Drug-eluting balloon angioplasty versus uncoated balloon angioplasty in patients with femoropopliteal arterial occlusive disease

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ABSTRACT

Objective

The optimal percutaneous treatment for femoropopliteal arterial occlusive disease has yet to be assessed. This systematic review and meta-analysis assessed the efficacy of drug-eluting balloons (DEBs) compared with uncoated balloons (UCBs) for the treatment of femoropopliteal arterial occlusive disease.

Methods

We used Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) standards to systematically search the electronic databases of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for trials comparing DEBs versus UCBs in the femoropopliteal arteries. All articles were critically assessed for relevance, validity, and availability of data regarding patient and lesion characteristics and outcomes. All data were systematically pooled, and meta-analysis was performed on binary restenosis, late lumen loss (LLL), target lesion revascularization (TLR), major amputation, mortality, and changes in the ankle-brachial index (ABI) and the Rutherford-Baker classification.

Results

From 364 screened articles we included nine trials, all of which had a low risk of bias. We found a significant reduction of binary restenosis at 6 months (14.3% versus 40.1%, $P < .0001$), binary restenosis at 1 year (26.6% versus 47.4%, $P = 0.008$), LLL at 6 months (–0.80 mm, $P < .00001$), TLR at 1 year (10.4% versus 26.9, $P = .0008$), and TLR at 2 years (13.8% versus 40.7%, $P = .0003$) after DEB angioplasty compared with UCB angioplasty. The difference in amputation rate and mortality was not significant. Definitions on changes in ABI and Rutherford classifications were heterogeneous and therefore could not be pooled in sufficient numbers.

Conclusions

Compared with UCB angioplasty, the use of DEBs increases the durability of the treatment effect in femoropopliteal arterial disease, expressed by a significant decrease of binary restenosis, LLL, and TLR at short-term and midterm follow-up.

BACKGROUND

Percutaneous transluminal angioplasty is an established treatment in many clinical and anatomic settings of peripheral arterial occlusive disease.[1, 2] Venous bypass surgery has been the gold standard treatment of femoropopliteal arterial occlusive disease for many years. However, due to the growth of the frail and aging vascular population and the rapid development of endovascular techniques and improved competence, experienced centers advocate an "endovascular-first" approach.[3, 4] Although the technical success of endovascular revascularization is high, long-term patency remains limited. Restenosis rates of up to 60% have been described after the treatment of femoropopliteal arterial lesions with uncoated balloon (UCB) angioplasty.[5] Randomized controlled trials (RCTs) have demonstrated superior patency of bare-metal stents and drug-eluting stents compared with conventional percutaneous transluminal angioplasty.[6-9] However, the presence of a stent also has limitations despite improved outcomes. Intra-arterial stenting may lead to stent thrombosis and flow pattern disruption, which may result in stent fracture or in-stent restenosis.[10, 11]

Drug-eluting balloons (DEBs) have been developed to provide homogeneous transfer of the antiproliferative drug to the arterial wall without the use of a stent. Multiple trials have tested DEBs against UCBs in femoropopliteal arterial lesions, and the data appear encouraging. A 2012 meta-analysis by Cassese et al of the first four RCTs comparing DEBs versus UCBs[12-15] showed that DEBs possess antirestenotic features compared with UCBs in the femoropopliteal arteries.[16] Several RCTs with larger cohorts and follow-up up to 2 years have been conducted in recent years to assess the efficacy of DEBs in the endovascular treatment of femoropopliteal arterial stenosis and occlusions.

The objective of this meta-analysis was to assess the efficacy of DEBs compared with UCBs for the treatment of femoropopliteal arterial occlusive disease.

METHODS

Search Strategy and Selection Criteria

The electronic databases of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for articles. All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA)[17] were followed to ensure a high-quality review. No formal protocol was published for this review. The actions undertaken for this review are stated in the following section. The search was conducted on December 1, 2015, and only published data were included. There were no restrictions on publication date or publication language.

The search syntax included the keywords "drug-eluting balloon," "coated balloon," "releasing balloon," "femoral," "femoral artery," "femoropopliteal," and "infrainguinal."

Studies were included if they met the following criteria: (1) participants: patients with arterial occlusions or stenoses in the superficial femoral or popliteal artery; (2) intervention: DEBs with or without bare-metal stent placement; uncoated balloons, with or without bare-metal stent placement, must be used in the control group; (3) outcome measures: binary restenosis, late lumen loss (LLL), target lesion revascularization (TLR), amputation, mortality, improvement of ankle-brachial index (ABI), or improvement in Rutherford-Baker classification; (4) types of study: RCTs. Studies were excluded if only restenotic in-stent lesions were evaluated.

Data Collection

Studies were evaluated for inclusion independently by two investigators (H.J. and J.B.) based on title and abstract and finally evaluated independently based on the full text. Any disagreement was resolved by a third investigator (B.F.). Two investigators (H.J. and J.B.) independently extracted data from the eligible studies, and data were entered on a standardized data form.

Assessment of Risk of Bias

The risk of bias of the included studies was scored using The Cochran Collaboration's "Risk of Bias" tool for assessing risk of bias.[18] This tool provides a protocol for judgments on the bias domains sequence generation, allocation methods, blinding, incomplete outcome data, selective outcome reporting, and any other relevant biases. The investigators (H.J. and J.B.) judged the domains to be of high, low, or unclear risk of bias. Any disagreements were resolved by discussion or with the third investigator (B.F.).

