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Efficacy, Safety, and Clinical Outcomes of Paclitaxel-Coated Balloon Angioplasty for De-Novo Femoropopliteal Peripheral Arterial Disease: A Systematic Review and Meta-analysis of Randomized Clinical Trials

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Review Article

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Abstract

Background and Aim: The objective of this study is to compare two of the main endovascular treatment options, drug-coated balloon (DCB) and plain old balloon angioplasty (POBA) for patients with de-novo femoropopliteal peripheral arterial disease.

Methods: A comprehensive review of all relevant manuscripts and abstract studies from inception to May 2021 were obtained. A meta-analysis was performed using a random-effects model to calculate risk ratios (RR) with 95% confidence intervals (CI).

Results: Fifteen randomized controlled trials were included with a total of 2,825 patients and a median-weighted follow-up period of 1.73 years. The experimental group was defined as patients who were treated with paclitaxel DCB whereas, the control group received POBA. A pooled analysis of the data showed that target lesion revascularization (TLR) freedom significantly favored the DCB arm with a greater effect seen after 2 years (risk ratio [RR] 1.40, 95% CI 1.28-1.53, p <0.00001, I2=23%). Subgroup analysis also showed greater benefit with higher paclitaxel densities greater than or equal to 3.0 ug/mm^2 (RR 1.39, 95% CI 1.29-1.51, p <0.00001, I2=10%). All-cause mortality and major/minor limb amputation were similar between both arms. Primary patency significantly favored DCB, especially in the first year of follow-up. After 2 years of follow-up, the improvement in ABI insignificantly favored DCB. Rutherford classification significantly favored DCB at 1 year, but there was no difference at 2 years. Finally, improvement in WIQ score was similar between both arms.

Conclusion: This meta-analysis demonstrates that femoropopliteal PAD has significantly improved TLR freedom and a similar safety profile with DCB as compared to POBA. The effect was more pronounced at the 2-year follow-up and with a higher paclitaxel density.

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Introduction

Through lower extremity atherosclerosis and chronic arterial occlusive disease, peripheral arterial disease (PAD) can cause intermittent claudication. However, 11% of patients develop chronic limb-threatening ischemia, which requires amputation [1, 2]. Although prevalence rates of PAD are inaccurate due to under diagnosis, it is estimated to affect 8.5-12 million Americans [3]. Furthermore, the presentation of PAD has been increasing since 2000 in both high- and middle-income countries [4]. The most recent guidelines to guide treatment of PAD were released by the American Heart Association (AHA) and American College of Cardiology (ACC) in 2016 [5] and by the European Society of Cardiology (ESC) and European Society for Vascular Surgery (ESVS) in 2017 [6]. While both guidelines agree that supervised exercise programs are first-line treatment methods for PAD, they differ on the indications for endovascular revascularization in patients with femoropopliteal PAD. The AHA/ACC indicates that endovascular procedures are reasonable for patients with femoropopliteal occlusions who develop lifestyle-limiting claudication and are hemodynamically significant (Class IIa recommendation, Level of evidence B-R) [5]. On the other hand, the ESC/ESVS recommend endovascular procedures for de-novo femoropopliteal occlusions that are less than 25 centimeters, otherwise known as short lesions (Level of evidence C). Patients with occlusions longer than 25 centimeters, or long lesions, can consider endovascular procedures if they are deemed high-risk candidates for surgery (Class IIb recommendation, Level of evidence C) [6]. The current types of endovascular procedures for PAD consist of plain old balloon angioplasty (POBA), bare-metal stents, drug-eluting stents, polymer-covered metal stents, and drug-coated balloons (DCB) [7,8.9]. DCB's are an emerging method that has demonstrated superiority compared to POBA in target lesion revascularization and reduction of restenosis in multiple randomized control trials.

In the current guidelines, there is limited data on the indications of endovascular procedures for femoropopliteal PAD. This is especially the case as to the type of procedure, drug, and dosage as well as the recommended treatment course in de-novo lesions and long lesions. Additionally, the safety of the DCBs in patients with femoropopliteal PAD is uncertain. We conducted an updated meta-analysis with the addition of a new randomized controlled trial (RCT) along with new sub-group studies to evaluate and address these aforementioned unknown issues in the current guidelines.

Materials and Methods

We conducted a comprehensive review of previous publications of all relevant studies from inception to May 2021. We searched the electronic databases of PUBMED, EMBASE, and COCHRANE. The inclusion criteria consisted of: (1) an RCT that evaluated the efficacy and/or safety outcomes of PCB angioplasty versus POBA for femoropopliteal PAD and (2) the study reported more than one clinical or safety outcome. Exclusion criteria were the following: (1) follow-up data in less than 90% of patients, (2) ongoing or irretrievable data, (3) use of bare-metal stents or drug-eluting stents in the control group, and (4) no clinical outcome endpoint. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

The search included the following keywords: "peripheral arterial disease", "PAD", "femoropopliteal", "paclitaxel", "angioplasty", "randomized trial", "efficacy", "safety", "mortality", and "clinical". Two authors (RMP and MM) independently reviewed the search results, extracted potential articles, and assessed their eligibility. The Cochrane Collaboration risk-of-bias tool was used by two different authors (RMP and MM) to assess the quality of the included studies.

