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Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs (Review)

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[Intervention Review]

Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs

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ABSTRACT

Background

Atherosclerotic peripheral arterial disease (PAD) can lead to disabling ischemia and limb loss. Treatment modalities have included risk factor optimization through life-style modifications and medications, or operative approaches using both open and minimally invasive techniques, such as balloon angioplasty. Drug-eluting balloon (DEB) angioplasty has emerged as a promising alternative to uncoated balloon angioplasty for the treatment of this difficult disease process. By ballooning and coating the inside of atherosclerotic vessels with cytotoxic agents, such as paclitaxel, cellular mechanisms responsible for atherosclerosis and neointimal hyperplasia are inhibited and its devastating complications are prevented or postponed. DEBs are considerably more expensive than uncoated balloons, and their efficacy in improving patient outcomes is unclear.

Objectives

To assess the efficacy of drug-eluting balloons (DEBs) compared with uncoated, nonstenting balloon angioplasty in people with symptomatic lower-limb peripheral arterial disease (PAD).

Search methods

The Cochrane Vascular Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched December 2015) and Cochrane Register of Studies (CRS) (2015, Issue 11). The TSC searched trial databases for details of ongoing and unpublished studies.

Selection criteria

We included all randomized controlled trials that compared DEBs with uncoated, nonstenting balloon angioplasty for intermittent claudication (IC) or critical limb ischemia (CLI).

Data collection and analysis

Two review authors (AK, TA) independently selected the appropriate trials and performed data extraction, assessment of trial quality, and data analysis. The senior review author (DKR) adjudicated any disagreements.

Main results

Eleven trials that randomized 1838 participants met the study inclusion criteria. Seven of the trials included femoropopliteal arterial lesions, three included tibial arterial lesions, and one included both. The trials were carried out in Europe and in the USA and all used the taxane drug paclitaxel in the DEB arm. Nine of the 11 trials were industry-sponsored. Four companies manufactured the DEB devices

(Bard, Bavaria Medizin, Biotronik, and Medtronic). The trials examined both anatomic and clinical endpoints. There was heterogeneity in the frequency of stent deployment and the type and duration of antiplatelet therapy between trials. Using GRADE assessment criteria, the quality of the evidence presented was moderate for the outcomes of target lesion revascularization and change in Rutherford category, and high for amputation, primary vessel patency, binary restenosis, death, and change in ankle-brachial index (ABI). Most participants were followed up for 12 months, but one trial reported outcomes at five years.

There were better outcomes for DEBs for up to two years in primary vessel patency (odds ratio (OR) 1.47, 95% confidence interval (CI) 0.22 to 9.57 at six months; OR 1.92, 95% CI 1.45 to 2.56 at 12 months; OR 3.51, 95% CI 2.26 to 5.46 at two years) and at six months and two years for late lumen loss (mean difference (MD) -0.64 mm, 95% CI -1.00 to -0.28 at six months; MD -0.80 mm, 95% CI -1.44 to -0.16 at two years). DEB were also superior to uncoated balloon angioplasty for up to five years in target lesion revascularization (OR 0.28, 95% CI 0.17 to 0.47 at six months; OR 0.40, 95% CI 0.31 to 0.51 at 12 months; OR 0.28, 95% CI 0.18 to 0.44 at two years; OR 0.21, 95% CI 0.09 to 0.51 at five years) and binary restenosis rate (OR 0.44, 95% CI 0.29 to 0.67 at six months; OR 0.38, 95% CI 0.15 to 0.98 at 12 months; OR 0.26, 95% CI 0.10 to 0.66 at two years; OR 0.12, 95% CI 0.05 to 0.30 at five years). There was no significant difference between DEB and uncoated angioplasty in amputation, death, change in ABI, change in Rutherford category and quality of life (QoL) scores, or functional walking ability, although none of the trials were powered to detect a significant difference in these clinical endpoints. We carried out two subgroup analyses to examine outcomes in femoropopliteal and tibial interventions as well as in people with CLI (4 or greater Rutherford class), and showed no advantage for DEBs in tibial vessels at six and 12 months compared with uncoated balloon angioplasty. There was also no advantage for DEBs in CLI compared with uncoated balloon angioplasty at 12 months.

Authors' conclusions

Based on a meta-analysis of 11 trials with 1838 participants, there is evidence of an advantage for DEBs compared with uncoated balloon angioplasty in several anatomic endpoints such as primary vessel patency (high-quality evidence), binary restenosis rate (moderate-quality evidence), and target lesion revascularization (low-quality evidence) for up to 12 months. Conversely, there is no evidence of an advantage for DEBs in clinical endpoints such as amputation, death, or change in ABI, or change in Rutherford category during 12 months' follow-up. Well-designed randomized trials with long-term follow-up are needed to compare DEBs with uncoated balloon angioplasties adequately for both anatomic and clinical study endpoints before the widespread use of this expensive technology can be justified.

PLAIN LANGUAGE SUMMARY

Uncoated balloon angioplasty versus drug-eluting balloon angioplasty for peripheral arterial disease of the lower limbs

Background

Peripheral arterial disease (PAD) of the lower limbs is a widespread condition that affects many people. In its advanced form, PAD can lead to pain, infections, and amputation. People with PAD are usually first treated with medicines and lifestyle modifications including strategies to stop smoking and a walking program to optimize their general health. People who require an operation might have a traditional open surgery or a less invasive procedure known as angioplasty, which uses a balloon to open the blockages in the arteries. A new type of angioplasty, known as drug-eluting balloon (DEB) angioplasty, has emerged as a promising alternative to traditional balloon angioplasty for the treatment of patients with PAD. By using DEBs to balloon and coat the inside of the blood vessels (tubes that carry blood around the body) with medicines to treat cancer (chemotherapy) such as paclitaxel, the hope is to halt the progression of PAD and prevent or postpone its devastating complications. The goal of this review was to determine how DEB angioplasty compares with traditional balloon angioplasty for the treatment of PAD of the lower limbs.

Study characteristics and key results

Our review included 11 clinical trials that randomized 1838 participants (current until December 2015). The trials included thigh and leg arteries above and below the knee. The trials were carried out in Europe and the USA, and all used DEBs that contained paclitaxel. Four companies manufactured the DEB devices: Bard, Bavaria Medizin, Biotronik, and Medtronic. Most participants were followed for 12 or more months (called follow-up). At six and 12 months of follow-up, DEBs were associated with improved primary vessel patency, which is an indicator of whether a vessel is still patent without any further interventions (blood flowing well), late lumen loss, which is the difference in millimeters between the angioplastied segment and how narrow it is on follow-up, target lesion revascularization, which is an indicator of whether a person received more than one treatment to the same artery during the period covered by the study, and binary restenosis, which occurs when a treated artery becomes narrowed again after being previously treated.

Unfortunately, early anatomic (structural) advantages of DEBs were not accompanied by improvements in quality of life, functional walking ability, or in the occurrence of amputation or death. When we specifically examined arteries below the knee and people who had very advanced PAD, we found no clinical or angiographic advantage for DEBs at 12 months of follow-up compared with uncoated balloon angioplasty. In summary, DEBs have several anatomic advantages over uncoated balloons for the treatment of lower limb PAD for up to 12 months after undergoing the procedure. However, more data are needed to assess the long-term results of this treatment option adequately.

Quality of the evidence

All the trials had differences in the way in which they inserted the balloons, and in the type and duration of additional antiplatelet (anticlotting) therapy, leading to downgrading of the quality of the evidence. The quality of the evidence presented was moderate for target lesion revascularization and change in Rutherford category (a way of classifying PAD), and high for amputation, primary vessel patency, binary restenosis, death, and change in ankle-brachial index (which is used to predict the severity of PAD).

Summary of findings for the main comparison. Drug-eluting balloon versus uncoated balloon angioplasty at 12 months

Drug-eluting balloon compared to uncoated balloon angioplasty at 12 months

Patient or population: people with peripheral arterial disease of the lower limbs
Setting: hospital
Intervention: drug-eluting balloon angioplasty
Comparison: uncoated balloon angioplasty

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with uncoated balloon angioplasty at 12 months	Risk with drug-eluting balloon angioplasty at 12 months				
Amputation	Study population		OR 1.56 (0.73 to 3.33)	1649 (9 RCTs)	⊕⊕⊕⊕ High [1]	-
	14 per 1000	22 per 1000 (10 to 46)				
Primary vessel patency	Study population		OR 1.92 (1.45 to 2.56)	882 (3 RCTs)	⊕⊕⊕⊕ High [1]	-
	479 per 1000	638 per 1000 (571 to 702)				
	Moderate					
	487 per 1000	645 per 1000 (579 to 708)				
Target lesion revascularization	Study population		OR 0.40 (0.31 to 0.51)	1900 (11 RCTs)	⊕⊕⊖⊖ Low [1, 2, 3]	-
	264 per 1000	126 per 1000 (100 to 155)				
	Moderate					
	368 per 1000	189 per 1000 (153 to 229)				

Binary restenosis	Study population		OR 0.38 (0.15 to 0.98)	1094 (4 RCTs)	⊕⊕⊕⊖ Moderate [1, 3]	-
	350 per 1000	170 per 1000 (75 to 346)				
	Moderate					
	477 per 1000	257 per 1000 (120 to 472)				
Death	Study population		OR 1.09 (0.64 to 1.85)	1649 (9 RCTs)	⊕⊕⊕⊕ High [1]	-
	43 per 1000	46 per 1000 (28 to 76)				
	Moderate					
	45 per 1000	49 per 1000 (29 to 80)				
Change in Rutherford category	-	The mean change in Rutherford category in the intervention group was 0.1 lower (0.29 lower to 0.1 higher)	-	623 (3 RCTs)	⊕⊕⊕⊖ Moderate [1 4]	A positive change in Rutherford category reflects a worsening clinical status, although in this case the difference was not statistically significant
Change in ankle-brachial index	-	The mean change in ankle-brachial index in the intervention group was 0.03 lower (0.07 lower to 0.01 higher)	-	656 (3 RCTs)	⊕⊕⊕⊕ High [1]	A negative change in the ankle-brachial index reflects a worsening clinical status, although in this case the difference was not statistically significant

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT:** randomized controlled trial.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] All of the included trials were at a high risk of performance bias due to lack of blinding of operators. However, because this is an intrinsic limitation to intervention trials, we did not downgrade the GRADE class because of performance bias.
[2] Funnel plot analysis indicated a likely publication bias, which resulted in downgrading of the GRADE class.
[3] There was moderate heterogeneity between the included studies (P < 0.001), which resulted in downgrading of the GRADE class.
[4] There was moderate heterogeneity between the included studies (P = 0.04), which resulted in downgrading of the GRADE class.

BACKGROUND

Description of the condition

Peripheral arterial disease (PAD) is a major healthcare challenge resulting in significant age-related patient morbidity. It is estimated to affect 4% of adults aged 40 years or older and 14.5% of adults aged 70 years or older in the USA (Selvin 2004). The presence of PAD does not always lead to symptoms, and asymptomatic PAD has been reported in 8% of Scottish adults (Fowkes 1991).

People with symptomatic lower-limb PAD commonly present with intermittent claudication (IC). The prevalence of IC in people with PAD is estimated to be 3% in people aged 40 years and 6% in people aged 60 years (Norgren 2007). About 25% of people with IC will develop more severe claudication and a deterioration in functional status of their affected limb. Some of those people will also eventually develop critical limb ischemia (CLI) (Norgren 2007). Major amputation is required in less than 10% of people with IC (Aquino 2001).

Description of the intervention

The medical management of lower-limb PAD is based on an appropriate diet and exercise regimen and vascular disease risk-factor modification through smoking-cessation, blood pressure control, tight control of blood sugar levels in people with diabetes, and the prescription of lipid-lowering and antiplatelet medications (Hirsch 200). Surgical management is indicated when people develop CLI or debilitating IC that is refractory to nonoperative management.