Outcome Variables

The outcomes of this meta-analysis were binary restenosis, defined as a reduction of >50% of lesion diameter assessed on angiography or duplex ultrasound imaging with a peak systolic velocity ratio of >2.5; LLL, defined as the difference in minimum lumen diameter at procedure completion and at follow-up; TLR, defined as repeat revascularization of the target lesion; improvement of ABI, calculated as mean improvement with standard deviation (SD); clinical improvement according to the Rutherford-Baker classification, defined as improvement of at least one class[19]; major amputation, defined as amputation above the ankle; and all-cause mortality. Primary patency was not assessed because many different definitions were used.

Meta-analysis and Statistical Methods

Meta-analysis was performed when at least two RCTs existed with similar outcome and similar treatment and control groups. A random effects model, which takes into account the variance between studies and the variance within a study, was used to pool data and calculate the pooled mean for each outcome. The risk ratios (RRs) or mean differences with 95% confidence intervals (CIs) were calculated to evaluate the statistical difference between outcomes after DEB or UCB angioplasty. Statistical heterogeneity was assessed for TLR, binary restenosis, LLL, improvement in Rutherford-Baker classification, improvement in ABI, amputation, and mortality by calculating the Q statistic and the I^2 statistic.

Selective dissemination of evidence was assessed by plotting each outcome measure of each study against precision (1/standard error) in a plot with p-value contours. Funnel plot asymmetry, specifically with an apparent lack of studies in high p-value areas of the plot, can be indicative of publication bias. Furthermore, we examined the individual study effects on the results by removing each study one at a time to determine whether removing a particular study would change the significance of the pooled effect. A two-sided $P < .05$ was considered statistically significant. Analyses were performed with Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Search Results

We screened 364 titles and identified nine RCTs, with a total of 1448 patients, meeting the inclusion criteria.[12, 13, 20-29] The PRISMA flow diagram for systematic reviews is depicted in Figure 1.

One study contained an additional treatment arm of 52 patients allocated to paclitaxel in addition to contrast medium.[12] These patients were excluded from the analysis, resulting in 1396 patients available for analysis. One study reported multilevel disease and included 92 femoropopliteal and 30 below-the-knee (BTK) lesions in 50 patients.[23] Not all outcomes were reported separately for femoropopliteal lesions and BTK lesions, and these outcomes were excluded from analysis. When outcomes were reported separately, only outcomes from femoropopliteal lesions were included.

Study Characteristics

Study characteristics are reported in Table I. Lesion characteristics are reported in Table II. The inclusion and exclusion criteria, as well as the end points of the studies, are summarized in Table III. Patients with >50%[21] or >70%[12, 13, 20, 24, 26-28] stenosis or occlusion in the femoropopliteal artery were randomized to treatment with DEBs or UCBs. All studies but one[23] used the Rutherford-Baker classification. All studies included patients from

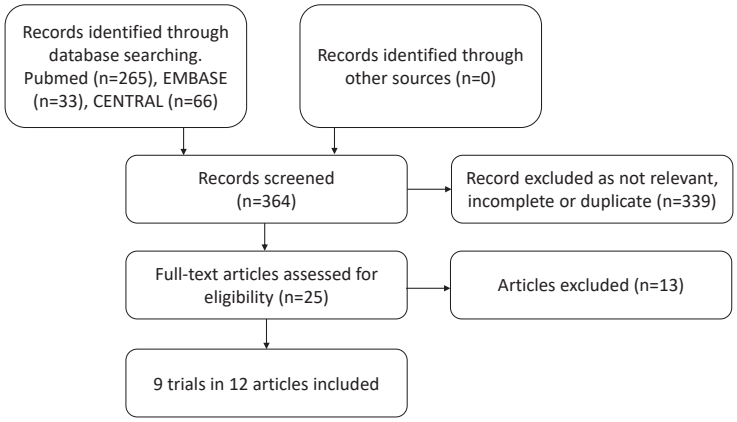

Figure 1. Trial selection process according to the PRISMA statements.[22]

Rutherford-Baker class 2 to 4, five studies also included class 5,[12, 13, 20, 26, 28] and one study included all classes.[21] Two studies only accepted de novo lesions,[21, 23] whereas all other studies also accepted restenotic lesions. Three studies[12, 13, 28] included small portions of in-stent restenotic lesions as well.

All DEBs used in the studies were coated with paclitaxel at a dose on the balloon surface of 2 μg/mm^2,[26, 27] 3 μg/mm^2,[12, 13, 20, 21, 28] or 3.5 μg/mm^2.[23, 24] In four studies the excipient was Urea (FreePac),[21, 23, 24, 28] Polysorbate/sorbitol in two,[26, 27] Iopromide in two,[12, 13] and butyryl-tri-n-hexyl citrate (BTHC) in one.[20] UCBs were used in the control group. In all but two studies, [21, 23] bail out stenting with bare metal stents was indicated after residual stenosis of >30%[12, 26] or >50%,[20, 24, 27, 28] or if flow-limiting dissection occurred. In the DEBATE SFA trial,[21] bare-metal stents were used for primary stenting and were post dilated with DEBs or UCBs. Primary stenting with bare-metal stents was allowed in the DEBELLUM trial.[23] The decision for stent placement was left to the judgment of the operator and was typically driven by lesion length and presence of severe calcification. Bail out stenting due to recoil or flow-limiting dissection after angioplasty was not allowed, and these patients were excluded.