The primary outcome of this meta-analysis was target lesion revascularization (TLR) freedom and all-cause mortality. Subgroup analyses were performed on these outcomes based on the follow-up period and density of paclitaxel in the experimental group. Secondary outcomes included major and/or minor limb amputation, primary patency, ankle-brachial index (ABI), Rutherford classification improvement, and walking improvement questionnaire (WIQ) score improvement. All secondary outcomes, except WIQ score improvement, were all evaluated via subgroup analysis based on the follow-up period. Improvement in ABI and WIQ scores were analyzed as the change in values from baseline to last follow-up period. On the other hand, improvement in Rutherford classification was defined as the number of patients who improved by at least one class. We also collected baseline characteristics of the included studies and patients (Tables 1 and 2), as well as lesion and procedural characteristics (Tables 3 and 4). Statistical analysis was conducted using Review Manager (RevMan), Version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). The Mantel-Haenszel random-effects models were used to estimate risk ratios (RR), mean differences (MD), and the corresponding 95% confidence intervals (CI). Two-sided p values of ,<0.05 were considered statistically significant. I^2 statistics were used to assess statistical heterogeneity. When the I^2 statistics were higher than 60%, the study creating the most heterogeneity was excluded.

Table 1: Characteristics of the included Randomized Controlled Trials

First author	Publication year	Study name	Enrollment	Study design	Number of patients (DCB | POBA)	Latest follow-up (years)	Type of DCB	Paclitaxel density (ug/mm²)
Jia Xu	2016 2018	AcoArt I	2013-2014	Multicenter Multicenter	100 | 100	1 2	Orchid Paclitaxel coated Admiral Xtreme peripheral balloon catheter	3.0
Scheinert	2015	BIOLUX P-1	2010-2011	Multicenter	30 | 30	1	Passeo-18 Lux Paclitaxel coated	3.0
Tepe Altrech	2017 2018	CONSEQUENT	2013-2015	Multicenter	78 | 75	2	SeQuent Please OTW	3.0
Liistro	2013	DEBATE-SFA	2010-2011	Single center	53 | 51	1	In.Pact Admiral, Invatec/Medtronic	3.0
Werk	2008	FemPac	2010-2012	Multicenter	45 | 42	2	FDA-GMP	3.0
Schroeder Brodmann	2017 2018	ILLUMENTATE EU	2012-2015	Multicenter	222 | 72	2	Stellarex DCB	2.0
Krishnan	2017	ILLUMENATE Pivotal	2013-2015	Multicenter	200 | 100	1	EverCross™ 0.035 PTA Balloon Catheter	2.0
Tepe Schneider	2015 2018	IN.PACT SFA	2010-2013	Multicenter	220 | 111	1 3	IN.PACT Admiral DCB	3.5
Ott	2017	ISAR-STATH	2009-2013	Multicenter	48 | 52	2	In.PACT Admiral, Invatec/Medtronic	3.5
Scheinert	2014	LEVANT 1	2009	Multicenter	49 | 52	2	The Lutonix DCB	2.0
Rosenfield	2015	LEVANT II	2011-2012	Multicenter	316 | 160	1	Lutonix DCB	2.0
Werk	2012	PACIFIER	2010-2011	Multicenter	44 | 47	1	IN.PACT Pacific DEB	3.0
Steiner	2018	RANGER SFA	2014-2015	Multicenter	71 | 34	1	NR	2.0
Tepe Tepe	2008 2015	THUNDER	2004-2005	Multicenter	48 | 54	2	Bavaria Medizintechnologie	3.0
Sachar	2021	RANGER II SFA	2017-2018	Multicenter	278 | 98	1	Ranger DCB	2.0

Study-specific characteristics of the included randomized controlled trials were depicted. DCB, Paclitaxel drug-coated balloon; POBA, Plain old balloon angioplasty.

Results

Fifteen RCTs were included with a total of 2,825 patients and a median-weighted follow-up of 1.73 years (Figure 1). [10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28]. The characteristics of the included studies, patients, lesions, and procedures are described in Tables 1, 2, 3, 4].

A pooled analysis of the data showed that TLR freedom significantly favored the DCB arm at 1-year follow-up (RR 1.19, 95% CI 1.12-1.27, p <0.00001, I^2=51%) when AcoArt I 2016 by Jia et al was excluded due to high I^2. A greater benefit was seen after 2 years (RR 1.40, 95% CI 1.28-

