5 y follow-up also indicate that patients in the DCBs group have a higher risk of MAEs and major amputation. Moreover, this meta-analysis concludes more participants (4911 *versus* 612) and results of long-term follow-up than the previously published review, and the results of this study are similar to those of Wu R *et al*.[29] This confirms the conclusion that DCBs has no obvious advantage in the treatment of BTK artery lesions. The release of the results of the . PACT Amphirion trial leads to the withdrawal of In. PACT Amphirion drug eluting balloons from the market. Therefore, further application of DCBs in the treatment of BTK artery stenosis and other diseases requires more clinical evidence and the innovation of DCB technology.

In a simple comparison of single rate meta-analysis, the results of the single-arm trial of DCBs are superior to the results of the previously published single-arm trial of PTA in the treatment of BTK artery disease. First, a systematic review and meta-analysis of 31 studies involving 3164 patients with PTA for the treatment of BTK artery disease indicates that the primary patency rate is about 60%, the secondary patency rate is about 65%, the limb salvage rate is about 85%, and the one-y survival rate is about 80%.[30] Compared with this study, the 6-mo follow-up study shows that the primary patency rate is 87%, 95% CI: 0.81, 0.93, the 12-mo follow-up study shows the patency rate is 68%, 95% CI: 0.53, 0.83, and the 24-mo patency rate is 78%, 95% CI: 0.70, 0.86, also, one-y limb salvage rate is 95%, 95%CI: 0.93, 0.98, and 1-year survival rate is 92% (shown in Table 2). Moreover, another RCT study that is not included in the previous meta-analysis, Scheinert *et al*., also shows a survival rate of 88.1%, a TLR rate of 16.5%, a limb salvage rate of 80% and a patency rate of 57.1% after treatment with PTA.[31] The TLR rate of the 12-mo follow-up in this meta-analysis is 13%, but, the sensitivity test on TLR rate suggests that this result is unstable, and direct comparison may lead to erroneous conclusions. Considering the differences in baseline characteristics, lesion characteristics, lesion length, whether the surgical procedure is smooth or not, and whether emergency stents are placed, a simple comparison of single rate meta-analysis could not draw definitive conclusion, but it could provide ideas for further clinical research and clinical decision-making.

The length and location of the lesion may affect the effectiveness of treatment. The treatment outcome of DCBs and PTA may vary depending on the length and site of the lesion. In the trial comparing the DCBs group and the control group (mainly PTA) involved in our meta-analysis, there is no statistical difference in the length of the lesion. Therefore, the role of the length and location of the injury in the treatment of BTK artery stenosis needs to be further studied. Furthermore, in the treatment of complex lesions, such as multi-level diseases in CLI patients, the performance of DCBs and PTA should be further evaluated.

In this meta-analysis, we provide the current status of research on DCB in the treatment of BTK revascularizations. As you noticed, only one study has reported indicators of all-cause mortality and ABI at 6 mo follow-up. And same situation could be observed in indicators of LLL, ABI and primary patency at 12 mo follow-up. The limited study and small sample size might cause publication bias in meta-analysis and provide inaccurate results. There's nothing we can do about it except to show research status and to call

on researchers to report fully when implementing studies that relate to it, no matter it's long-term effects or short-term effects.

The main limitations of this meta-analysis are: 1) The outcome indicators of this review have high heterogeneity, which may be caused by the different treatment methods and the different capsule balloon used in the control group. After more follow-up research results come out, it should be limited to a certain type of balloon for further analysis to better guide clinical treatment applications. 2) The coated balloon used in this review is mainly paclitaxel coated balloon, which cannot represent the effect of other types of coated balloon in the treatment of BTK artery disease. 3). The indications for revascularization in different trials are not exactly the same, which may be the reason for the obvious publication bias and unstable results in the TLR rate of this meta-analysis.

In conclusion, the meta-analysis results of RCT focusing on comparing DCBs and other treatments suggest that DCBs do not have significant advantages in the treatment of BTK artery disease when compare with percutaneous transluminal angioplasty (PTA), but better than control intervention except PTA in both safety and efficacy end-points. However, the results of meta-analysis of single arm trial reported DCBs in treating BTK artery lesions are significantly improved compared with the meta-analysis concentrating on PTA.

Supplementary Materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jss.2022.04.055.

Author Contributions

CH, DJ, YYP, LSY: Critical revision of the manuscript; CH, DJ, LSY: Substantial contribution to the conception and design of the work, manuscript drafting; CH, DJ, YYP, SQ: Acquisition, analysis, and interpretation of the data; CH, DJ, YYP, SQ, LSY: Revising the manuscript critically, final approval of the version to be published. All authors have read and approved the final manuscript.

Disclosure

None declared.

Funding

None.