Patients in the LEVANT 1 trial[26] were stratified in a balloon angioplasty–only group and a stent group. Patients who had flow-limiting dissections or clinically significant residual stenosis (>70%) after predilation were considered likely to require stent placement and were placed in the stent group. In the LEVANT 2 trial,[27] these patients who had flow-limiting dissections or clinically significant residual stenosis (>70%) and were likely to require stent placement were excluded from the study. Patients who did not meet these criteria and were included in the study, but eventually did require bail out stenting, were not excluded from the study.

In all included studies, patients received dual-antiplatelet therapy with aspirin indefinitely and clopidogrel postoperatively for at least 4 weeks (Table II).

Table I. Study characteristics

Study	Year of patient inclusion	Patients (DEB/UCB)	Lesions (DEB/UCB)	Mean age DEB/UCB	Diabetes mellitus DEB/UCB	Critical limb ischemia DEB/UCB,	DEB	Pacitaxel dose	Excipient
		(n)	(n)	(year)	(%)	(%)		(μg/mm^2)	
BIOLUX P1[20]	2010-2011	60 (30/30)	68 (33/35)	70.1/71.4	36/30	20/13	Passeo-18 Lux	3	BTHC
DEBATE SFA[21]	2010-2011	104 (53/51)	110 (55/55)	74/76	41/36	80/69	IN.PACT Admiral	3	Urea (FreePac)
DEBELLUM[22]	2010-2011	50 (25/25)	92 (44/48)	66/67	52/36	36/40	IN.PACT Admiral	3.5	Urea (FreePac)
FemPac[13]	2004-2006	87 (45/42)	Not reported	67.3/70.2	40/55	4.0/7.0	Paccocath	3	Iopromide (iodinated contrast)
IN.PACT SFA[24]	2010-2013	331 (220/111)	334 (221/113)	67.5/68	41/49	5.0/6.3	IN.PACT Admiral	3.5	Urea (FreePac)
LEVANT 1[26]	2009	101 (49/52)	101 (49/52)	67/70	45/50	6.0/8.0	Lutonix DCB (Moxy)	2	Polysorbate/sorbitol
LEVANT 2[27]	2011-2012	476 (316/160)	487 (322/165)	67.8/69	43/42	7.9/8.1	Lutonix DCB (Moxy)	2	Polysorbate/sorbitol
PACIFIER[28]	Not specified	85 (41/44)	117 (62/55)	71/71	43/28	4.5/4.3	IN.PACT Pacific	3	Urea (FreePac)
THUNDER[13]	2004-2005	102 (48/54)	Not reported	69/68	50/46	15/11	Paccocath	3	Iopromide (iodinated contrast)

BTHC = butyryl-tri-*n*-hexyl citrate; DEB: Drug-eluting balloon; UCB: Uncoated balloon

Table II. Lesion characteristics

Study	Mean lesion length DEB/UCB	Chronic total occlusion, DEB/UCB	Lesion location in SFA, DEB/UCB	Calcified lesions[b], DEB/UCB	Severely calcified lesions, DEB/UCB	Restenotic lesion	In-stent restenosis	Provisional stenting DEB/UCB
	(cm)	(%) of	(%)	(%)	(%)	(%)	(%)	(%)
BIOLUX P1[20]	5.1/6.9	Ns	85/77	Ns	Ns	58	0	6.6/27
DEBATE SFA[21]	9.4/9.6	55/69	75/82	40/35	22/20	0	0	Primary stenting
DEBELLUM[22a]	7.6/7.8	8.7/14	74/71	1: 19.3/12.3, 2: 35.1/44.6, 3: 21.1/30.7, 4: 24.512.3[c]	Ns	0	0	Primary stenting
FemPac[13]	4.0/4.7	13/19	87/81	53/52	Ns	34	7.0	8.8/14
IN.PACT SFA[24]	8.9/8.8	26/20	93/93	Ns	8.1/6.2	5	0	7.2/13
LEVANT 1[26]	8.1/8.0	41/42	92/94	Ns	Ns	11	0	27/24
LEVANT 2[27]	6.3/6.3	21/22	90/93	59/58	11/8.1	15	0	2.5/6.9
PACIFIER[28]	7.0/6.6	23/38	Ns	64/66	Ns	24	14.2	21/34
THUNDER[13]	7.5/7.4	27/26	69/65	50/52	Ns	33	13.7	4.1/22

[a] only femoral lesions; [b] Calcified lesions and severely calcified lesions combined; [c] Calcification was estimated from axial CTA images and/or intravascular ultrasound and stratified to grade 1 (<45°), grade 2 (<90°), grade 3 (<135°), or grade 4 (circumferential);
DEB = Drug-eluting balloon; Ns = Not specified; SFA = Superficial femoral artery; UCB = Uncoated balloon

Risk of Bias

The risk of bias is summarized in Figure 2. All trials randomly assigned patients to the DEB or UCB group. The DEBATE SFA and THUNDER trials did not describe the allocation concealment.[12, 21] In the FemPac trial, portions of the random list were assigned to centers that enrolled patients in the sequence of the randomization list and therefore at risk of selection bias.[13] Blinding the operators for intervention was not possible in any of the trials because of the visual differences between DEBs and UCBs. This resulted in high risk of performance bias in all of the trials. Poststudy evaluations in the THUNDER trial were performed by investigators who could recognize DEBs from UCBs rather than by blinded core angiography laboratories, as used in all other studies, resulting in risk of detection bias.[12] The risk of attrition bias was low in all trials. Trial protocols of the DEBELLUM and FemPac trials[13, 23] were not registered at clinicaltrials.gov, resulting in high risk of reporting bias. In general, all of the studies were considered of high quality, with a low risk of bias.