Table 2: Patient Characteristics of the Included Studies

Study name	Patients (n)	Age	Males	Smokers (Current or former)	Diabetes mellitus	Hypertension	Dyslipidemia
AcoArt I							
DCB	100	65.9 ± 9.0	73 (73)	29 (29)	54 (54)	62 (62)	27 (27)
POBA	100	65.6 ± 8.6	74 (74)	33 (33)	57 (57)	72 (72)	29 (29)
BIOLUX P-1							
DCB	30	70.1 ± 10.4	57 (17)	63 (19)	37 (11)	77 (23)	60 (18)
POBA	30	71.4 ± 10.0	57 (17)	73 (22)	30 (9)	70 (21)	63 (19)
CONSEQUENT							
DCB	78	68.2 ± 8.5	60 (47)	46 (36)	35 (27)	77 (60)	56 (44)
POBA	75	68.0 ± 9.0	67 (57)	49 (37)	39 (29)	80 (60)	52 (39)
DEBATE-SFA							
DCB	53	74.0 ± 9.0	75 (40)	47 (25)	77 (41)	89 (47)	62 (33)
POBA	51	76.0 ± 8.0	63 (32)	55 (28)	71 (36)	88 (45)	53 (27)
FemPac		67.3 (63.5-75.4)					
DCB	45		60 (27)	32 (21)	40 (18)	78 (35)	58 (26)
POBA	42	70.2 (66.2-77.6)	60 (25)	36 (15)	55 (23)	81 (34)	57 (24)
ILLUMENATE EU							
DCB	22	67.0 ± 9.0	72 (160)	89 (198)	37 (83)	78 (173)	62 (137)
POBA	72	69.0 ± 9.0	68 (49)	83 (60)	36 (26)	83 (60)	68 (49)
ILLUMENATE Pivotal							
DCB	200	68.3 ± 10.3	56 (112)	84 (168)	50 (99)	94 (187)	88 (176)
POBA	100	69.8 ± 9.8	64 (64)	75 (75)	52 (52)	94 (94)	90 (90)
IN.PACT-SFA							
DCB	220	67.5 ± 9.5	65 (143)	39 (85)	41 (89)	91 (201)	85 (186)
POBA	111	68.0 ± 9.2	68 (75)	36 (40)	49 (54)	88 (98)	82 (91)
ISAR-STATH							
DCB	48	69.7 ± 9.4	69 (33)	75 (36)	21 (10)	83 (40)	94 (45)
POBA	52	69.2 ± 8.0	71 (37)	65 (34)	29 (15)	77 (40)	87 (45)
LEVANT 1							
DCB	49	67.0 ± 8.0	69 (34)	31 (15)	47 (22)	96 (47)	59 (29)
POBA	52	70.0 ± 10.0	58 (30)	39 (20)	50 (26)	87 (45)	69 (36)
LEVANT II							
DCB	316	67.8 ± 10.0	61 (193)	79 (250)	44 (137)	89 (282)	90 (283)
POBA	160	69.0 ± 9.0	67 (107)	83 (132)	42 (67)	88 (140)	86 (138)
PACIFIER							
DCB	44	71.7 ± 7.0	59 (26)	48 (21)	43 (19)	66 (29)	50 (22)
POBA	47	71.0 ± 9.0	64 (30)	60 (28)	28 (13)	66 (31)	47 (22)
RANGER SFA							
DCB	71	68.8 ± 8.0	75 (53)	86 (61)	39 (28)	82 (58)	69 (49)
POBA	34	67.9 ± 9.0	68 (23)	70 (24)	35 (12)	76 (26)	62 (21)
THUNDER							
DCB	48	69.0 ± 8.0	65 (31)	NR	50 (24)	79 (38)	69 (33)
POBA	54	68.0 ± 9.0	63 (34)	NR	46 (25)	83 (45)	63 (34)
RANGER II SFA							
DCB	278	70.6 ± 9.5	62 (173)	86 (238)	42 (118)	90 (251)	76 (211)
POBA	98	69.1 ± 10.3	68 (67)	85 (83)	43 (43)	81 (80)	80 (78)

Patient population characteristics from the included studies were reported. Values are reported as n (%), mean ± SD, or median (IQR). DCB, Paclitaxel drug-coated balloon; POBA, Plain old balloon angioplasty