While bypass with an autologous vein or prosthetic conduit is the mainstay of open surgical management of PAD, percutaneous endovascular interventions provide another treatment alternative. Percutaneous interventions use ultrasound and fluoroscopic guidance to access and cannulate the diseased artery. A balloon catheter is then employed to provide pneumatic dilation of the stenotic or occluded vessel segment. The first balloon catheters used for this purpose were not coated with any medications and showed excellent efficacy in treating these diseased arteries (Norgren 2007). More recently, drug-eluting balloons (DEBs), in addition to stents, have been placed to provide additional support when balloon angioplasty results are not satisfactory.

Balloon angioplasty, with or without stent placement, has the advantage of a shorter hospital stay and fewer short-term postinterventional complications compared with bypass surgery. It has also been shown to be similar to open surgery in overall and amputation-free survival at two years (BASIL 2005). However, on long-term follow-up, bypass surgery with autologous venous conduit was associated with a seven-month increase in overall survival while amputation-free survival remained the same (Bradbury 2010). In cases where autologous venous conduit is not available for bypass, the differences between balloon angioplasty and bypass using a prosthetic graft are probably minimal in terms of outcome (Bradbury 2010).

How the intervention might work

Elastic recoil and vessel restenosis secondary to neointimal hyperplasia remain a challenge for all of the available lower-limb PAD treatment interventions. Numerous strategies have sought to delay vessel restenosis, including the use of drug-eluting stents and DEBs. To date, there is only one commercially available drug-eluting stent for use in the superficial femoral artery (Dake 2013).

DEBs were developed to provide a complete and homogenous coating of an antiproliferative agent to the arterial wall (Seedial 2013). The most commonly used agent is paclitaxel, a highly lipophilic drug that has been shown to prevent neointimal hyperplasia after balloon angioplasty (Axel 1997). The immunosuppressant agent sirolimus has also been used to prevent neointimal hyperplasia (Seedial 2013). The advantages of DEBs compared with other percutaneous treatment modalities include the absence of stent thrombosis or scaffolding to disrupt patterns of flow, immediate drug release, and no residual foreign body (Seedial 2013). However, DEBs are more costly and carry the potential for long-term negative vessel remodeling and elastic recoil.

Why it is important to do this review

Randomized controlled trials have demonstrated the safety and efficacy of angioplasty using DEBs compared with conventional uncoated balloon angioplasty. Our goal is to review the evidence for the use of DEBs in the management of lower-limb PAD systematically. This will help guide decision-making when considering whether to use this costly treatment modality and determine whether it is associated with improved clinical outcomes compared with conventional balloon angioplasty.

OBJECTIVES

To assess the efficacy of drug-eluting balloons (DEBs) compared with uncoated, nonstenting balloon angioplasty in people with symptomatic lower-limb peripheral arterial disease (PAD).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) that compare DEBs with uncoated balloon angioplasty for IC or CLI.

Types of participants

People with IC or CLI undergoing drug-eluting or uncoated balloon angioplasty for symptomatic lower-limb PAD.

Types of interventions

We compared DEBs for PAD of the lower limbs with uncoated, nonstenting balloon angioplasty. Endovascular access in the included studies was established percutaneously or through a limited incision. We did not include studies of DEBs for the treatment of instent restenosis of the lower-limb, as well as studies where DEBs were used simultaneously in combination with other angioplasty techniques (such as hybrid procedures involving surgery and DEBs). Our review focused on primary arterial interventions only. We excluded reinterventions and studies using cutting balloon angioplasty.

Types of outcome measures

Primary outcomes

- Incidence of amputation.

- Amputation-free survival, defined as the probability of being alive without an amputation.
- Amputation-free rate, defined as the patency of the target vessels and freedom from amputation.
- Vessel patency (primary and secondary), as determined by delayed arterial lumen loss, target lesion revascularization, and binary restenosis rate measured with duplex ultrasound or angiography.
- Death.

Secondary outcomes

- Change in Fontaine stage or Rutherford category of PAD (Norgren 2007).
- Change in ankle-brachial index (ABI).
- Change in quality of life (QoL) scores.
- Change in functional walking ability, as measured by the Walking Impairment Questionnaire (WIQ).

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Trials Search Co-ordinator (TSC) searched the Specialised Register (December 2015). In addition, the TSC searched the Cochrane Register of Studies (CRS) (www.metaxis.com/CRSWeb/Index.asp; (CENTRAL) 2015, Issue 11). See Appendix 1 for details of the search strategy used to search the CRS. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, Embase, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals, and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular module in the*Cochrane Library* (www.cochranelibrary.com).

In addition, the TSC searched the following trial databases for details of ongoing and unpublished studies. See Appendix 2 for details of the search.

- World Health Organization International Clinical Trials Registry (apps.who.int/trialsearch/).
- ClinicalTrials.gov (clinicaltrials.gov/).
- ISRCTN registry (www.controlled-trials.com/).

Searching other resources

We examined the bibliographies of relevant papers found from the electronic searches to identify other studies. We also attempted to contact study authors for additional information when necessary.

Data collection and analysis

Selection of studies

Two review authors (AK and TA) independently selected trials for inclusion in this review. These trials were sent to a third review author (DR), who assessed and confirmed their suitability for inclusion and acted as an adjudicator in the event of disagreement. The Criteria for considering studies for this review section details the inclusion criteria used in this selection process.

Data extraction and management

Two review authors (AK and TA) extracted the data from each trial, including participant demographics (age, gender, comorbidities, Fontaine stage or Rutherford category of PAD, and ABI), interventions (DEBs and other balloon types, vessels treated, history of previous stent placement), and outcomes (as specified in the Criteria for considering studies for this review section). A third review author (DR), then cross-checked the data and acted as an adjudicator in the event of disagreement. Statistical analysis complied with the standard methods of Cochrane Vascular. We used the computer software package Review Manager 5 to perform all statistical analyses and generate figures (RevMan 2014).

Assessment of risk of bias in included studies

Two review authors (AK and TA) assessed potential risks of bias for all included studies using the Cochrane's tool for assessing risk of bias (Higgins 2011). The tool assesses bias in six different domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Each domain receives a score of high, low, or unclear depending on each review author's judgment. A third review author (DR) acted as an adjudicator in the event of disagreement. Where doubt existed as to a potential risk of bias, we contacted the study authors for clarification.

Measures of treatment effect

We calculated and reported continuous outcome measures such as lumen loss using the mean difference (MD) and associated 95% confidence interval (CI) between the two treatment groups. We calculated and reported dichotomous outcome measures including the occurrence of a postprocedural complication such as death using the odds ratio (OR) and associated 95% CI, depending on the reported data. We based calculations on an intention-to-treat approach and all randomized participants were included in the analysis regardless of loss to follow-up. In one study (FemPac 2008), where the late lumen loss and change in ABI were reported as medians, rather than means, we converted the median values to means as per the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

The unit of analysis was the treated limb for outcomes in which repeat or additional procedures on the contralateral side were possible and reported. The unit of analysis was the individual participant when considering participant death, QoL scores, and change in functional walking ability.

Dealing with missing data

We contacted authors of the included studies to inquire about missing or incomplete data, such as information on participants who dropped out of the study, and missing statistics. We excluded no studies from the meta-analysis due to concerns about missing data.

Assessment of heterogeneity

We assessed inter-study heterogeneity visually using a forest plot. We also calculated the I^2 statistic to measure the amount of inter-study heterogeneity. We considered I^2 values less than 50% as

indicative of low heterogeneity, I^2 values between 50% and 75% as indicative of moderate heterogeneity, and I^2 values greater than 75% as indicative of significant heterogeneity (Higgins 2011).

Assessment of reporting biases

We constructed a funnel plot to test for reporting bias in meta-analyses that included 10 or more studies (Higgins 2011).

Data synthesis

We used a fixed-effect model to calculate the pooled treatment effect data and 95% CIs for continuous and dichotomous outcome variables, as detailed under Measures of treatment effect. We used a random-effects model when we found significant heterogeneity (defined as I^2 greater than 75%). We created a forest plot for each treatment effect, as per Cochrane Vascular guidelines.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses by the arterial segments treated (femoropopliteal versus tibial), and the severity of PAD (studies that only included participants with a Rutherford's class greater than 4). We were unable to perform subgroup analyses by type of DEB pharmacologic agent, as all the studies used paclitaxel.

Sensitivity analysis

We sequentially excluded studies with a high risk of bias in several domains (as described in the Assessment of risk of bias in included studies section) and performed a pooled sensitivity analysis in order to assess whether the included studies, deemed to be biased, impacted the final analysis.

'Summary of findings' table

We prepared 'Summary of findings' tables to present the evidence for DEB versus uncoated balloon angioplasty at 12 months of follow-up in participants who underwent endovascular lower-limb interventions for symptomatic PAD. We chose this time point because the greatest amount of data from the included trials was available at 12 months of follow-up. We used no external information in generating the 'Assumed risk' column. We used the GRADE approach to evaluate the evidence and assign one of four levels of quality: high, moderate, low, or very low (Higgins 2011). No departures from the standard methods for generating these tables were required. We included the following primary and secondary endpoints described under the Types of outcome measures section: amputation, primary vessel patency, target lesion revascularization, binary restenosis, death, change in Rutherford category, and change in ABI. These endpoints were chosen because we deemed them to be the most clinically relevant.

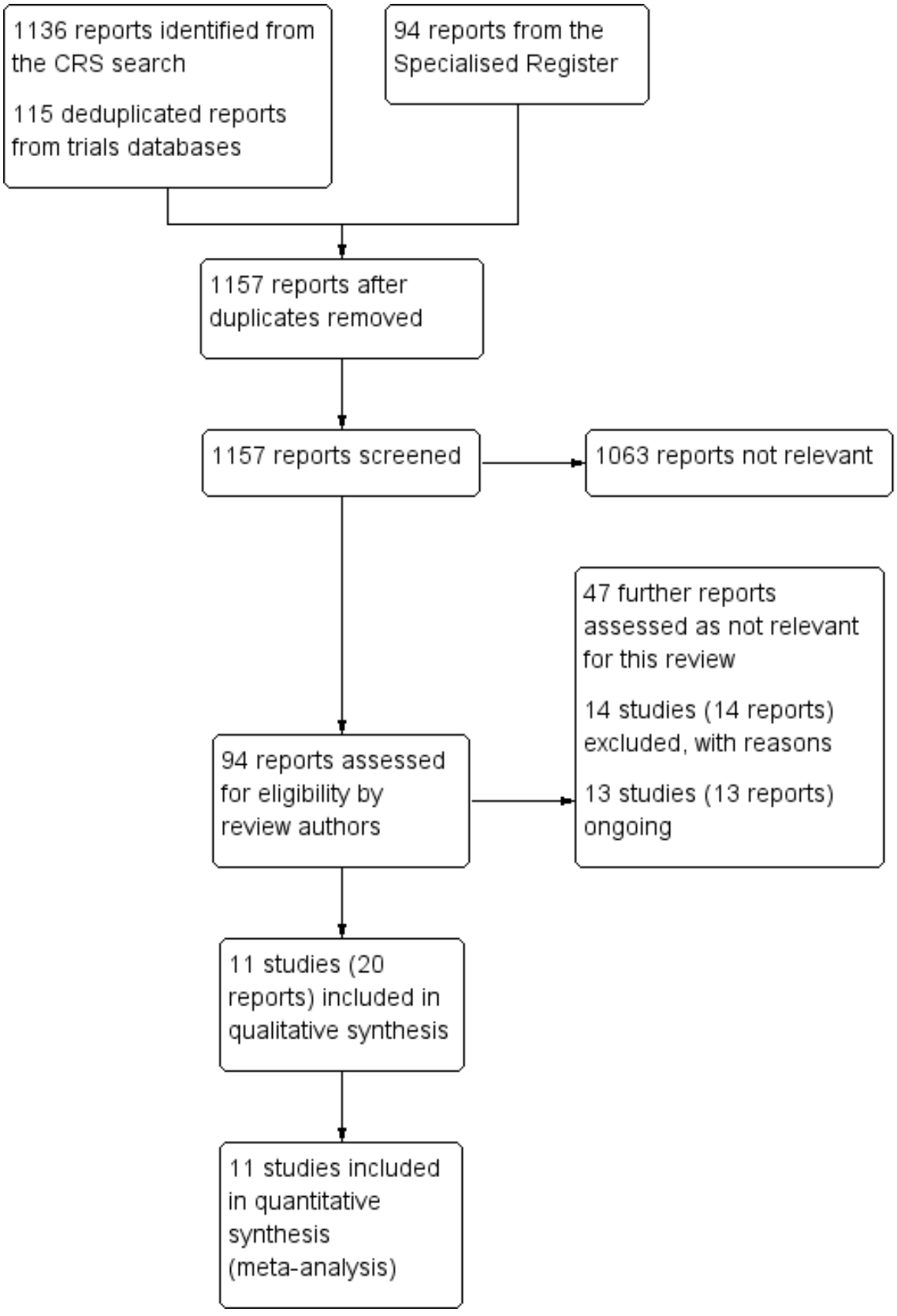
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

The review included 11 randomized controlled trials that compared DEB with uncoated balloon angioplasty for lower extremity IC or CLI (BIOLUX P-I; BIOLUX P-II; DEBATE-BTK 2013; DEBELLUM 2012; FemPac 2008; IN.PACT DEEP 2014; IN.PACT SFA 2015; LEVANT I 2014; LEVANT II 2015; PACIFIER 2012; THUNDER 2008). The Characteristics of included studies table lists these in more detail.