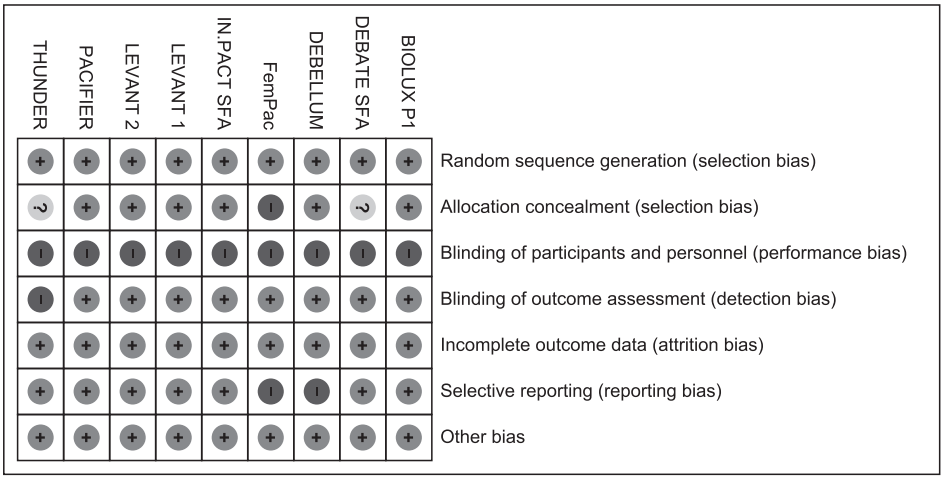

Figure 2. Evaluation of risk of bias

Binary Restenosis

Four studies reported binary restenosis outcomes at 6 months.[12, 13, 20, 28] Data from these 275 patients (19.6%) were pooled. A significant reduction of binary restenosis was found in DEBs versus UCBs (14.3% versus 40.1%; Risk Ratio by Mantel-Haenszel [RR_{M-H}], 0.37; 95% CI, 0.23-0.58; P < .0001, Figure 3A). Three trials [21, 24, 27] (801 patients) published results at 12 months, also reporting a significant reduction in favor of DEBs versus UCBs (26.6% versus 47.4%; Risk Ratio by Mantel-Haenszel [RR_{M-H}], 0.48; 95% CI, 0.28 -0.82; P = .008, Figure 3B).

Table III. Summary of inclusion and exclusion criteria and endpoints of trials

Trial	BIOLUX P1	DEBATE SFA	DEBELLUM	FemPac
Inclusion criteria	Rutherford 2 to 5. Single or sequential de novo or restenotic lesions (>70% diameter reduction) between 30 and 200 mm long in the femoropopliteal segment, diameter 3–7 mm. Inflow free from flow limiting dissection. At least 1 nonoccluded runoff vessel.	All Rutherford classifications, >18 years, de novo stenosis >50% or occlusion of at least 40 mm in length located in the SFA of popliteal artery. Clear healty segment between lesion and CFA and between popliteal and tibioperoneal trunk. At least 1 tibial vessel with distal runoff.	Fontaine stage IIB, III and IV. SFA, popliteal, and BTK lesions isolated or concomitant. De novo lesions. Stenosis or occlusions 3–30 cm.	Age 18–90 years; Rutherford 1–5; occlusion or stenosis ≥70% of vessel diameter; successful guidewire passage.
Exclusion criteria	Thrombus in the target vessel, severe calcification per site assessment, prior bypass surgery of the target vessel, prior stent placement in the target lesion, planned amputation of the target limb, and additional hemodynamically relevant distal lesions with stenosis >50%.	Life expactancy <1 year, contraindication for combined antiplatelet therapy, known allergy to nickel or paclitaxel, and the need for major aputation at the time of enrollment. Failure to recanalize intended BTK arteries and CLI patients at risk of major amputation.	In-stent restenosis, acute thrombus of the index limb, aneurysm in the index vessel, pregnancy, life expectancy <1 year, provisionally stented lesions due to persistent >50% residual stenosis or flow-limiting dissection.	Acute symptom onset, leg-threatening ischemia, distal outflow <1 vessel, manifest hyperthyreodism, renal insufficiency, major gastrointestinal bleeding in last 6 months, life expectancy <2 years.
Primary end point	6-month LLL.	12-month binary restenosis.	6-month LLL.	6-month LLL.
Secondary end points	Binary restenosis at 6 months, clinically driven TLR, changes in ABI and Rutherford, and major adverse events at 6 and 12 months.	12-month freedom from cd-TLR, amputation, LLL.	TLR, restenosis rate, thrombosis and amputation at 6, 12, and 24 months.	6-month restenosis rate, TLR, Rutherford stage change, ABI, amputation, thrombotic complications, clinical adverse events.
Postprocedure antiplatelet therapy	Aspirin (100 to 325 mg/d indefinitely); clopidogrel loading dose (75 or 300 mg) with maintenance for 1 month in balloon-only subjects and 3 months in stented subjects.	Aspirin (100 mg/d) indefinitely; clopidogrel (75 mg/d) 1 month after UCB + BMS, 3 months after DEB + BMS.	Aspirin 100 mg/d indefinitely; clopidogrel 75 mg/d for 4 weeks.	Aspirin (100 mg/d) indefinitely; clopidogrel (75 mg/d) indefinitely.
Longest follow-up, months	12	12	12	24