Table 3: Lesion Characteristics of Included Studies

Study Name	Lesions (n)	Total lesion length (mm)	Reference vessel diameter	Diameter stenosis (%)	Calcification	Severe Calcification	Total occlusion
AcoArt I							
DCB	100	147 ± 110	3·8 ± 0·6	84 ± 20	NR	NR	57 (57)
POBA	100	152 ± 109	3·7 ± 0·5	83 ± 21	NR	NR	52 (52)
BIOLUX P-1							
DCB	33	51 ± 47	4·6 ± 0·8	80 ± 21	NR	NR	NR
POBA	35	69 ± 57	4·7 ± 0·9	73 ± 25	NR	NR	NR
CONSEQUENT							
DCB	78	137 ± 122	5·1 ± 0·8	76 ± 18	NR	NR	27 (21)
POBA	75	126 ± 82	5·4 ± 0·9	77 ± 19	NR	NR	33 (25)
DEBATE-SFA							
DCB	55	94 ± 60	5·0 ± 0·5	91 ± 10	40 (22)	22 (12)	55 (30)
POBA	55	96 ± 69	5·1 ± 0·5	94 ± 9	40 (19)	20 (11)	69 (38)
FemPac							
DCB	45	40 (21–61)	5·0 (4·7–5·6)	85 (75-90)	53 (25/45)	NR	13 (6)
POBA	42	47 (27–85)	5·2 (4·9–6·2)	85 (80-90)	52 (22/42)	NR	19 (8)
ILLUMENATE EU							
DCB	254	72 ± 52	5·0 ± 0·8	79 ± 16	NR	3 (32)	19 (48)
POBA	79	71 ± 53	4·8 ± 0·7	81 ± 16	NR	10 (8)	19 (15)
ILLUMENATE Pivotal							
DCB	200	80 ± 45	4·9 ± 0·9	74 ± 17	NR	44 (87)	19 (38)
POBA	100	89 ± 46	5·2 ± 1·1	75 ± 17	NR	43 (43)	18 (18)
IN.PACT-SFA							
DCB	221	89 ± 51	4·6 ± 0·8	81 ± 16	NR	8 (18)	26 (57)
POBA	113	88 ± 51	4·7 ± 0·8	81 ± 14	NR	6 (7)	20 (22)
ISAR-STATH							
DCB	48	68 ± 44	5·0 ± 1·0	95 ± 8	90 (43)	29 (14)	58 (28)
POBA	52	74 ± 56	5·0 ± 0·9	93 ± 18	85 (44)	17 (9)	67 (35)
LEVANT 1							
DCB	49	81 ± 38	4·1 ± 0·6	85 ± 17	NR	NR	41 (20)
POBA	52	80 ± 38	4·2 ± 0·7	85 ± 17	NR	NR	42 (22)
LEVANT II							
DCB	322	63 ± 41	4·8 ± 0·8	81 ± 15	59 (187)	10 (33)	20 (65)
POBA	165	63 ± 40	4·8 ± 0·8	81 ± 15	58 (93)	8 (13)	21 (35)
PACIFIER				73 ± 16			
DCB	44	70 ± 53	4·9 ± 0·9	80 ± 16	64 (28)	NR	23 (10)
POBA	47	66 ± 55	4·9 ± 0·9		66 (31)	NR	38 (18)
RANGER SFA							
DCB	71	68 ± 46	5·0 ± 0·9	85 ± 15	87 (61)	36 (25)	34 (24)
POBA	34	60 ± 48	4·5 ± 0·8	82 ± 18	84 (27)	22 (7)	34 (11)
THUNDER							
DCB	48	75 ± 62	5·0 ± 0·7	90 ± 8	50 (24)	NR	27 (13)
POBA	54	74 ± 67	4·7 ± 0·6	92 ± 7	52 (28)	NR	26 (14)
RANGER II SFA							
DCB	NR	82.5 ± 48.9	5.1 ± 0.9	73.7 ± 16.9	51 (143)	11 (32)	18 (51)
POBA	NR	79.9 ± 49.3	5.1 ± 0.9	78.2 ± 18.4	67 (66)	10 (10)	30 (29)

Lesion-specific characteristics from the included studies were reported. Values are reported as mean ± SD, median (IQR), or % (n). DCB, drug-coated balloon; NR, not reported; POBA, plain old balloon angioplasty.

1.53, p <0.00001, I^2=23%) (Figure 2). TLR freedom was also significant in both paclitaxel densities, but the effect was more pronounced in studies that utilized greater than or equal to 3.0 ug/mm^2 (RR 1.39, 95% CI 1.29-1.51, p <0.00001, I^2=10%) (Figure 3). There was no difference in all-cause mortality between the two arms, but the rates were high in both arms (DCB 3.8% vs POBA 3.4%, p=0.16) (Figures 4 and 5). Additionally, major/minor limb amputations were similar between DCB and POBA (Figure 6). Primary patency favored DCB, especially in the first year of follow-up (RR 1.43, 95% CI 1.29-1.58, p <0.00001, I^2=54%) (Figure 7). As for clinical outcomes, the improvement in ABI insignificantly favored DCB at after 2 years of follow-up (MD 0.05, 95% CI 0.00 to 0.10, p=0.05, I^2=0%) (Figure 8). Improvement in the Rutherford classification significantly favored DCB at 1 year (RR 1.07, 95% CI 1.00-1.15, p=0.04, I^2=41%), but there was no difference at 2 years (Figure 9). Finally, improvement in WIQ score was similar in both the DCB and POBA arms (RR 0.35, 95% CI -3.66 to 4.36, p=0.86, I^2=0%) (Figure 10).

Table 4: Procedural Characteristics of Included Studies.

Study Name	Procedures (n)	Predilation	Postdilation	Stent implant*	Final diameter stenosis <30%	Residual diameter stenosis (%)	Dissection
AcoArt I							
DCB	100	100%	NR	19%	NR	33 ± 11	NR
POBA	100	85%	NR	21%	NR	35 ± 11	NR
BIOLUX P-1							
DCB	33	67%	NR	7%	77%	25 ± 8	58%
POBA	35	30%	NR	27%	47%	24 ± 1	49%
CONSEQUENT							
DCB	78	53%	NR	14%	100%	NR	NR
POBA	75	59%	NR	19%	100%	NR	NR
DEBATE-SFA							
DCB	55	100%	100%	100%	100%	NR	NR
POBA	55	100%	100%	100%	100%	NR	NR
FemPac							
DCB	45	NR	16%	9%	NR	23 ± 13	NR
POBA	42	NR	10%	14%	NR	27 ± 14	NR
ILLUMENATE EU							
DCB	254	100%	50%	15%	100%	24 ± 11	0-4%
POBA	79	99%	34%	11%	100%	23 ± 10	0%
ILLUMENATE Pivotal							
DCB	200	100%	17%	6%	99%	25 ± 12	0%
POBA	100	100%	16%	6%	98%	27 ± 10	0%