All of the included studies were partially or entirely conducted in Europe. Three studies also enrolled people in the USA (IN.PACT SFA 2015; LEVANT I 2014; LEVANT II 2015). Most studies examined treatments for femoropopliteal arteries (BIOLUX P-I; FemPac 2008; IN.PACT SFA 2015; LEVANT I 2014; LEVANT II 2015; PACIFIER 2012; THUNDER 2008), and three studies only examined tibial arteries (BIOLUX P-II; DEBATE-BTK 2013; IN.PACT DEEP 2014). The DEBELLUM 2012 trial examined both femoropopliteal and tibial arteries. Every included trial used paclitaxel as the balloon-coating drug.

Medtronic manufactured the most-frequently studied DEBs and sponsored three trials (IN.PACT DEEP 2014; IN.PACT SFA 2015; PACIFIER 2012). Two trials also used Medtronic devices but did not report receiving any industry sponsorship (DEBATE-BTK 2013; DEBELLUM 2012). Bavaria Medizin (FemPac 2008; THUNDER 2008), Bard (LEVANT I 2014; LEVANT II 2015), and Biotronik (BIOLUX P-I; BIOLUX P-II) sponsored two trials each.

We also identified 13 trials that were either ongoing or awaiting publication (see Characteristics of ongoing studies table). We contacted authors of all ongoing studies to request study data.

Excluded studies

We excluded 14 trials from our review (COPA CABANA; DEBATE-ISR; DEBATE SFA; DEFINITIVE AR; EURO CANAL; FAIR; Freeway Stent Study; IDEAS; ISAR-PEBIS; ISAR-STATH; PACUBA 1; PHOTOPAC; RAPID; SWEDEPAD). The reasons for exclusion are outlined in the Characteristics of excluded studies table. Studies were most commonly excluded for comparing DEB and bare-metal or drug-eluting stenting (DEBATE SFA; IDEAS; RAPID), DEB and uncoated balloon angioplasty for the management of instent restenosis (COPA CABANA; DEBATE-ISR; FAIR; Freeway Stent Study; ISAR-PEBIS; PACUBA 1), or DEB with or without atherectomy (DEFINITIVE AR; ISAR-STATH). One trial compared DEB with or without photoablation therapy for the prevention of instent restenosis (PHOTOPAC). The SWEDEPAD trial compared drug-eluting technologies (balloon or stents) with nondrug-eluting technologies (balloons or stents). The EURO CANAL was terminated early before any data were collected because the manufacturer withdrew the product from the market.

Risk of bias in included studies

See 'Risk of bias' tables in the Characteristics of included studies table and summary results in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

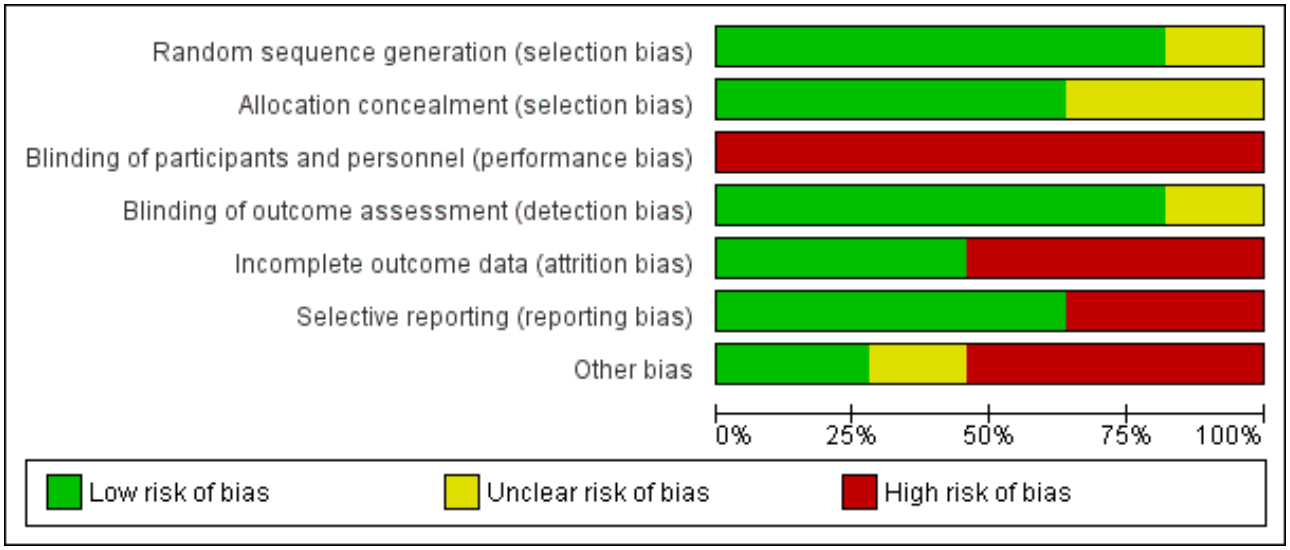
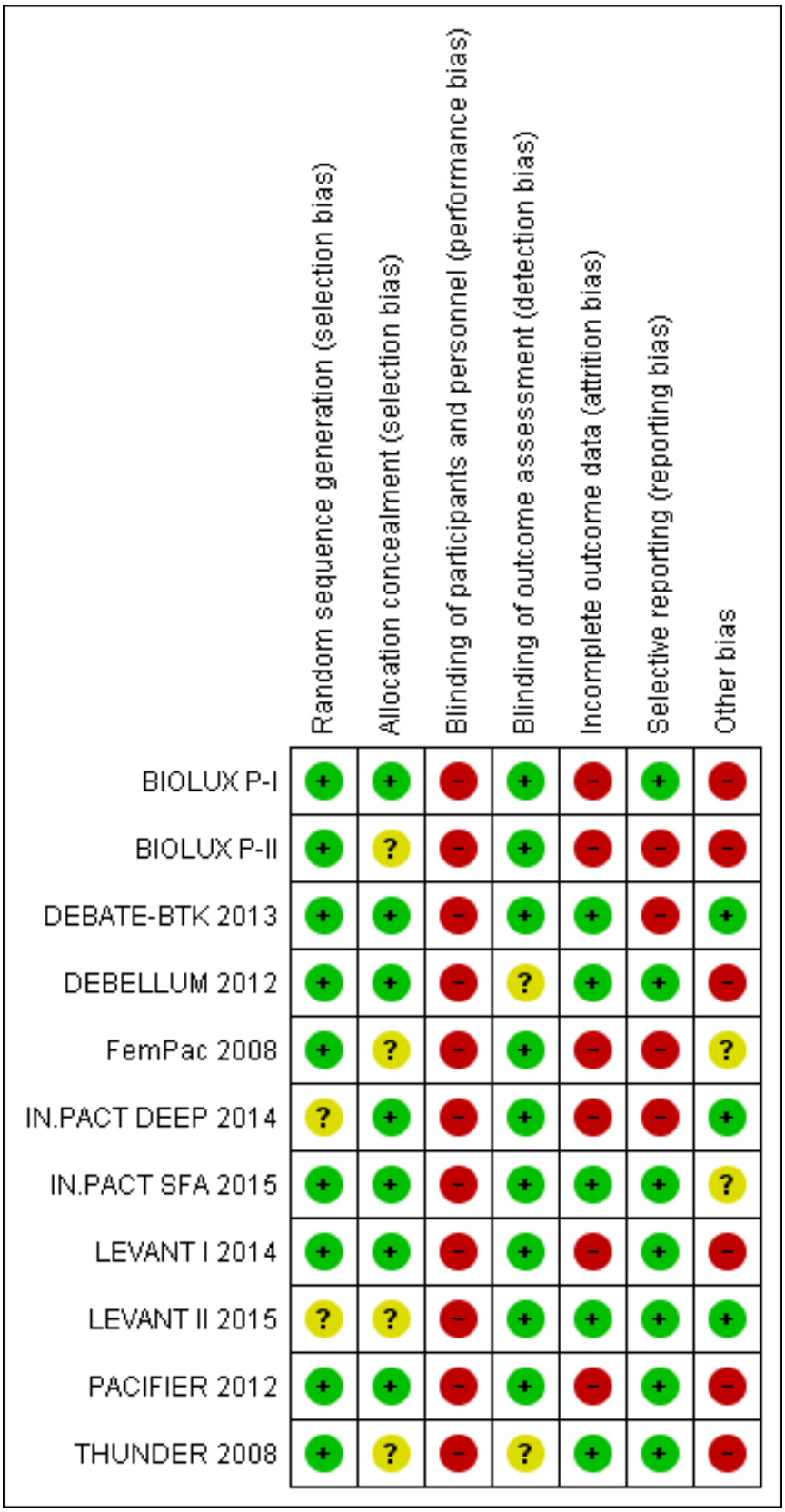


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Of the included studies, three were at high risk of bias and were excluded in sensitivity analyses to determine their impact (BIOLUX P-I; BIOLUX P-II; FemPac 2008). BIOLUX P-I was at high risk of bias because of a low follow-up compliance and a high rate of bailout stenting (26.7%) in the control arm. Furthermore, more than half of the participants in both arms had a history of peripheral vascular interventions, and it is unclear whether the lesions studied in the trial had been previously treated. BIOLUX P-II did not blind the operators or the participants to the procedure. Approximately 20% of the participants in the intervention arm were lost to follow-up, and the rate of technical success in the study was relatively low for both arms (54.5% for the DEB arm and 59.6% for the control arm). FemPac 2008 similarly did not have adequate follow-up data on 27% of the DEB arm and 17% of the control arm. Furthermore, approximately 11% of the trial participants were stented, but the outcomes of those participants were not reported separately.

Allocation

Most of the included studies were at a low risk for sequence generation selection bias. IN.PACT DEEP 2014 randomized participants using "blocks of sealed envelopes" without specifying the methodology for generating those randomization blocks. LEVANT II 2015 did not specify how participants were randomized or allocated to either study arm.

Similarly, most studies were at a low risk for allocation concealment selection bias. However, four studies did not specify how allocation concealment bias was addressed (BIOLUX P-II; FemPac 2008; LEVANT II 2015; THUNDER 2008).

Blinding

All of the included studies were at high risk for performance bias because the operators were not blinded to the procedure. In BIOLUX P-II, neither the participants nor the operators were blinded.

Conversely, the risk of detection bias was low as study authors mostly ensured that outcome assessment was carried out by other blinded investigators. The DEBELLUM 2012 authors stated that "postoperative evaluation was deferred to different physicians not informed about the assigned intervention", but it was unclear what type of physicians performed those evaluations and what type of qualifications they had. The THUNDER 2008 authors stated that some of the operators also performed some of the poststudy evaluations.