ABI = Ankle-brachial index; BMS = Bare-metal stent; cd-TLR = (Clinically driven) target lesion revascularization; CFA = Common femoral artery; CLI = Critical limb ischemia; DEB = Drug-eluting balloon;

	IN.PACT SFA	LEVANT 1	LEVANT 2	PACIFIER	THUNDER
	Rutherford 2–4, stenosis >70%, 4–18 cm or occlusion <10 cm in SFA or proximal PA.	Rutherford 2–5. Single de novo or (non-in-stent) restenotic lesions (operator-determined >70% stenosis; length between 4 and 15 cm; reference vessel diameter between 4 and 6 mm).	Age >18 years. Rutherford 2–4 and angiographic occlusions or significant stenosis of >70% in the SFA or popliteal artery. Lesions < 15 cm, de novo or nonstented restenotic.	Rutherford 2–5. Occlusion or stenosis (>70%) in the SFA or popliteal artery. Lesion length 3-30 cm. No contraindication to dual- antiplatelet therapy.	Age 18–95 years; Rutherford 1–5; ≥1 lesion (de novo or restenosis); ≥70% of vessel diameter; ≥2 cm in length in SFA or PA.
	Unwilling or unlikely to comply with follow-up schedule, stroke or STEMI ≤3 months before enrollment, acute or subacute thrombus in the target vessel.	Life expectancy <2 years, creatinine >2.5 mg/dL or history of hemorrhagic stroke <3 months, previous or planned intervention <30 days, severe lesion calcification, sudden symptom onset, acute or subacute target vessel thrombus or occlusion, absence of 1 patent untreated runoff vessel, or significant inflow disease.	Life expectancy <5 years, significant inflow disease, known inadequate distal outflow; sudden symptom onset, acute vessel occlusion, or acute or subacute thrombus in target vessel. If stent placement was required after predilatation, patients were excluded.	Acute thrombus or aneuysm in target vessel, failure to cross with guidewire, inflow lesions that cannot be successfully pretreated, dignificant disease of all 3 infrapopliteal vessels, renal failure, known intolerance or allergy to study medications, life expectancy <2 years.	Poor inflow, absence of a patent crural artery, acute onset of symptoms, pregnancy, life expectancy <1 year, and contraindications to required medication.
	12-month primary patency.	6-month LLL.	12-month primary patency.	6-month LLL.	6-month LLL.
	30-day device and procedure-related death, all cause death, major target limb amputation, target vessel thrombosis. Acute procedurall success, TLR, primary sustained clinical improvemen.	Clinical follow-up at 1, 2, 6, 12, and 24 months; primary patency, TLR, binary restenosis, major adverse events, Rutherford classification, ABI.	Procedural succes, changes is Rutherford-Baker, TLR, TVR, feath, major amputation, teintervention for trombosis.	Binary restenosis, change in Rutherford, cd-TLR, major adverse events.	Technical success; 6-month angiographic restenosis rate, Rutherford stage change, ABI, patency rate, TLR incidence.
	Aspirin (81–325 mg/d) for a minimum of 6 months; clopidogrel (75 mg/d) for 1 month for nonstented and 3 months for stented.	Aspirin (100–325 mg/d) indefinitely; clopidogrel loading dose (75 or 300 mg) with maintenance for 1 month in balloon-only subjects and 3 months in stented subjects.	Aspirin (75–100 mg/d) indefinitely; clopidogrel (75 mg/d) or prasugrel (5–10 mg/d) for at least 1 month.	All patients were pretreated with aspirin and thienopyridines, which were continued for >2 months after PTA.	Aspirin (100 mg/d) indefinitely; clopidogrel (75 mg/d) for 1 month.
	24	24	12	24	60

LLL = Late lumen loss; PTA = Percutaneous transluminal angioplasty; STEMI = ST-elevated myocardial infarction; TVR = Target vessel revascularization; UCB = Uncoated balloon

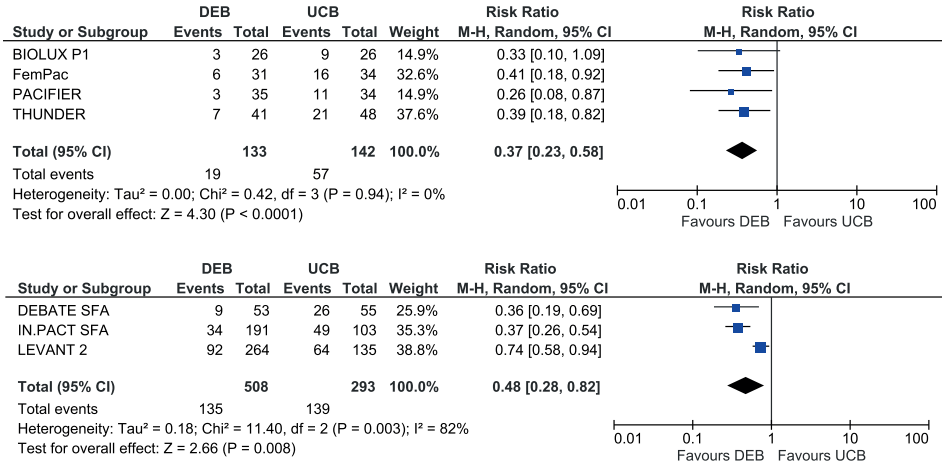

Figure 3. Binary restenosis (A) after 6 months and (B) after 1 year. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *diamond* indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI. The *solid vertical line* indicates no effect. M-H: Mantel-Haenszel; DEB: Drug-eluting balloon; UCB: Uncoated balloon.