IN.PACT-SFA							
DCB	221	96%	27%	8%	100%	20 ± 10	64%
POBA	113	86%	19%	13%	98%	19 ± 10	61%
ISAR-STATH							
DCB	48	100%	NR	100%	100%	19 ± 10	NR
POBA	52	100%	NR	100%	100%	20 ± 9	NR
LEVANT 1							
DCB	49	100%	NR	27%	100%	NR	18%
POBA	52	100%	NR	38%	98%	NR	10%
LEVANT II							
DCB	322	100%	22%	3%	89%	21 ± 10	63%
POBA	165	100%	20%	7%	86%	21 ± 10	71%
PACIFIER							
DCB	44	14%	NR	21%	100%	NR	47%
POBA	47	6%	NR	34%	100%	NR	74%
RANGER SFA							
DCB	71	NR	NR	21%	92%	30 ± 12	18%
POBA	34	NR	NR	12%	94%	26 ± 15	9%
THUNDER							
DCB	48	NR	NR	4%	100%	NR	NR
POBA	54	NR	NR	22%	98%	NR	NR
RANGER II SFA							
DCB	278	NR	NR	6%	97%	NR	75%
POBA	98	NR	NR	2%	99%	NR	36%

Procedural characteristics of the included studies were reported. Values are reported as mean ± SD, median (IQR), or % (n). * Bailout or systematic stenting (bare-metal stent); DCB, drug-coated balloon; NR, not reported; POBA, plain old balloon angioplasty.

Discussion

This updated meta-analysis comparing DCB versus POBA in de-novo femoropopliteal PAD had a median-weighted follow-up duration of 1.73 years. The analysis demonstrated that TLR freedom significantly favored the DCB arm. A subgroup analysis showed a more pronounced effect at 2-year follow-up, suggesting a possibility of greater benefit with longer follow-up periods. The statistics showed that excluding Jia et al's AcoArt I 2016 trial decreased the level of heterogeneity for the rate of TLR after 2 years. This is possible because they used two different methods in the experimental group: Orchid paclitaxel DCB (Acotec Scientific) or Admiral Xtreme peripheral balloon catheter (Medtronic) [10]. However, 3-year data from an observational study reported similar outcomes between DCB and POBA [29]. The "catch-up phenomenon" of drug-coated devices has been previously described in the literature [30-31]. The longer-term effects of DCBs need further investigation. All-cause mortality and major/minor amputations were similar in both arms. Moreover, primary patency significantly favored DCB. After 2 years of follow-up. improvement in ABI insignificantly favored the DCB arm. Improvement in the Rutherford classification favored DCB and was significant at 1 year, but there was no difference at 2 years. Finally, improvement in WIQ score was similar between both arms.

Recently, there was a new RCT that evaluated DCB versus POBA in the specific patient population of de-novo femoropopliteal PAD. Sachar et al [28] conducted a trial involving 376 patients and illustrated that DCB with paclitaxel density of 2.0 ug/mm^2 had significantly increased effectivity and fewer adverse effects as compared to POBA. This meta-analysis confirms the previously known associations that TLR freedom is significantly higher in the DCB arm and all-cause mortality was similar between both arms. The mean lesion length of the included studies in the DCB for this meta-analysis was 84.1 ± 17.1mm, which indicates that DCB may be beneficial in patients with long lesions and should be considered in this group of patients. Another objective of this meta-analysis was to evaluate if paclitaxel density had a difference in primary outcomes of TLR freedom and all-cause mortality. The analysis showed that both paclitaxel density dosages had similar significance in TLR freedom and all-cause mortality, but were more significant when a higher dose was used. The superiority of DCB's can be attributed to the anti-hyperplastic effects of paclitaxel. The improved primary patency in DCB patients compared to POBA can be attributed to paclitaxel's ability to prevent neo-intimal proliferation, neo-atherosclerosis, and restenosis. The analysis showed that significant long-term TLR freedom is seen with DCB, but Rutherford classification may decrease after the first year of the DCB angioplasty. Therefore, a confounding factor is affecting the clinical improvement in patients with DCB. One possible theory is that the sample size after 2 years of follow-up is not large enough to determine the true significance of the clinical improvement of DCB angioplasty. The WIQ score should also be evaluated in the short- and long-term setting before determining the clinical significance.

The theory of DCB's benefits was that it would decrease the rate of restenosis and all-cause mortality. However, our meta-analysis demonstrates that there was no difference in the all-cause mortality in regards to DCB vs POBA or paclitaxel density dosage. Of note, the trials included in this study did not classify the etiology of the patient's death. We propose classifying the cardiovascular etiologies as stroke vs myocardial infarction vs PAD and then analyzing if DCB vs POBA has an effect on PAD-related mortality.