Incomplete outcome data

Six trials were at high risk of attrition bias (BIOLUX P-I; BIOLUX P-II; FemPac 2008; IN.PACT DEEP 2014; LEVANT I 2014; PACIFIER 2012). In BIOLUX P-I, four participants withdrew consent and five participants were lost to follow-up, which equals a 15% attrition of the study population. Similarly, in BIOLUX P-II, 19% of participants of the DEB arm either withdrew from the study or were lost to follow-up at 12 months. FemPac 2008 had six-month data available on only 73% of participants in the intervention arm and 83% of participants in the control arm. In IN.PACT DEEP 2014, the authors stated that low angiographic and wound imaging compliance may have limited the full assessment of the interventions. In LEVANT I 2014, six-month angiographic follow-up was available for 80% of the intervention arm and 69% of the control arm. The PACIFIER 2012 authors reported missing primary outcome data on 20.5% of the intervention arm and 27.3% of the control arm.

Selective reporting

Four trials were at high risk of bias due to incomplete reporting of data (BIOLUX P-II; DEBATE-BTK 2013; FemPac 2008; IN.PACT DEEP 2014). In BIOLUX P-II, all prespecified outcomes were reported, but the results were not stratified by the type of treated infra-popliteal vessels (i.e. anterior tibial, posterior tibial, or peroneal arteries). The authors also did not specify whether those participants with more than one target lesion (33.3% of DEB participants and 44.4% of percutaneous transluminal angioplasty (PTA) participants) had several target vessels and whether the outcomes differed by the number of treated lesions and vessels. DEBATE-BTK 2013 was designed to assess infra-popliteal arterial lesions but some of the participants also received treatment for femoropopliteal lesions. The study authors stated that inflow lesions located in the femoropopliteal segment were "treated by standard techniques during the same session" without elaborating on the nature or number of those techniques. FemPac 2008 reported that "no Doppler or angiographic information was obtained from 7 patients in the control and 9 patients in the coated balloon group", which amounts to approximately 18% of the study participant population. IN.PACT DEEP 2014 did not report several outcomes that were prespecified in the study protocol, such as change in Rutherford classification and QoL scores.

Other potential sources of bias

A major source of bias in many of the included studies was the concurrent use of stenting without separate reporting of the outcomes of stented participants. One quarter of the BIOLUX P-I control arm (26.7%) required bailout stenting. LEVANT I 2014 randomized participants to the intervention or control arms after successful predilation or stenting "based on whether the interventionalist intended to use only balloon dilation of the lesion or intended concomitant stenting". Twenty-six per cent of trial participants were stented prior to randomization, and a further 3% in the intervention and 16% in the control arm received "bailout stenting" after undergoing the intended therapy. The DEBELLUM 2012 authors reported that the "decision to implant a nitinol stent in the SFA [superficial femoral artery] territory was left to the judgment of the operator and typically driven by lesion length and presence of severe calcification". However, these stent-deployment criteria were unclear, and approximately 37% of the treated lesions in the study were stented. The FemPac 2008 authors similarly reported that 11% of all participants received a stent, the PACIFIER 2012 authors reported that 21% of intervention and 34% of control participants received a stent, and in THUNDER 2008, 4% of intervention and 22% of control participants received a stent. The clinical outcomes of those stented participants were not reported separately. LEVANT II 2015 addressed this potential source of bias by only randomizing participants who did not require a stent after an initial angiogram.

In BIOLUX P-I, predilation was performed more often in DEB than PTA participants (66.7% with DEB versus 30% with PTA, P = 0.01), and technical success was higher in the DEB group (76.7% with DEB versus 46.7% with PTA, P = 0.02). Most of the DEB (56.7%) and PTA (60%) participants had a history of previous peripheral interventions, although the type and location of those interventions was not specified.

In BIOLUX P-II, while no bailout stenting was required in either treatment arm, the authors had a relatively low technical success rate (defined as less than 30% residual stenosis) in both arms (54.2% with DEB, 59.6% with PTA).

Device malfunction in LEVANT I 2014 was another potential source of bias. Eight DEB devices (16%) malfunctioned and failed to deploy. It was unclear how those participants were managed.

The approach to antiplatelet therapy also varied between trials. While FemPac 2008 did not specify the duration of antiplatelet therapy, participants in all the other trials received acetylsalicylic acid (ASA; aspirin) and at least four weeks of a second antiplatelet agent, most commonly clopidogrel. However, in IN.PACT DEEP 2014 and IN.PACT SFA 2015, the duration of the second antiplatelet agent depended on by whether a stent was deployed. Nonstented participants received a minimum of one month, while stented participants received a minimum of three months of a second antiplatelet agent.

While paclitaxel was used in the intervention arm of all the analyzed studies, there was variability in the paclitaxel dose and balloon drug carrier according to the type of DEB device used.

Finally, DEB device manufacturers sponsored nine of the 11 included studies (BIOLUX P-I; BIOLUX P-II; FemPac 2008; IN.PACT DEEP 2014; IN.PACT SFA 2015; LEVANT I 2014; LEVANT II 2015; PACIFIER 2012; THUNDER 2008). In the IN.PACT SFA 2015 study, every author listed in the published manuscript declared a financial relationship with the DEB device manufacturer.

Effects of interventions

See: **Summary of findings for the main comparison** Drug-eluting balloon versus uncoated balloon angioplasty at 12 months

Primary outcomes

Amputation

The incidence of amputation was reported as a secondary endpoint in the included trials. While this outcome was not listed in the study protocol, we included it in the analysis because only one trial reported amputation-free survival (IN.PACT DEEP 2014). There was no significant difference in the incidence of amputations between DEB and uncoated balloon angioplasty at six months (Analysis 1.1; OR 1.21, 95% CI 0.39 to 3.80; 541 participants; 7 studies); 12 months (Analysis 2.1; OR 1.56, 95% CI 0.73 to 3.33; 1649 participants; 9 studies); two years (Analysis 3.1; OR 0.65, 95% CI 0.11 to 3.88; 493 participants; 3 studies); or five years (Analysis 4.1; OR 4.82, 95% CI 0.52 to 44.70; 102 participants; 1 study).

Exclusion of BIOLUX P-I, BIOLUX P-II, and FemPac 2008 at six and 12 months and two years did not result in any significant differences in amputation outcomes (Analysis 1.11; OR 1.77, 95% CI 0.42 to 7.54; 322 participants; 4 studies at six months; Analysis 2.12; OR 1.78, 95% CI 0.79 to 4.04; 1517 participants; 7 studies at 12 months; Analysis 3.11; OR 3.16, 95% CI 0.12 to 80.19; 406 participants; 2 studies at two years). The sensitivity analysis was carried out due to concerns about participant follow-up (BIOLUX P-I; BIOLUX P-II; FemPac 2008), and technical success rate (BIOLUX P-II) in the study population.

Amputation-free survival

Only IN.PACT DEEP 2014 reported amputation-free survival at 12 months in (Analysis 2.2; OR 0.68, 95% CI 0.38 to 1.19; 358 participants; 1 study). The trial showed a trend towards improved amputation-free survival among control arm participants compared with the DEB arm, although this difference did not reach statistical significance.

Amputation-free rate

None of the included studies reported amputation-free rate.

Vessel patency

Primary vessel patency

There was no significant difference in primary vessel patency between DEB and uncoated balloon angioplasty at six months (Analysis 1.2; OR 1.47, 95% CI 0.22 to 9.57; 162 participants; 2 studies). However, exclusion of FemPac 2008 resulted in a significant advantage for DEB compared with uncoated balloon angioplasty at six months (Analysis 1.12; OR 3.84, 95% CI 1.43 to 10.31; 75 participants; 1 study). FemPac 2008 was excluded due to concerns about incomplete participant follow-up. DEBs were associated with significantly greater odds of primary vessel patency at 12 months (Analysis 2.3; OR 1.92, 95% CI 1.45 to 2.56; 882 participants; 3 studies) and two years (Analysis 3.2; OR 3.51, 95% CI 2.26 to 5.46; 406 participants; 2 studies).

Secondary vessel patency

None of the included trials reported secondary vessel patency rates.

Late lumen loss

Participants treated with DEB were less likely to develop late lumen loss at six months compared with the control participants (Analysis 1.3; MD -0.64 mm, 95% CI -1.00 to -0.28; 603 participants; 7 studies). However, this advantage was lost after 12 months, primarily due to the inclusion of IN.PACT DEEP 2014 (Analysis 2.4; MD -0.73 mm, 95% CI -1.59 to 0.13; 535 participants; 3 studies), which was limited to infra-popliteal vessels that were smaller than the femoropopliteal vessels studied in the other trials. When the analysis excluded IN.PACT DEEP 2014, there was less late lumen loss with DEBs compared with uncoated balloon angioplasty (Analysis 2.15; MD -1.10 mm, 95% CI -1.41 to -0.79; 177 participants; 2 studies). There was an advantage for DEB compared with uncoated balloon angioplasty at two years (Analysis 3.3; MD -0.80 mm, 95% CI -1.44 to -0.16; 102 participants; 1 study).

Exclusion of FemPac 2008, which reported late lumen losses as medians, and the BIOLUX P-I and BIOLUX P-II studies did not impact the late lumen loss advantage of DEB compared with uncoated balloon angioplasty at six months (Analysis 1.13; MD -0.96 mm, 95% CI -1.21 to -0.71; 343 participants; 4 studies).

Target lesion revascularization

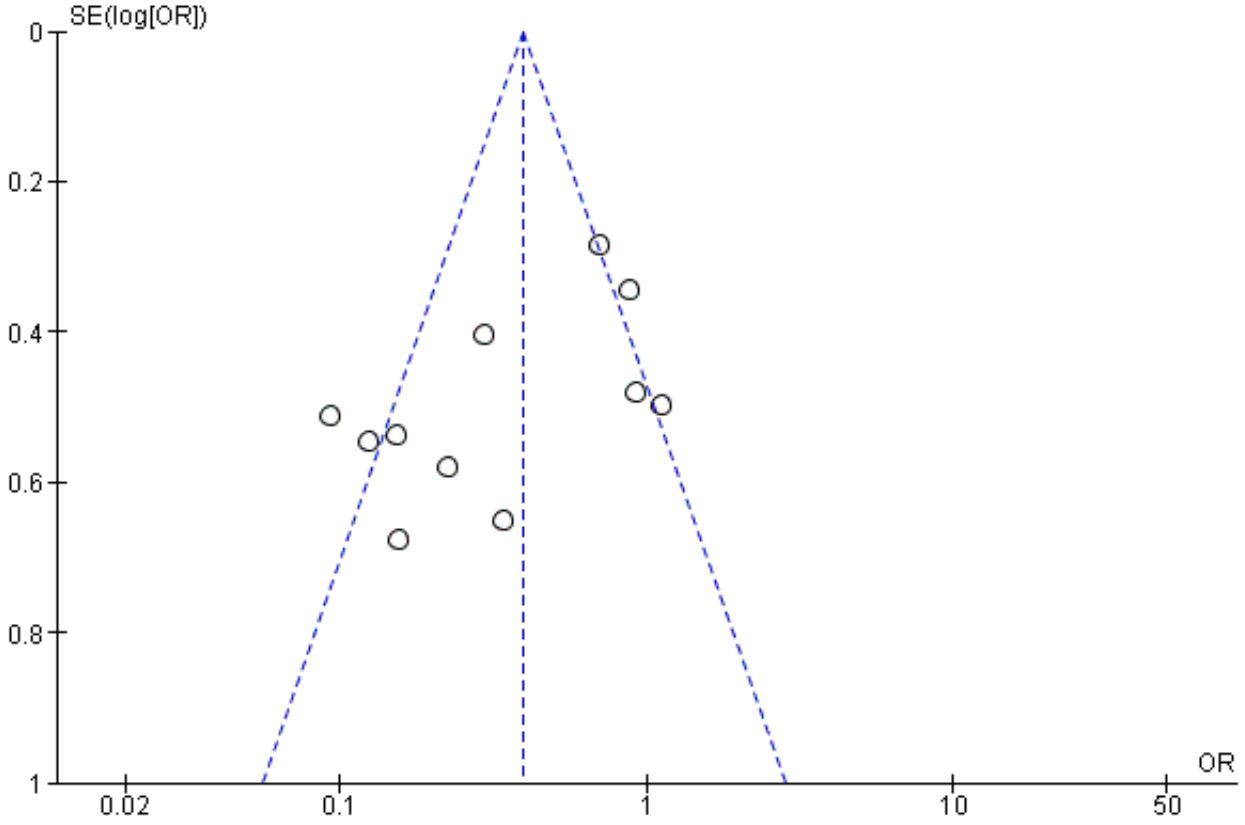
The DEB arm of the trials had a clear advantage in target lesion revascularization compared with uncoated balloon angioplasty at six months (Analysis 1.4; OR 0.28, 95% CI 0.17 to 0.47; 603 participants; 7 studies), 12 months (Analysis 2.5; OR 0.40, 95% CI 0.31 to 0.51; 1900 participants; 11 studies), two years (Analysis 3.4; OR 0.28, 95% CI 0.18 to 0.44; 508 participants; 3 studies), and five

years (Analysis 4.2; OR 0.21, 95% CI 0.09 to 0.51; 102 participants; 1 study).