Late Lumen Loss

LLL data after 6 months were available in seven trials.[12, 13, 20, 21, 23, 26, 28] Data from the DEBATE SFA trial could not be pooled because no SDs were available. In 433 patients (31.0%), DEBs showed a significant superiority against UCBs (range, –0.05 to 0.51 mm versus 0.61 to 1.55 mm; weighted mean difference, –0.80; –1.07 to –0.53; P < .00001, Figure 4). Two trials[12, 23] reported LLL data after 1 year in 161 patients (11.5%). Again, DEBs showed significant superiority against UCBs (range, –0.61 to 0.7 mm versus 1.84 to 1.9 mm; weighted mean difference, –1.23; range, –1.37 to –1.09; P < .00001).

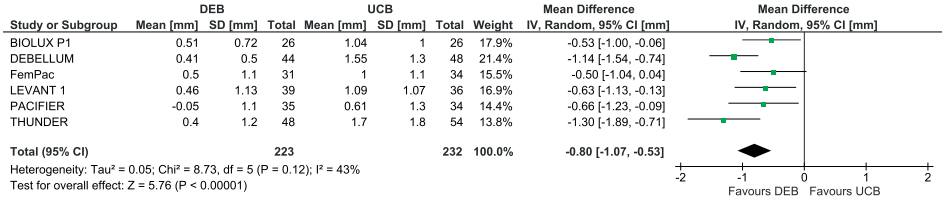

Figure 4. Late lumen loss after 6 months. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *diamond* indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI. The *solid vertical line* indicates no effect. IV: inverse variance.

Target Lesion Revascularization

Eight trials reported TLR data.[12, 13, 20, 21, 24, 26-28] Five studies reported clinically driven TLR; in three trials, this was not explicitly stated.[12, 13, 26] Data on TLR could be pooled in 1170 patients (83.8%) after 1 year and in 576 patients (41.3%) after 2 years. A significant reduction in TLR was found in DEBs versus UCBs after 1 year (10.4% versus 26.9%; $RR_{[M-H]}$, 0.39; 95% CI, 0.23–0.67; P = .0007, Figure 5A). A significant reduction was also found after 2 years in favor of DEBs (13.8% versus 40.7%; $RR_{[M-H]}$, 0.38; 95% CI, 0.23–0.64; P = .0003, Figure 5B). The THUNDER trial reported a significant reduction in TLR in DEBs versus UCBs after 5 years (21% versus 56%, P = .0005)

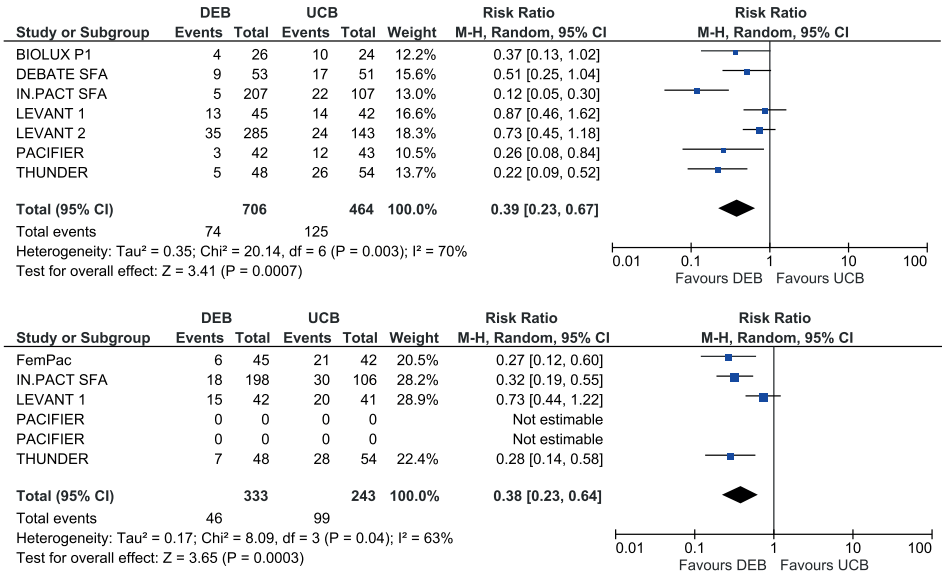

Figure 5. Target lesion revascularization (A) after 1 year and (B) after 2 years. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *diamond* indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI. The *solid vertical line* indicates no effect. M-H: Mantel-Haenszel; DEB: Drug-eluting balloon; UCB: Uncoated balloon.

Major Amputation

Major amputation data were available in eight trials.[12, 13, 20, 21, 24, 26-28] Meta-analysis was performed on 1253 patients (89.8%). The difference in the major amputation rate between DEBs and UCBs after 1 year was not significant (0.7% versus 0.2%; $RR_{[M-H]}$, 1.89; 95% CI, 0.40–8.99; P = .42, Figure 6).