Furthermore, the RCTs included did specify what or if oral anticoagulation was used after the stent placement. A recently published RCT, named VOYAGER PAD, compared rivaroxaban/aspirin versus placebo/aspirin in patients with lower extremity PAD that were undergoing revascularization. They demonstrated that rivaroxaban/aspirin was associated with a decrease in major adverse limb and cardiovascular events [32]. However, the lesions of the patients included in the VOYAGER PAD trial were not differentiated. This brings up the point of analyzing DCB and Xarelto vs POBA and Xarelto in patients that specifically have femoropopliteal PAD.

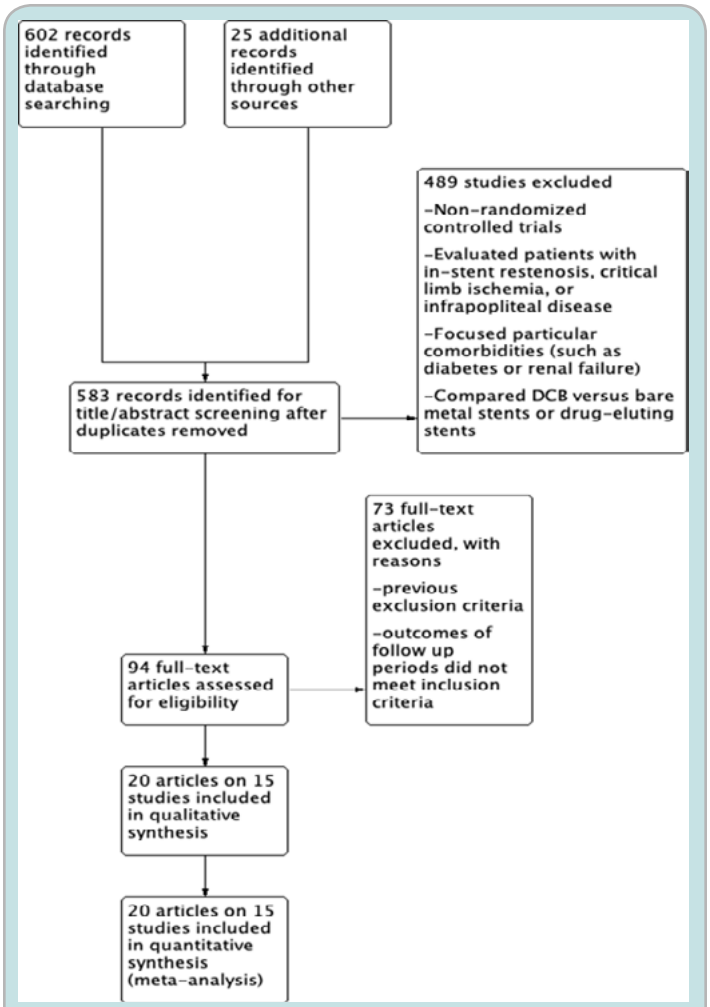

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

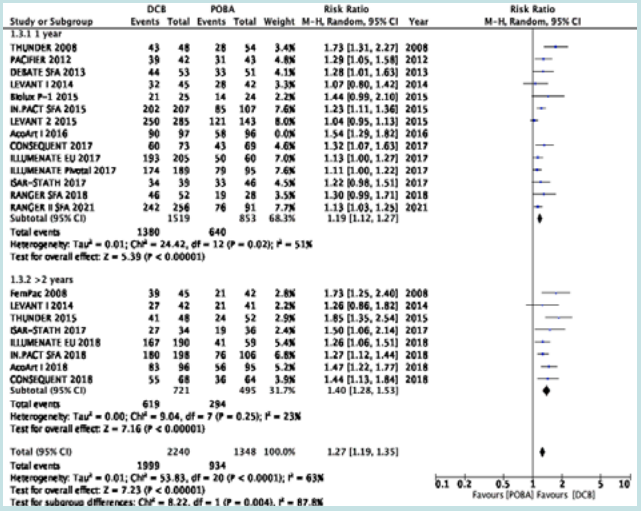

Figure 2: Forest Plot of Target Lesion Revascularization Freedom based on follow-up Duration.

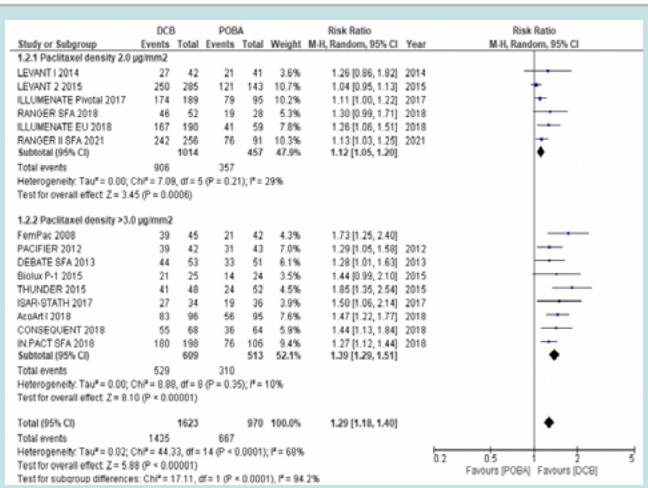

Figure 3: Forest Plot of Target Lesion Revascularization Freedom based on Paclitaxel Density.