Exclusion of BIOLUX P-I, BIOLUX P-II, and FemPac 2008 at six and 12 months did not impact the target lesion revascularization advantage of DEB compared with uncoated balloon angioplasty (Analysis 1.14; OR 0.22, 95% CI 0.11 to 0.44; 343 participants; 4 studies at six months; Analysis 2.13; OR 0.33, 95% CI 0.18 to 0.61; 1640 participants; 8 studies at 12 months).

A funnel plot constructed to test for publication bias in target lesion revascularization at 12 months demonstrated asymmetry, which was consistent with the heterogeneity observed in the analysis (Chi^2 test for heterogeneity $P < 0.0001$) (Figure 4).

Figure 4. Funnel plot of comparison: 2 Drug-eluting balloon versus uncoated balloon angioplasty at 12 months, outcome: 2.5 Target lesion revascularization.



Binary restenosis rate

Participants treated with DEBs had significantly lower odds of developing binary restenosis compared with participants in the control group at six months (Analysis 1.5; OR 0.44, 95% CI 0.29 to 0.67; 528 participants; 6 studies), 12 months (Analysis 2.6; OR 0.38, 95% CI 0.15 to 0.98; 1094 participants; 4 studies), two years (Analysis 3.5; OR 0.26, 95% CI 0.10 to 0.66; 87 participants; 1 stud), and five years (Analysis 4.3; OR 0.12, 95% CI 0.05 to 0.30; 102 participants; 1 study).

Exclusion of BIOLUX P-I, BIOLUX P-II, and FemPac 2008 at six months did not impact the binary restenosis rate advantage of DEB compared with uncoated balloon angioplasty (Analysis 1.15; OR 0.25, 95% CI 0.13 to 0.50; 268 participants; 3 studies).

Death

There was no significant difference in mortality between participants who underwent DEB or uncoated balloon angioplasty at six months (Analysis 1.6; OR 0.81, 95% CI 0.31 to 2.14; 541 participants; 7 studies), 12 months (Analysis 2.7; OR 1.04, 95% CI 0.64 to 1.71; 1649 participants; 9 studies), and five years (Analysis 4.4; OR 1.92, 95% CI 0.71 to 5.19; 102 participants; 1 study). At two years, uncoated balloon angioplasty had a slight mortality advantage compared with DEB (Analysis 3.6; OR 2.13, 95% CI 1.08 to 4.20; 595 participants; 4 studies).

Exclusion of BIOLUX P-I, BIOLUX P-II, and FemPac 2008 at six months, 12 months, and two years did not result in a significant difference in mortality between the treatment groups (Analysis 1.16; OR 0.57, 95% CI 0.15 to 2.11; 322 participants; 4 studies at six months; Analysis 2.14; OR 1.09, 95% CI 0.64 to 1.85; 1517 participants; 7 studies at 12 months; Analysis 3.12; OR 2.16, 95% CI 1.00 to 4.67; 508 participants; 3 studies at two years).

Secondary outcomes

Change in Fontaine stage or Rutherford category of peripheral arterial disease

There was no significant difference in the change in Rutherford category between the DEB and uncoated balloon angioplasty arms

at six months (Analysis 1.7; MD -0.07, 95% CI -0.49 to 0.36; 249 participants; 3 studies), 12 months (Analysis 2.8; MD -0.10, 95% CI -0.29 to 0.10; 623 participants; 3 studies), and two years (Analysis 3.7; MD -0.30, 95% CI -0.80 to 0.20; 75 participants; 1 study).

Exclusion of BIOLUX P-II at six and 12 months did not result in a significant change in Rutherford category from baseline between the two treatment groups (Analysis 1.17; MD 0.04, 95% CI -0.42 to 0.50; 177 participants; 2 studies at six months; Analysis 2.16; MD 0.09, 95% CI -0.58 to 0.77; 551 participants; 2 studies at 12 months).

One trial reported the Fontaine stage rather than the Rutherford classification system (DEBELLUM 2012). Our analysis did not include these data, however, because the authors reported the Fontaine class at six and 12 months rather than the change in Fontaine class from baseline. At six months, the DEB participants were 92% Fontaine class I, 8% class IIa, and 0% class IIb or III, versus uncoated balloon angioplasty participants who were 67% class I, 13% class IIa, 7% class IIb, and 13% class III. At 12 months, the DEB participants were 77% class I, 8% class IIa, 15% class IIb, and 0% class III, versus uncoated balloon angioplasty participants who were 60% class I, 13% class IIa, 13% class IIb, and 13% class III.

Change in ankle-brachial index

There was no significant advantage for DEB when evaluating change in ABI at six months (Analysis 1.8; MD -0.00, 95% CI -0.19 to 0.18; 369 participants; 4 studies), 12 months (Analysis 2.9; MD -0.03, 95% CI -0.07 to 0.01; 656 participants; 3 studies), and two years (Analysis 3.8; MD 0.02, 95% CI -0.12 to 0.16; 83 participants; 1 study).

Exclusion of FemPac 2008, which reported changes in ABI as medians, and BIOLUX P-II demonstrated no advantage in ABI change for DEB compared with uncoated balloon angioplasty at six and 12 months (Analysis 1.18; MD -0.01, 95% CI -0.09 to 0.08; 177 participants; 2 studies at six months; Analysis 2.17; MD -0.01, 95% CI -0.05 to 0.03; 551 participants; 2 studies at 12 months).

Change in quality of life scores

The Euro-Qol Group 5-Dimension Self-Report Questionnaire (EQ-5D) QoL scores were reported at six months (BIOLUX P-II), 12 months (BIOLUX P-II; IN.PACT SFA 2015; LEVANT II 2015) and two years (IN.PACT SFA 2015). There was no significant difference in the change of EQ-5D scores between the DEB and uncoated balloon angioplasty arms (Analysis 1.9; MD -0.10, 95% CI -0.22 to 0.02; 72 participants; 1 study at six months, Analysis 2.10; MD 0.01, 95% CI -0.02 to 0.04; 879 participants; 3 studies at 12 months; Analysis 3.9; MD 0.04; 95% CI -0.01 to 0.09; 331 participants; 1 study at two years).

Exclusion of BIOLUX P-II at 12 months did not result in a significant change in QoL scores from baseline between the two treatment groups (Analysis 2.18; MD 0.02, 95% CI -0.01 to 0.05; 807 participants; 2 studies).

LEVANT II 2015 also reported 36-item Short Form (SF-36) Physical and Mental component scores at 12 months but demonstrated no significant difference. The MD and standard deviation (SD) in the Physical component score between the intervention and control arms was 0.6 ± 11 (95% CI -1.7 to 2.9). Similarly, the difference in the Mental component score between the intervention and control arms was -0.2 ± 12.8 (95% CI -2.9 to 2.5).

Change in functional walking ability

Two trials assessed the change in functional walking ability using the WIQ (LEVANT I 2014; LEVANT II 2015). There were no significant differences in WIQ scores between DEB and uncoated balloon angioplasty at six months (Analysis 1.10; MD -0.70, 95% CI -16.00 to 14.60; 75 participants; 1 study), 12 months (Analysis 2.11; MD 3.57, 95% CI -1.23 to 8.38; 513 participants; 2 studies), and two years (Analysis 3.10; MD 0.50, 95% CI -13.42 to 14.42; 75 participants; 1 study).

Subgroup analysis

Arterial segments

Seven trials included only femoropopliteal arterial lesions (BIOLUX P-I; FemPac 2008; IN.PACT SFA 2015; LEVANT I 2014; LEVANT II 2015; PACIFIER 2012; THUNDER 2008), and three trials included only tibial arterial lesions (BIOLUX P-II; DEBATE-BTK 2013; IN.PACT DEEP 2014). DEBELLUM 2012 included both femoropopliteal and tibial lesions, but did not stratify the outcomes by type of arterial segment and as such was excluded from this subgroup analysis. Data were available to permit subgroup analysis by arterial segment at six and 12 months for the following outcomes: amputation, late lumen loss, target lesion revascularization, binary restenosis, death, change in Rutherford category, and change in ABI.

Amputation

There was no significant difference in the incidence of amputation by arterial segment at six months (Analysis 5.1; OR 1.87, 95% CI 0.40 to 8.75; 415 participants; 5 studies for femoropopliteal vessels versus OR 1.00, 95% CI 0.06 to 16.63; 72 participants; 1 study for tibial vessels; P = 0.70) or 12 months (Analysis 6.1; OR 2.21, 95% CI 0.23 to 21.51; 1033 participants; 5 studies for femoropopliteal vessels versus OR 1.95, 95% CI 0.78 to 4.89; 562 participants; 3 studies for tibial vessels; P = 0.92).

Exclusion of BIOLUX P-I and FemPac 2008 did not result in a significant change in the incidence of amputation for DEB compared with uncoated balloon angioplasty at six months (Analysis 5.8; OR 4.47, 95% CI 0.49 to 40.67; 268 participants; 3 studies for femoropopliteal vessels) and 12 months (Analysis 6.9; OR 2.21, 95% CI 0.23 to 21.51; 973 participants; 4 studies for femoropopliteal vessels versus OR 2.10, 95% CI 0.79 to 5.59; 490 participants; 2 studies for tibial vessels).

Late lumen loss

Comparison of the arterial segment subgroups demonstrated a significant difference in late lumen loss favoring the DEB arm of the femoropopliteal group at six months (Analysis 5.2; MD -0.65 mm, 95% CI -0.86 to -0.45; 423 participants; 5 studies for femoropopliteal vessels versus MD 0.02 mm, 95% CI -0.23 to 0.27; 105 participants; 1 study tibial vessels; P < 0.0001) and 12 months (Analysis 6.2; MD -1.20 mm, 95% CI -1.86 to -0.54; 102 participants; 1 study for femoropopliteal vessels versus MD -0.01 mm, 95% CI -0.18 to 0.16; 358 participants; 1 study for tibial vessels; P = 0.0006).

Exclusion of BIOLUX P-I and FemPac 2008 did not result in a significant change in the late lumen loss advantage of DEB compared with uncoated balloon angioplasty at six months (Analysis 5.9; MD -0.92 mm, 95% CI -1.27 to -0.57; 268 participants; 3 studies for femoropopliteal vessels).

Given the intrinsic lumen diameter differences between femoropopliteal and tibial vessels, the implications of this analysis are limited.

Target lesion revascularization

Comparison of the arterial segment subgroups demonstrated a significant advantage in target lesion revascularization for the DEB arm of the femoropopliteal subgroup, but there was no significant difference between the DEB and control arms of the tibial subgroup at six months (Analysis 5.3; OR 0.22, 95% CI 0.12 to 0.41; 423 participants; 5 studies for femoropopliteal vessels versus OR 0.91, 95% CI 0.26 to 3.18; 105 participants; 1 study for tibial vessels; P = 0.05) and 12 months (Analysis 6.3; OR 0.26, 95% CI 0.13 to 0.56; 1230 participants; 7 studies for femoropopliteal vessels versus OR 0.65, 95% CI 0.30 to 1.44; 595 participants; 3 studies for tibial vessels; P = 0.10).