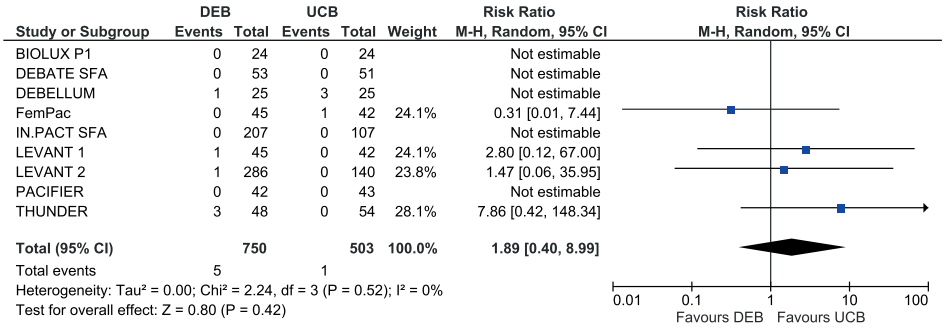

Figure 6. Major amputation after 12 months. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *diamond* indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI. The *solid vertical line* indicates no effect. M-H: Mantel-Haenszel; DEB: Drug-eluting balloon; UCB: Uncoated balloon.

Mortality Rate

Data on mortality rates were available in seven trials.[13, 20, 21, 24, 26-28] Meta-analysis was performed on 1168 patients (83.7%). The difference in mortality between DEBs and UCBs after 1 year was not significant (2.2% versus 2.5%; $RR_{[M-H]}$, 0.89; 95% CI, 0.40–1.97; P = .77, Figure 7).

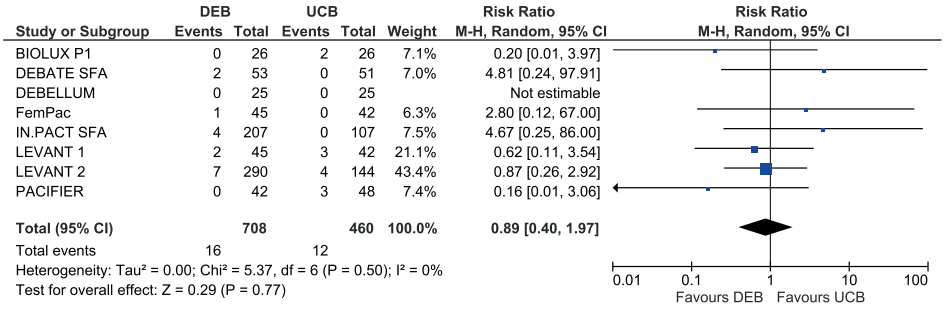

Figure 7. Mortality after 12 months. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *diamond* indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI. The *solid vertical line* indicates no effect. M-H: Mantel-Haenszel; DEB: Drug-eluting balloon; UCB: Uncoated balloon.

Changes in ABI

Seven trials[12, 13, 20, 24, 26, 27] reported changes in ABI. Two trials reported ABI at baseline and after 6 and 24 months but did not report mean changes.[20, 24] Both trials reported improvement in the DEB and UCB groups. The FemPac trial[13] reported mean improvement on ABI; however, the SD was not reported and therefore could not be included in the

meta-analysis. No significant difference was reported in ABI after DEB compared with UCB. Data from the THUNDER trial[12] could not be used because mean changes in ABI were not measured from baseline but rather at 6 hours after the procedure compared with 6 months. Data from two trials[26, 27] were pooled for 556 patients (39.8%) because these reported absolute numeric changes in ABI. No significant difference was found between DEBs and UCBs (range, 0.17–0.18 versus 0.18–0.20; weighted mean difference, –0.01; range, –0.05 to 0.03; p = 0.64). There was low heterogeneity across the trials (I^2=0%, P = .92 for heterogeneity).

Changes in Rutherford-Baker Classification

Six trials reported changes in the Rutherford-Baker classification.[12, 13, 20, 26-28] One trial reported changes in the Fontaine classification.[23] The BIOLUX P1, FemPac, and PACIFIER trials[13, 20, 28] reported percentages of improvement of at least one Rutherford-Baker class preoperatively and after 6 months. When pooled (n = 238), improvement of at least one class was found in 68.8% of patients treated with DEBs versus 54.8% of patients treated with UCBs (P = .02). There was low heterogeneity across trials (I^2=0%, P = .82 for heterogeneity). In the THUNDER trial,[12] mean changes in Rutherford-Baker classification between 72 hours postoperatively and 6 months follow up were reported. The difference between DEBs and UCBs was not significant (0.1±1.7 versus 0.3±1.8, P = .48). The LEVANT 1 and 2 trials[26, 27] reported mean changes in Rutherford-Baker classification preoperatively and after 12 months. Data were pooled (n = 559), and no significant difference was found between DEBs and UCBs (range, –1.9 to –1.6 versus –2.1 versus –1.7; weighted mean difference, –0.11; range, –0.31 to 0.08; P = .25). Heterogeneity across trials was high (I^2=81%, P = .02 for heterogeneity).

DISCUSSION

In the current analysis, our review of all RCTs comparing DEBs versus UCBs in femoropopliteal arteries showed a significant reduction of binary restenosis after 6 and 1 year and reduced LLL after 6 months. The evidence for a reduction in the development of restenosis after treatment with DEBs in the femoropopliteal artery seems convincing.

However, the clinical end points are even more important in daily practice. We have shown a significant reduction in TLR after 1 and 2 years. TLR is mostly a clinically driven end point, although this was not defined as such in all studies. Some trials defined primary patency as a combined end point of freedom from binary restenosis and freedom from clinically driven TLR. However, there are many definitions of primary patency, and we therefore decided not to analyze this outcome in this meta-analysis.