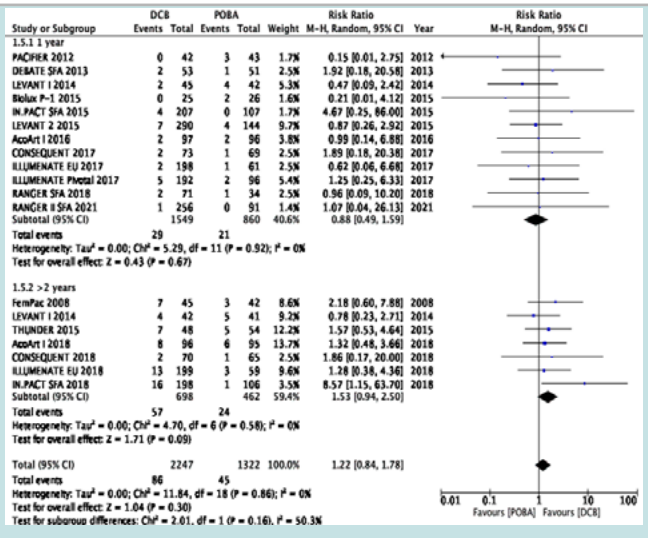

Figure 4: Forest Plot of all-cause Mortality based on follow-up duration.

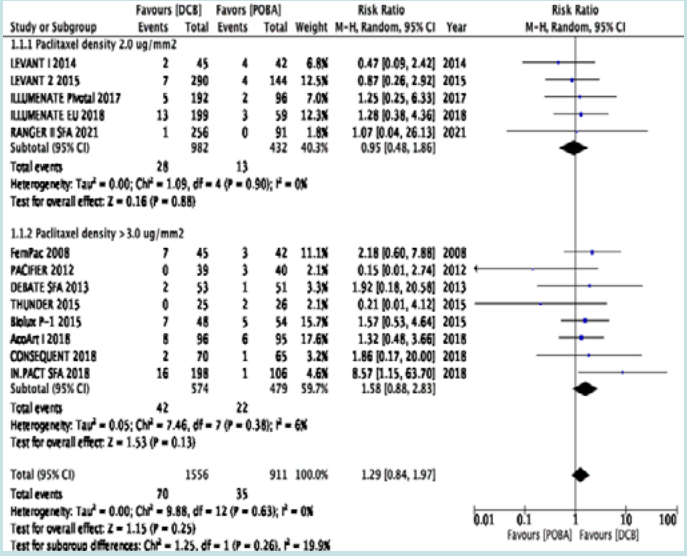

Figure 5: Forest plot of all-cause mortality based on Paclitaxel Density.

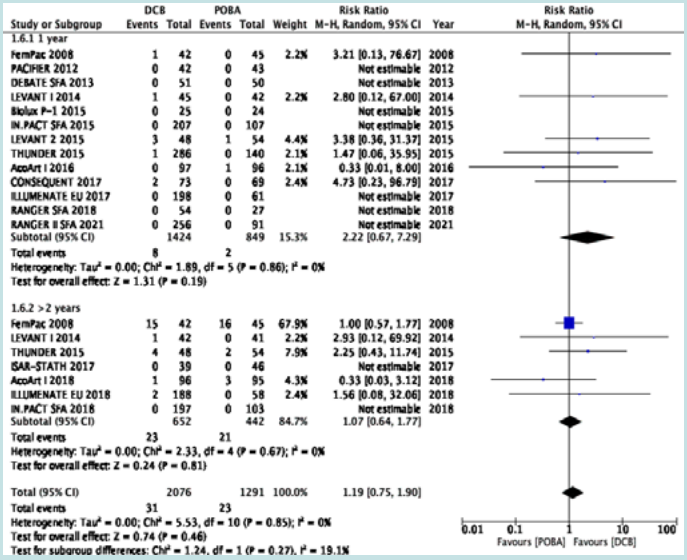

Figure 6: Forest plot of major and/or minor Amputation.

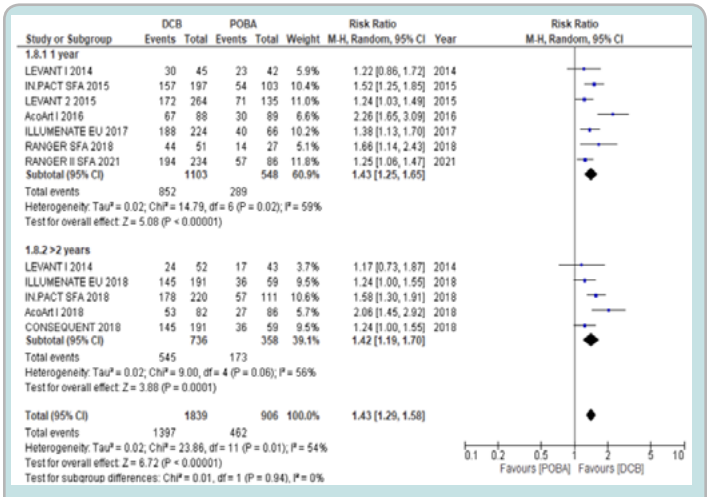

Figure 7: Forest plot of Primary Patency.