Exclusion of BIOLUX P-I, BIOLUX P-II, and FemPac 2008 did not result in a significant change in the target lesion revascularization advantage of DEB compared with uncoated balloon angioplasty at six months (Analysis 5.10; OR 0.23, 95% CI 0.11 to 0.48; 268 participants; 3 studies for femoropopliteal vessels) and 12 months (Analysis 6.10; OR 0.28, 95% CI 0.10 to 0.73; 1075 participants; 5 studies for femoropopliteal vessels versus OR 0.52, 95% CI 0.18 to 1.52; 490 participants; 2 studies for tibial vessels; P = 0.23).

Binary restenosis

There was a significant advantage for DEB in the incidence of binary femoropopliteal vessel restenosis compared with uncoated balloon angioplasty at six months (Analysis 5.4; OR 0.26, 95% CI 0.15 to 0.46; 348 participants; 4 studies for femoropopliteal vessels versus OR 1.85, 95% CI 0.78 to 4.39; 105 participants; 1 study for tibial vessels; P = 0.0002). However, this effect was not sustained at 12 months (Analysis 6.4; OR 0.37, 95% CI 0.11 to 1.26; 578 participants; 2 studies for femoropopliteal vessels versus OR 0.40, 95% CI 0.05 to 3.14; 516 participants; 2 studies for tibial vessels; P = 0.96).

Exclusion of BIOLUX P-I and FemPac 2008 did not result in a significant change in the binary restenosis advantage of DEB compared with uncoated balloon angioplasty at six months (Analysis 5.11; OR 0.26, 95% CI 0.12 to 0.57; 193 participants; 2 studies).

Death

Comparison of the arterial segment subgroups demonstrated no difference in mortality between DEB and uncoated balloon angioplasty at six months (Analysis 5.5; OR 0.66, 95% CI 0.22 to 1.97; 415 participants; 5 studies for femoropopliteal vessels versus OR 2.06, 95% CI 0.18 to 23.77; 72 participants; 1 study for tibial vessels; P = 0.41) and 12 months (Analysis 6.5; OR 0.67, 95% CI 0.31 to 1.46; 1033 participants; 5 studies for femoropopliteal vessels versus OR 1.41, 95% CI 0.73 to 2.74; 562 participants; 3 studies for tibial vessels; P = 0.15).

Exclusion of BIOLUX P-I, BIOLUX P-II, and FemPac 2008 did not result in a significant change in mortality for DEB compared with uncoated balloon angioplasty at six months (Analysis 5.12; OR 0.57, 95% CI 0.15 to 2.11; 268 participants; 3 studies for femoropopliteal vessels) and 12 months (Analysis 6.11; OR 0.77, 95% CI 0.34 to 1.73; 973 participants; 4 studies for femoropopliteal vessels versus OR 1.40, 95% CI 0.69 to 2.83; 490 participants; 2 studies for tibial vessels; P = 0.27).

Change in Rutherford category

Comparison of the arterial segment subgroups demonstrated no difference in Rutherford category between DEB and uncoated balloon angioplasty at six months (Analysis 5.6; MD 0.04, 95% CI -0.42 to 0.50; 177 participants; 2 studies for femoropopliteal vessels versus MD -0.60, 95% CI -1.64 to 0.44; 72 participants; 1 study for tibial vessels; P = 0.27) and 12 months (Analysis 6.6; MD 0.09, 95% CI -0.58 to 0.77; 551 participants; 2 studies for femoropopliteal vessels versus MD 0.60, 95% CI -0.46 to 1.66; 72 participants; 1 study for tibial vessels; P = 0.43).

Exclusion of FemPac 2008 did not result in a significant change in Rutherford category between DEB and uncoated balloon angioplasty at six months (Analysis 5.13; MD -0.01, 95% CI -0.09 to 0.08; 177 participants; 2 studies for femoropopliteal vessels).

Change in ankle-brachial index

There was a significant change in ABI advantage for uncoated balloon angioplasty compared with DEB in tibial vessels, but this advantage was not seen in femoropopliteal vessels at six months (Analysis 5.7; MD 0.07, 95% CI -0.09 to 0.22; 264 participants; 3 studies for femoropopliteal vessels versus MD -0.20, 95% CI -0.31 to -0.09; 105 participants; 1 study for tibial vessels; P = 0.007) and 12 months (Analysis 6.7; MD -0.01, 95% CI -0.05 to 0.03; 551 participants; 2 studies for femoropopliteal vessels versus MD -0.20, 95% CI -0.31 to -0.09; 105 participants; 1 study for tibial vessels; P = 0.003).

Exclusion of FemPac 2008 did not result in a significant change in ABI between DEB and uncoated balloon angioplasty for femoropopliteal vessels at six months (Analysis 5.13; MD -0.01, 95% CI -0.09 to 0.08; 177 participants; 2 studies for femoropopliteal vessels).

Severity of peripheral arterial disease

Two trials included only participants with CLI (Rutherford class 4 or greater) (DEBATE-BTK 2013; IN.PACT DEEP 2014). The other trials included participants with varying degrees of PAD but did not stratify the outcomes by severity of PAD and as such were excluded from this subgroup analysis. Data were only available to permit subgroup analysis for participants with CLI at 12 months for the following outcomes: amputation, late lumen loss, target lesion revascularization, binary restenosis, and death.

There was no significant difference in the incidence of amputation between the DEB and control arms in participants with CLI (Analysis 7.1; OR 2.10, 95% CI 0.79 to 5.59; 490 participants; 2 studies). Similarly, there was no difference in late lumen loss (Analysis 7.2; MD -0.01 mm, 95% CI -0.18 to 0.16; 358 participants; 1 study), target lesion revascularization (Analysis 7.3; OR 0.52, 95% CI 0.18 to 1.52; 490 participants; 2 studies); binary restenosis (Analysis 7.4; OR 0.40, 95% CI 0.05 to 3.14; 516 participants; 2 studies); or death (Analysis 7.5; OR 1.40, 95% CI 0.69 to 2.83; 490 participants; 2 studies), between the DEB and control arms in participants with CLI.

DISCUSSION

Summary of main results

DEB angioplasty was associated with improved primary vessel patency and late lumen loss for up to two years and target lesion revascularization and binary restenosis rates for up to five years.

However, there was no advantage for DEB in clinical endpoints such as amputation, change in Rutherford class, QoL scores, functional walking ability, or mortality compared with uncoated balloon angioplasty. On subgroup analysis, DEB angioplasty showed improved late lumen loss, target lesion revascularization, and binary restenosis for up to six months, and late lumen loss and target lesion revascularization for up to 12 months in femoropopliteal vessels. However, DEB angioplasty of tibial vessels was not superior to uncoated balloon angioplasty in any domains. Furthermore, DEB angioplasty was not superior to uncoated balloon angioplasty in people with CLI.

Overall completeness and applicability of evidence

We included 11 prospective randomized trials that were designed to compare clinical differences after DEB versus uncoated balloon angioplasty. The trial endpoints in all of the included studies were clinically relevant, patient-oriented, and included a widely utilized mix of anatomic and clinical endpoints, which makes our findings clinically applicable.

While the trials had several limitations (listed in Assessment of risk of bias in included studies), most were conducted at high-volume centers with experience in device-efficacy trials. Three trials were at a high risk of bias and their impact was assessed with serial sensitivity analyses, but in most instances their exclusion had no significant impact (BIOLUX P-I; BIOLUX P-II; FemPac 2008).

A limitation of our subgroup analysis was that there were only three trials available for the tibial vessel analysis (BIOLUX P-II; DEBATE-BTK 2013; IN.PACT DEEP 2014), and only two trials for the CLI subgroup analysis (DEBATE-BTK 2013; IN.PACT DEEP 2014). As such, it is unclear whether the subgroup analysis results were due to the effects of tibial arteries or CLI. Furthermore, we were unable to carry out any subgroup analyses by severity of PAD because none of the trials reported their outcomes by degree of severity.

Finally, several of the ongoing trials (listed in Characteristics of ongoing studies table) have not published their results in peer-reviewed publications despite having completed enrolment for several years. Two of those trials started enrolling participants in 2008 (Advance 18PTX Balloon Catheter Study; PICCOLO). This is concerning for possible reporting bias if those privately sponsored trials were not published because of unfavorable results. We have attempted to contact the authors of all ongoing trials with limited success.

We have identified several trials that are still enrolling participants or have not published their results, and several of the studies included in our analysis have not yet published their long-term results. As such, future versions of this review will hopefully be able to provide better evidence for the efficacy of DEB in managing lower-limb ischemia.

Quality of the evidence

There was heterogeneity in the frequency of stent deployment and the type and duration of antiplatelet therapy between trials. Using GRADE assessment criteria, the quality of the evidence presented was low for the outcome of target lesion revascularization; moderate for binary restenosis and change in Rutherford category; and high for amputation, primary vessel patency, death, and change in ABI.

The included studies were powered to detect anatomic endpoints that were measured according to angiographic and ultrasound imaging criteria. As such, caution must be taken in interpreting the clinical endpoint results, since the included studies were unlikely to be powered to specifically assess those endpoints.

Risk of selection bias was low in most of the studies. Conversely, performance bias was uniformly high because of the difficulty in blinding operators to the interventions. However, this, is a limitation intrinsic to most surgical and procedural trials. The included studies mostly took adequate steps to address this limitation by implementing measures, such as independent core lab evaluation, to avoid detection bias. While follow-up compliance was good in half of the included studies, most studies were at low risk for reporting bias.

There was a substantial amount of heterogeneity in the studies that may have biased the analysis. First, while the DEB in all of the included studies employed the mitotic inhibitor paclitaxel, the medication doses varied and were not consistently reported. Second, the DEB devices in the studies employed different drug carriers, as described in Schnorr 2013. The effect of different drug carriers on the results was not clear. Third, the type and duration of antiplatelet therapy differed between trials. Finally, the wide use of stenting in most of the included trials invariably affected the outcomes, but few data were available on the stented subgroups of participants.

It is unclear what criteria were used to determine the need for target lesion revascularization, resulting in heterogeneity between studies reporting this outcome. While most studies stated that target lesion revascularization was carried out for clinically driven indications (BIOLUX P-I; DEBATE-BTK 2013; DEBELLUM 2012; IN.PACT DEEP 2014; IN.PACT SFA 2015; LEVANT II 2015; PACIFIER 2012), those indications were not defined or explained.

Those limitations notwithstanding, our analysis demonstrates an advantage for DEB compared with uncoated balloon angioplasty in the management of PAD for up to two years of follow-up in several anatomic endpoints. There is insufficient evidence to support an advantage for either treatment modality beyond two years. However, with many other ongoing or unreported studies, short- and long-term data will hopefully become available to assess the efficacy of this treatment modality better in the near future.

Potential biases in the review process

We carried out our review in a transparent manner consistent with Cochrane guidelines. We conducted intention-to-treat analysis on all of the data in this study, and used the initial number of randomized participants in each study arm for all subsequent calculations regardless of participant death or loss to follow-up. We encountered difficulty in obtaining unpublished information from some study authors (IN.PACT SFA 2015; LEVANT I 2014; LEVANT II 2015). Despite several attempts to contact the authors with requests for information, only three authors provided us with data for this analysis (BIOLUX P-I; BIOLUX P-II; DEBELLUM 2012). One trial reported medians instead of means for late lumen loss and change in ABI (FemPac 2008). We converted the median values to means and included them in the analysis. A subsequent sensitivity analysis did not demonstrate a significant impact of this study's inclusion on our results. Finally, our analysis at five years was based on only one study (THUNDER 2008).

Agreements and disagreements with other studies or reviews

In the past few years, several meta-analyses have compared DEB with uncoated balloon angioplasty for femoropopliteal and tibial arterial lesions.