Availability of Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval was not needed because this is a meta-analysis.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340.
2. Uccioli L, Meloni M, Izzo V, Giurato L, Merolla S, Gandini R. Critical limb ischemia: current challenges and future prospects. *Vasc Health Risk Manag*. 2018;14:63–74.
3. Karnabatidis D, Spiliopoulos S, Katsanos K, Siablis D. Below-the-knee drug-eluting stents and drug-coated balloons. *Expert Rev Med Devices*. 2012;9:85–94.
4. Feldman DN, Armstrong EJ, Aronow HD, et al. SCAI consensus guidelines for device selection in femoral-popliteal arterial interventions. *Catheter Cardiovasc Interv*. 2018;92:124–140.
5. Aboyans V, Ricco JB, Bartelink MEL, et al, Document Reviewers. Editor's choice - 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:305–368.
6. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358:689–699.
7. Tepe G, Laird J, Schneider P, et al. IN.PACT SFA Trial Investigators. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131:495–502.
8. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv*. 2012;5:831–840.
9. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation*. 2013;128:615–621.
10. Zeller T, Beschorner U, Pilger E, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (BIOTRONIK'S-first in man study of the passeo-18 LUX drug releasing PTA balloon catheter vs. the uncoated passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). *JACC Cardiovasc Interv*. 2015;8:1614–1622.
11. Zeller T, Baumgartner I, Scheinert D, et al. IN.PACT DEEP Trial Investigators. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol*. 2014;64:1568–1576.
12. Schmidt A, Piorkowski M, Werner M, et al. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol*. 2011;58:1105–1109.
13. Zeller T, Micari A, Scheinert D, et al. IN.PACT DEEP trial investigators. The IN.PACT DEEP clinical drug-coated balloon trial: 5-year outcomes. *JACC Cardiovasc Interv*. 2020;13:431–443.
14. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*; 2022. Cochrane; 2022. Available at: www.training.cochrane.org/handbook.

15. Moher D, Shamseer L, Clarke M. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
16. Harris RJDJ, Altman DG, Bradburn MJ. Metan: fixed- and random-effects meta-analysis. *Stata J*. 2008;8:3–28.
17. Nyaga VN Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72:39.
18. Egger M Davey Smith G, Schneider M. Bias in meta-analysisdetected by a simple, graphical test. *BMJ*. 1997;315:629–634.
19. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455–463.
20. Fanelli F, Cannavale A, Boatta E, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther*. 2012;19:571–580.
21. Tepe G, Wang J, Corpataux JM, et al. BIOLUX P-III passeo-18 lux all-comers registry: 24-month results in below-the-knee arteries. *Cardiovasc Intervent Radiol*. 2021;44:10–18.
22. Jia X, Zhuang B, Wang F, et al. Drug-coated balloon angioplasty compared with uncoated balloons in the treatment of infrapopliteal artery lesions (AcoArt II-BTK). *J Endovasc Ther*. 2020;28:215–221.
23. Palena LM, Diaz-Sandoval LJ, Gomez-Jaballera E, et al. Drug-coated balloon angioplasty for the management of recurring infrapopliteal disease in diabetic patients with critical limb ischemia. *Cardiovasc Revasc Med*. 2018;19(1 Pt B):83–87.
24. Teichgräber U, Lehmann T, Thieme M, et al. Drug-coated balloon angioplasty of infrapopliteal lesions in patients with critical limb ischaemia: 1-year results of the APOLLO trial. *Cardiovasc Intervent Radiol*. 2019;42:1380–1390.
25. Heidemann F, Peters F, Kuchenbecker J, et al. Long term outcomes after revascularisations below the knee with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg*. 2020;60:549–558.
26. Steiner S, Schmidt A, Bausback Y, et al. Single-center experience with lutonix drug-coated balloons in infrapopliteal arteries. *J Endovasc Ther*. 2016;23:417–423.
27. Thieme M, Lichtenberg M, Brodmann M, Cioppa A, Scheinert D. Lutonix® 014 DCB global below the knee registry study: interim 6-month outcomes. *J Cardiovasc Surg (Torino)*. 2018;59:232–236.
28. Dorros G, Jaff MR, Dorros AM, Mathiak LM, He T. Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up. *Circulation*. 2001;104:2057–2062.
29. Wu R, Tang S, Wang M, Li Z, Yao C, Wang S. Drug-eluting balloon versus standard percutaneous transluminal angioplasty in infrapopliteal arterial disease: a meta-analysis of randomized trials. *Int J Surg*. 2016;35:88–94.
30. Lejay A, Georg Y, Bajcz C, et al. Endovascular treatment of infra-popliteal arteries in patients with critical limb ischemia. *Acta Chir Belg*. 2009;109:684–693.
31. Scheinert D, Katsanos K, Zeller T, et al, ACHILLES Investigators. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. *J Am Coll Cardiol*. 2012;60:2290–2295.