Similar amputation and mortality rates may indicate the DEB is safe—or at least similar in safety—compared with the UCB. Morbidity and mortality rates were both low in both groups, which seems obvious because most patients were treated for intermittent claudication. The presence of patients with CLI did not exceed more than 20% in most trials.

In this review we opted to include clinical endpoint such as pain-free walking distance, ankle-brachial index and changes in Rutherford-Baker classification. Data on changes in ABI and changes in Rutherford-Baker classification were available in most trials. However, definitions were often heterogeneous and could not be pooled in large numbers. We did not find convincing evidence of significant differences between outcomes in these two parameters.

Evaluation of pain free walking distance after endovascular treatment of femoropopliteal arterial disease in RCTs is challenging. A proper comparison of pain free walking distance between 2 groups can only be done if patients are denied a secondary intervention. If patients develop a symptomatic re-stenosis, a secondary intervention will be performed. This secondary intervention strongly influences the pain free walking distance at any point in time.

High risk of performance bias was found in all trials because DEBs and UCBs have different appearances and cannot be blinded to the operator. Almost every trial used blinded core angiography laboratories to perform postoperative assessments, resulting in low risk of detection bias. In general, all of the studies were considered of high quality with a low risk of bias.

The duration of follow-up was relatively short. The follow-up was 12 months in four trials and 24 months in four other trials. Long-term data up to 5 years were only available in the THUNDER trial.[12] Unfortunately, 39.2% of patients in the THUNDER trial had died or were lost to follow-up at 5 years. Although the numbers were small, a significant TLR reduction at the 5-year follow-up after DEB angioplasty was observed.

The DEBATE SFA and DEBELLUM trial[21, 23] implemented primary stenting. All other trials allowed stenting in case of residual stenosis or flow-limiting dissection persisting after prolonged balloon dilatation (bail out or provisional stenting). Data from the DEBELLUM trial could often not be used in the meta-analysis because separating the femoropopliteal lesions from the BTK lesions in this multilevel study was not always possible. Data from the DEBATE SFA trial were consistent with the other trials and did not change the significance of the pooled effect when removed from the meta-analysis. By excluding patients who were likely to receive stent placement before randomization, there was a very low rate of stent placement in the LEVANT 2 trial. The role of primary stenting in the femoropopliteal arteries is still unclear. Primary stenting leads to high patency rates, in particular in complex and long lesions; however, its limitations, such as stent fracture, stent thrombosis, or in-stent restenosis,[10, 11] may advocate techniques where nothing is left behind.

Several differences in inclusion strategy existed across the trials. Two trials only included de novo lesions,[21, 23] whereas other trials accepted restenotic lesions. The percentage of restenotic lesions was highest in the BIOLUX P1 trial (58%). Three trials included small portions of in-stent restenosis.[12, 13, 28] Morphologic characteristics of in-stent stenosis are different from de novo lesions;[30] therefore, analysis of treatment outcomes of both entities should be separated.[31, 32]

Although some studies accepted lesion lengths of up to 20 cm[20] and 30 cm,[23, 28] the mean lesion length in all studies was less than 10 cm (Table II). The longest mean lesion length was found in the DEBATE SFA trial, and the shortest mean lesion length was found in the FemPac trial.[13] Data from single-arm series considering the treatment of long SFA lesion with DEB are encouraging.[33, 34]

All included trials used a balloon covered with Paclitaxel. Paclitaxel is a broad-spectrum anti-mitotic agent that inhibits cell division in the G2/M phase. This inhibits cell replication of the smooth muscle cells, and reduces neo-intimal hyperplasia.[35] Paclitaxel has several chemical properties, which makes it ideal for local drug delivery including its hydrophobicity, ability to concentrate into the arterial intima layer and prolonged effect on cells even after brief exposure periods.[36] Dosages differed between balloons, ranging from 2 µg/mm^2 to 3.5 µg/mm^2. The Lutonix DEB from Bard, coated with 2 µg/mm^2 (LEVANT 1 and 2 trial), performs significantly better than the UCB angioplasty, however the difference is less striking compared with other balloons. In contrast with the pooled data, TLR in the LEVANT 2 trial was for example not significantly different. This result may be due to the lower Paclitaxel dosage. However, the excipient, varying per device, may be as important to the biologic efficacy of the therapy.[36] Animal studies have demonstrated significant differences between Paclitaxel coated balloons with similar Paclitaxel dosages, but different excipients with regard to the loss of Paclitaxel during passage through blood, uptake of Paclitaxel in the arterial wall and all parameters indicating neointimal proliferation.[37, 38] In a clinical coronary study, major differences in effective tissue doses and angiographic outcomes were demonstrated between different DEB devices despite equivalent loading doses.[39] Furthermore, higher inflation pressure and longer inflation time may change the availability of Paclitaxel in the vessel wall, in particular in atherosclerotic lesions.[32, 40]

Multiple balloon characteristics (eg. Paclitaxel dose, excipient, inflation time and pressure), as well as lesion characteristics (length, calcium and restenosis or in-stent restenosis) will ultimately determine the efficacy of each particular DEB in the femoropopliteal arteries. All DEBs are different and the specific effect of a DEB should always be verified in a RCT examining the DEB.

CONCLUSIONS

Compared with UCB angioplasty, the use of DEBs increases the durability of the treatment effect in femoropopliteal arterial disease, expressed by a significant decrease of binary restenosis, LLL, and TLR at short-term and midterm follow-up.

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