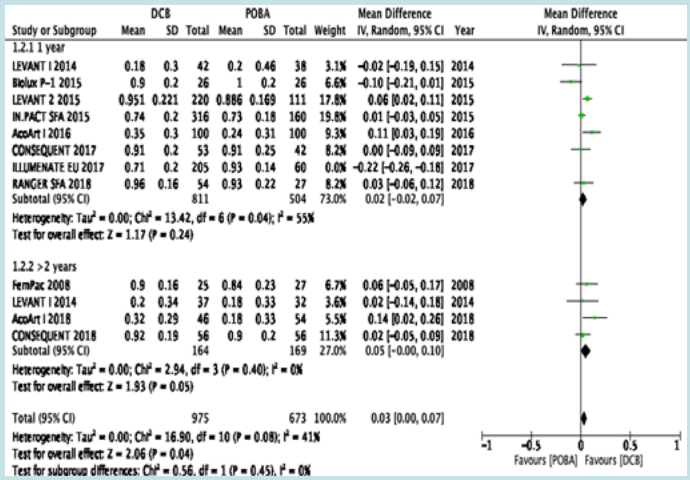

Figure 8: Forest plot of Improvement in Ankle-Brachial Index.

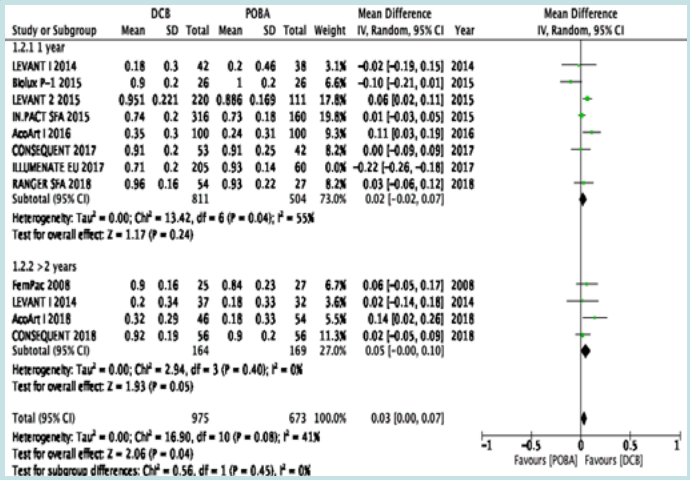

Figure 9: Forest plot of Improvement in Rutherford Classification.

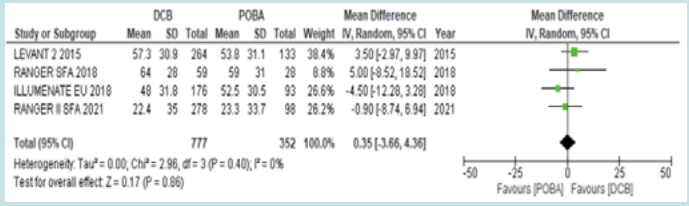

Figure 10: Forest plot of Improvement in Walking Impairment Questionnaire Score.

In addition to the limitations explained above regarding the small sample size, further RCTs should be done with a longer follow-up duration to compare DCB versus POBA. There is a high risk of performance bias as none of the included RCTs were double-blinded. A meta-regression analysis was unable to be performed with the existing data, as the data is at a study level and not at a patient level. Additionally, RCTs designed to compare paclitaxel densities of 2.0, 3.0, and 3.5 ug/mm^2 would help in determining which density has the highest efficacy, clinical, and safety outcomes. Other RCT's should compare DCB in short versus long lesions and DCB vs POBA in patients taking Xarelto after an angioplasty. Another recommendation for further studies is to measure the number of events per patient, instead of the number of patients who have events, in an effort to have enough clinical data that will illustrate a significant difference.

In conclusion, DCB significantly increases TLR freedom in patients with femoropopliteal PAD with a similar safety profile as compared to POBA. A more pronounced effect was seen with higher paclitaxel densities Further RCTs are required to determine the true effect on primary patency, ABI, and clinical improvement. Ideas for future femoropopliteal PAD trials are to directly compare paclitaxel densities and lesion length.

Conflict of interest:

None to disclose.

Author contributions:

Prasad: Conducted literature review and statistical analysis. Wrote the discussion. Edited the final draft.

Mujer: Conducted literature review, confirmed the statistical analysis. Helped in writing the discussion. Edited the final draft.

Baloch: Conducted literature review. Wrote the introduction. Edited the final draft.

Salam: Wrote the abstract and helped with the introduction. Edited the final draft.

Al-abcha: Wrote the methods. Edited the final draft.

Pandrangi: Made the tables and obtained the figures. Edited the final draft.

Rayamajhi: Provided supervision in the writing process. Edited the final draft.

Abela: Provided supervision with the statistical analysis. Edited the final draft.

Ali: Provided supervision with the entire project. Edited the final draft.

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