Baerlocher 2015 reported an advantage for DEB in the anatomic endpoints of late lumen loss, binary restenosis, and target lesion revascularization, and no advantage in clinical endpoints at 12 months. However, their analysis included IDEAS 2014, which compared DEB to drug-eluting stents. The authors also carried out a tibial vessel analysis using DEBATE-BTK 2013 and DEBELLUM 2012 and reported an advantage for DEBs in target lesion revascularization and binary restenosis at 12 months. We did not include DEBELLUM 2012 in our tibial vessel subgroup analysis because the authors of that study included both femoropopliteal and tibial lesions but did not report the results separately.

Canaud 2014 also reported an advantage for DEB in target lesion revascularization and binary restenosis. However, the authors included fewer randomized trials and included two case series (Micari 2012; Schmidt 2011).

Cassese 2012 analyzed four randomized controlled trials, which were also included in our analysis, and similarly reported an advantage for target lesion revascularization, binary restenosis, and late lumen loss compared with uncoated balloon angioplasty for femoropopliteal lesions.

Finally, Jens and colleagues reported an advantage for DEB compared with uncoated balloon angioplasty in target lesion revascularization of femoropopliteal arterial lesions but no difference in clinical endpoints (Jens 2014a). The authors also reported an advantage for DEB in wound healing, target lesion revascularization, binary restenosis, and change in Rutherford classification in treating tibial arterial lesions based on the DEBATE BTK trial (Jens 2014b). However, our tibial subgroup analysis included both DEBATE-BTK 2013 and IN.PACT DEEP 2014 and demonstrated no advantage for DEB compared with uncoated balloon angioplasty in anatomic or clinical endpoints. Furthermore, the change in Rutherford classification data reported by Jens and colleagues was not included in the manuscript published by Liistro and colleagues when DEBATE-BTK 2013 was published.

AUTHORS' CONCLUSIONS

Implications for practice

Our analysis has demonstrated an advantage for drug-eluting balloon (DEB) angioplasty compared with uncoated balloon angioplasty in treating lower extremity peripheral arterial disease (PAD) for up to five years in several domains. The quality of the evidence was low to high depending on the outcome. The advantage of DEB is limited to anatomic endpoints such as primary vessel patency, late lumen loss, target lesion revascularization, and binary restenosis. However, there is insufficient evidence to compare DEB and uncoated balloon angioplasty adequately in clinical outcomes such as change in quality of life (QoL) and walking impairment score.

Given the high re-intervention rates in people with PAD, the superiority of DEB compared with uncoated balloon angioplasty in the anatomic endpoints reported in our analysis is encouraging. However, rigorous long-term clinical outcome data are needed before one can conclude that DEB are superior to uncoated balloon angioplasty, especially given the considerably increased costs currently associated with DEB.

Implications for research

Future well-designed, publicly funded trials that are adequately powered to detect meaningful clinical endpoints, such as amputation and change in QoL, are needed to assess the utility of DEBs in the management of people with lower-extremity PAD better, and to allow for the stratification of outcomes by arterial segment and indication for the intervention. However, given the small effect size differences in clinical endpoints between DEB and uncoated balloon angioplasty, and the rapidly evolving endovascular treatment modalities for PAD, it is unlikely that there will be any future randomized controlled trials powered to detect clinical endpoints because of the substantial cost and logistic challenges involved. We identified 13 studies that are either ongoing or are pending publication, in addition to the 11 studies included in our analysis. The eventual publication of short- and long-term data from those studies will hopefully allow for a more rigorous analysis in future versions of this review. Furthermore, as data from more studies becomes available, we plan to perform more subgroup analyses by paclitaxel dose and type of carrier used in the DEB.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

BIOLUX P-I

Methods	Study design: randomized controlled trial
	Method of randomization: computer-generated randomization lists

BIOLUX P-I *(Continued)*

	Blinding: participants were blinded but the operators were not blinded Exclusions postrandomization: none Losses to follow-up: 5 Study enrollment period: October 2010 to August 2011 Cross-over: 0
Participants	Country: Austria and Germany Setting: 4 German hospitals and 1 Austrian hospital Number of participants: 60 (68 lesions) Age (mean ± SD): 71 ± 10 years Gender: male 57% Rutherford class: DEB: class 2: 23.3%, class 3: 56.7%, class 4: 13.3%, class 5: 6.7%; PTA: class 2: 30%, class 3: 56.7%, class 4: 6.7%, class 5: 6.7% ABI (± SD): 0.7 ± 0.2 Inclusion criteria: • Age ≥ 50 years • Informed consent signed by participant prior to randomization • Single or sequential de novo or re-stenotic lesions (stenosis ≥ 70% diameter reduction or occlusion) in the femoropopliteal arteries ≥ 30 mm and ≤ 200 mm long • Rutherford class 2 to 5 in the target limb • RVD 3 mm to 7 mm, based on visual estimation • Inflow free from flow-limiting lesion (< 50% stenosis) confirmed by angiography. People with flow-limiting inflow lesions (> 50% stenosis) could be included if lesion had been treated successfully before the index procedure • At least 1 nonoccluded crural vessel (e.g. without significant stenosis) with angiographically documented runoff to the foot • Successful wire crossing of the lesion • Willingness to comply with all specified follow-up evaluations • Male or negative pregnancy test of women in childbearing age Exclusion criteria: • Comorbid conditions limiting life expectancy ≤ 1 year • People currently participating in another clinical trial • Lesions that were untreatable with PTA or other intervention techniques • The target stenosis located distal to a stenosis ≥ 50% that could not be pretreated because the drug coating could get lost during crossing the proximal lesion • Thrombus in the target vessel, documented by angiography • Target lesion severely calcified, documented by angiography • Prior bypass surgery of target vessel • Previously implanted stent in the target lesion • Treatment of bifurcation required • Planned amputation of the target limb • Flow-limiting (> 50% DS) inflow lesion proximal to target lesion, left untreated • Failure to obtain < 30% residual stenosis in a pre-existing hemodynamically significant (> 50% DS) inflow lesion in the ipsilateral iliac or proximal SFA (DEB or DES not allowed for the treatment of inflow lesion)

BIOLUX P-I *(Continued)*

	• Additional hemodynamically relevant proximal and distal lesions with stenosis ≥ 50%, except iliac arteries, excluded. Iliac artery lesion treatments had to be successful with a residual stenosis ≤ 30% • Hemorrhagic diathesis or another disorder such as gastrointestinal ulceration or cerebral circulatory disorders that restricted the use of platelet aggregation inhibitor therapy and anticoagulation therapy • Phenprocoumon intake • Impaired renal function (creatinine ≥ 2.0 mg/dL to 2.5 mg/dL), according to investigator assessment • Known allergy to contrast media that could not be adequately controlled with premedication • Allergy, intolerance or hypersensitivity to paclitaxel structurally or related compounds or to the delivery matrix BTHC, or both
Interventions	Uncoated balloon angioplasty: 30 participants, 35 lesions Uncoated balloon angioplasty device: Passeo-18 PTA catheter DEB: 30 participants, 33 lesions DEB device: Passeo-18 Lux drug-releasing balloon catheter Drug used: paclitaxel 3 µg/mm^2 balloon surface Vessels treated: femoropopliteal arteries Anticoagulation/platelets: dual antiplatelet therapy recommended for 1 month postprocedure and for 3 months in case of bailout stenting with a bare metal stent Predilation before DEB: yes: 66.7% of DEB and 30% of PTA procedures
Outcomes	Primary: • Late lumen loss, assessed by QVA analysis Secondary: • Binary restenosis rate, defined as a diameter reduction > 50% at the time of follow-up • TLR rate • Change in mean ABI • Change in Rutherford classification • MAE rate (procedure- or device-related death or amputation, target lesion thrombosis and clinically driven TLV)
Notes	Clinical and angiographic follow-up was scheduled at 6 months ± 30 days and clinical follow-up at 12 months ± 30 days 6% of participants were treated in the anterior and posterior tibial arteries Sponsor: Biotronik AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization lists were computer generated"
Allocation concealment (selection bias)	Low risk	"Sealed envelopes with the randomization group included were provided to the sites"
Blinding of participants and personnel (performance bias)	High risk	"The operators could not be blinded to the assigned treatment, which might have affected the rate of predilation and bailout stenting"

BIOLUX P-I *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"QVA analysis was performed by an independent core laboratory (MedStar Health Research Institute, Washington, DC, USA), and the study was supervised by an independent clinical events committee and data safety monitoring board"
Incomplete outcome data (attrition bias) All outcomes	High risk	"Follow-up compliance was low, with 4 subjects withdrawing consent and 5 patients lost to follow-up"
Selective reporting (reporting bias)	Low risk	The authors reported all prespecified outcomes
Other bias	High risk	Predilation was performed more often in people receiving DEB than PTA (66.7% with DEB vs. 30% with PTA, P = 0.010), and technical success was higher in the DEB group (76.7% with DEB vs. 46.7% with PTA, P = 0.017). 26.7% of the control arm required bailout stenting. Most of the people receiving DEB (56.7%) and PTA (60%) had a history of previous peripheral interventions, although the type and location of those interventions was not specified

BIOLUX P-II

Methods	Study design: randomized controlled trial Method of randomization: electronic case report form after successful wire passage through the target lesion Blinding: neither the participants nor the operators were blinded to the procedure Exclusions postrandomization: 0 exclusions after randomization Losses to follow-up: 3 lost to follow-up and 4 withdrew (DEB), 2 lost to follow-up (PTA) Study enrollment period: July 2012 to June 2013 Cross-over: 0
Participants	Country: Austria, Belgium, and Germany. Setting: 1 hospital in Austria, 2 in Belgium, and 3 in Germany Number of participants: 72 Age (mean ± SD): 72.9 ± 10.3 years (DEB), 69.6 ± 8.9 years (PTA) Gender: males: DEB 27 (75%), PTA 30 (83%) Rutherford class: DEB: class 2: 2.8%, class 3: 19.4%, class 4: 5.6%, class 5: 72.2%; PTA: class 2: 8.3%, class 3; 13.9%, class 4: 5.6%, class 5: 72.2% ABI (± SD): DEB: 0.8 ± 0.3, PTA: 0.7 ± 0.3 Inclusion criteria: • Written informed consent • Willing and able to comply with follow-up evaluations • Age ≥ 18 years • Single or sequential de novo or restenotic lesions (stenosis ≥ 70% diameter reduction or occlusion) in the infrapopliteal arteries ≥ 30 mm. Lesions should not have extend beyond the ankle joint

BIOLUX P-II *(Continued)*

- Maximum of 2 different vessels could be treated: successful wire crossing required for the first target vessel before randomization occurred
- Participant with PAD or CLI according to the current guidelines in need for urgent revascularization to relieve symptoms and improve walking capacity
- RVD 2 mm to 4 mm, based on visual estimation
- Inflow free from flow-limiting lesion confirmed by angiography. People with flow-limiting inflow lesions (> 50% stenosis) could be included if lesion(s) had been treated successfully before the index procedure, with a maximum residual stenosis of 30% per visual assessment
- At least 1 nonoccluded crural vessel with angiographically documented runoff to the foot
- Successful wire crossing of the lesion

Exclusion criteria:

- Flow-limiting (> 50% DS) inflow lesion proximal to target lesion, left untreated
- Failure to obtain < 30% residual stenosis in a pre-existing hemodynamically significant (> 50% DS) inflow lesion (DEB or DES not allowed for the treatment of inflow lesions)
- Infrapopliteal lesions extending beyond the ankle joint and involving crural vessels
- Acute thrombus in the target vessel (e.g. complication of inflow lesion treatment) documented by angiogram, if not treated successfully prior to enrolment)
- Planned major amputation above the ankle of target limb, or any other planned major surgery within 30 days postprocedure
- Previous bypass surgery of target vessel
- Previously implanted stent in target lesion
- Hemorrhagic diathesis or coagulopathy or other disorders such as gastrointestinal ulcerations or cerebral disorders that would restrict prescription of dual antiplatelet therapy
- Hepatic failure, deep vein thrombosis, thrombophlebitis, systemic lupus erythematous, or taking immunosuppressant therapy.
- Acute MI ≤ 3 months
- Renal failure with a creatinine of ≥ 2.5 mg/dL, except people currently on regular dialysis
- Phenprocoumon intake, except for people treated for arterial fibrillation. For these people, phenprocoumon treatment could be interrupted and restarted after treatment with dual antiplatelet therapy for 4 weeks postprocedure
- Known allergy to contrast media used for angiography that could not be controlled by premedication with steroids, antihistamines, or both
- Allergy, intolerance, or hypersensitivity to paclitaxel or related compounds or to the delivery matrix BTHC, or both
- Comorbid conditions limiting life expectancy ≤ 1 year
- Under active treatment for cancer; people who had been successfully treated for cancer in the past could be included
- Participating in another clinical device trial where the primary endpoint had not yet been reached
- Pregnant, breastfeeding, or both or women who intend to become pregnant during the time of the study

Interventions	Uncoated balloon angioplasty: 36 participants (55 lesions) Uncoated balloon angioplasty device: uncoated Passeo-18 PTA balloon catheter DEB: 36 participants (50 lesions) DEB device: Passeo-18 LUX drug-releasing PTA balloon catheter Drug used: paclitaxel 3 µg/mm^2 balloon surface Vessels treated: infrapopliteal arteries Anticoagulation/platelets: dual antiplatelet therapy with ASA 100 mg/day to 325 mg/day and clopidogrel 75 mg/day for 1 month postprocedure and for 3 months in case of bailout stenting with a bare-metal stenting

BIOLUX P-II *(Continued)*

	Predilation before DEB: yes for DEB but not PTA
Outcomes	Primary: • MAE, defined as all-cause death, major amputation of target extremity, target lesion thrombosis, TLV and TVR at 30 days • Performance: target lesion primary patency rate at 6 months, defined as < 50% restenosis in the target lesion assessed by QVA without TLR Secondary: • Target lesion failure • TVR • Binary restenosis rate • MAE rate, defined as all-cause death, major amputation of target extremity, target lesion thrombosis, TLR and TVR at 6 months and 12 months • Change in mean ABI • Change in Rutherford classification • QoL evaluation, assessed by EQ-5D questionnaire • Duplex-based primary patency • Procedural success, defined as successful vascular access, completion of endovascular procedure and immediate morphologic success with a residual stenosis < 30% • Device success, defined as exact deployment according to instructions for use. • Technical success, defined as device or procedural success without the occurrence of MAEs during the hospital stay • Late lumen loss
Notes	Clinical follow-up scheduled at 30 days, 6 months, and 12 months, and angiographic follow-up at 6 months Sponsor: Biotronik AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed after successful wire passage through the lesion via the electronic case report form. Patients were allocated to DEB and PTA in a 1:1 ratio, with block sizes of 4 and 6"
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided to assess allocation concealment bias adequately
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither the participants nor the operators were blinded to the procedure
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Quantitative vascular angiography (QVA) analysis was performed by an independent core laboratory that was blinded to the treatment, and all adverse events were adjudicated by an independent clinical events committee"
Incomplete outcome data (attrition bias) All outcomes	High risk	19% of the DEB arm either withdrew from the study or were lost to follow-up at 12 months
Selective reporting (reporting bias)	High risk	All prespecified outcomes were reported in the paper or provided by the authors through electronic correspondence. However, the results were not strat-

BIOLUX P-II *(Continued)*

		ified by the type of treated infrapopliteal vessels (i.e. anterior tibial, posterior tibial, or peroneal arteries). The authors also did not specify whether those participants with more than 1 target lesion (33.3% of people with DEB and 44.4% with PTA) had several target vessels and whether the outcomes differed by the number of treated lesions and vessels
Other bias	High risk	While no bailout stenting was required in either treatment arm, the authors had a relatively low technical success rate (defined as < 30% residual stenosis) in both arms (54.2% DEB, 59.6% PTA)

DEBATE-BTK 2013

Methods	Study design: randomized controlled trial Method of randomization: concealed randomization in blocks of 10 using computer software and sealed envelopes after successful passage of the guidewire Blinding: participants and outcomes assessors were blinded Exclusions postrandomization: 24 Losses to follow-up: 0 Study enrollment period: November 2010 to October 2011 Cross-over: 0
Participants	Country: Italy Setting: hospital - single center Number of participants: 132 (158 lesions in 143 limbs) Age (mean): 75 years Gender: 106 men, 26 women Rutherford class: DEB: class 4: 2.8%, class 5: 78.9%, class 6: 18.3%; PTA: class 4: 4.2%, class 5: 81.9%, class 6: 13.9% ABI (± SD): DEB: 0.31 ± 0.2, PTA: 0.29 ± 0.3 Inclusion criteria: • Diabetes • Rutherford category ≥ 4 • Stenosis or occlusion ≥ 40 mm of ≥ 1 tibial vessel with distal runoff to the foot • Agreement to 12-month angiographic evaluation Exclusion criteria: • Life expectancy < 1 year • Allergy to paclitaxel • Contraindication to combined antiplatelet treatment • Planned major amputation before angiography
Interventions	Uncoated balloon angioplasty: 67 (78 lesions in 72 limbs) Uncoated balloon angioplasty device: Amphirion Deep, Medtronic DEB: 65 (80 lesions in 71 limbs)

DEBATE-BTK 2013 *(Continued)*

	DEB device: IN.PACT Amphirion, Medtronic Drug used: paclitaxel (dose unknown) Vessels treated: BTK vessels Anticoagulation/platelets: heparin 70 IU/kg after sheath insertion, ASA 100 mg and clopidogrel 75 mg ≥ 4 weeks then ASA 100 mg alone daily Predilation before DEB: yes
Outcomes	Primary: • Angiographic restenosis at 1 year Secondary: • Major amputation at 2 years • TLV at 2 years • Vessel reocclusion at 2 years
Notes	Clinic visits twice weekly for 2 months, then once weekly for third month, then every 2 weeks for duration of study Doppler ultrasound within 12 months Angiogram at 12 months or during target-lesion revascularization Sponsor: no industry support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed in blocks of 10 with the use of computer-generated random digits"
Allocation concealment (selection bias)	Low risk	"The assignments were placed in sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Double blind (subject, outcomes assessor)". The authors suggest that those performing the procedure were not blinded, although this was not addressed in the manuscript
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Acquired angiograms and DUS [duplex ultrasound] scans were reviewed by 2 blinded investigators who did not actively participate in recruitment […] and had no knowledge of clinical status and randomization group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No patient was lost to follow-up." Causes of participant mortality and lack of follow-up imaging were reported
Selective reporting (reporting bias)	High risk	While all prespecified outcomes were reported, the authors state that, "inflow lesions located in the femoropopliteal segment were treated by standard techniques during the same session." The authors did not clarify what those techniques were and how many such lesions were treated
Other bias	Low risk	The authors state that 1 participant in each group required a DES at the end of the procedure

DEBELLUM 2012

Methods	Study design: randomized controlled trial Method of randomization: participants were randomized (1:1) without stratification using computer-generated assignments when they entered the angiographic suite Blinding: participants but not operators were blinded to the assigned intervention Exclusions postrandomization: 4 Losses to follow-up: 0 Study enrollment period: September 2010 to March 2011 Cross-over: 0
Participants	Country: Italy Setting: hospital - single center Number of participants: 54 randomized, 50 analyzed, 28 participants meeting study criteria Age (mean ± SD): 66 ± 4 years Gender: male 74% Fontaine class: DEB: class IIb (64%), class III (28%), class IV (8%); PTA: class IIb (60%), class III (28%), class IV (12%) ABI (± SD): DEB: 0.55 ± 0.06, PTA: 0.57 ± 0.05 Inclusion criteria: • Single or multiple lesions (stenosis or occlusion 3 cm to 30 cm) in the native SFA, the popliteal, or the BTK arteries, or with concomitant multilevel disease Exclusion criteria: • Instent restenosis, aneurysms, acute thrombosis, pregnancy, life expectancy < 1 year, and absence of a patent crural artery • Requiring provisional or bailout stenting after angioplasty as a result of flow-limiting dissection or residual stenosis > 50%
Interventions	Uncoated balloon angioplasty: 27 participants Uncoated balloon angioplasty device: noncoated IN.PACT Admiral (SFA) and noncoated IN.PACT Amphirion (BTK), Medtronic DEB: 27 participants DEB device: IN.PACT Admiral (SFA) and IN.PACT Amphirion (BTK), Medtronic Drug used: paclitaxel (dose unknown) Vessels treated: femoropopliteal (75.4%) and BTK (24.6%) vessels Anticoagulation/platelets: ASA 100 mg/day and clopidogrel 75 mg/day for 3 days preprocedure. If participant was not receiving antiplatelet therapy preoperatively then clopidogrel 300 mg loading dose was administered. Heparin 5000 U administered after sheath insertion. Clopidogrel continued for 4 weeks Predilation before DEB: yes

DEBELLUM 2012 *(Continued)*

Outcomes	Primary: • Late lumen loss at 6 and 12 months in the SFA and BTK vessels Secondary: • Binary restenosis (> 50%) • Acute thrombotic occlusion of an artery within 48 hours of the procedure • Any reintervention performed for thrombosis or restenosis (> 50% DS) of the target lesion after documentation of recurrent ischemic symptoms (TLR) • Amputation at 6, 12, and 24 months
Notes	Late lumen loss was the difference in millimeters between the MLD immediately after the procedure and the MLD during follow-up One third of participants received stents Substantial number of participants with TASC II C (33.6%) and D (10.6%) lesions Participants were followed-up at 6, 12, and 24 months Duplex follow-up in femoropopliteal region and angiography in the BTK arterial region Sponsor: no industry support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized (1:1) without stratification using computer-generated assignments when they entered the angiographic suite"
Allocation concealment (selection bias)	Low risk	"Patients were randomized (1:1) without stratification using computer-generated assignments when they entered the angiographic suite"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Patients, but not operators, were blinded to the assigned intervention"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Postoperative evaluation was deferred to different physicians not informed about the assigned intervention". Unclear what type of physicians performed those evaluations and what type of qualifications they had
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 participants reported as lost to follow-up and no missing data
Selective reporting (reporting bias)	Low risk	Restenosis rate not reported at 1 year. While this omission was concerning, the remaining outcomes were reported and as such this single omission does not, in our opinion, place the study at a high risk of reporting bias
Other bias	High risk	"Patients requiring provisional or bailout stenting […] were excluded from the study". "The decision to implant a nitinol stent in the SFA territory was left to the judgment of the operator and typically driven by lesion length and presence of severe calcification" The stent deployment criteria are unclear and approximately 37% of the treated lesions were also stented

FemPac 2008

Methods	Study design: randomized controlled trial Method of randomization: central randomization in advance for all participants without stratification. Random list portions assigned to participating centers Blinding: attempt at blinding operators but success unclear because of differences in appearance between the coated and uncoated balloons Exclusions postrandomization: 0 Losses to follow-up: 19 (withdrew consent or declined angiography because of another reason) Study enrollment period: July 2004 to January 2006 Cross-over: 0
Participants	Country: Germany Setting: 2 academic hospitals Number of participants: 87 Age (median): 67.3 years (DEB), 70.2 years (PTA) Gender: males: DEB 27 (60%), PTA 25 (60%) Rutherford class: DEB: class 1: 4%, class 2: 22%, class 3: 69%, class 4: 4%; PTA: class 1: 2%, class 2: 17%, class 3: 74%, class 4: 7% ABI (median): DEB: 0.7, PTA: 0.7 Inclusion criteria: • Occlusion or stenosis 70% diameter of the SFA, popliteal artery, or both with clinical Rutherford class 1 to 5 • Age 18 to 90 years • Successful guidewire passage of the lesion Exclusion criteria: • Acute symptoms with an indication for thrombolytic therapy or operation • Leg-threatening ischemia • Distal outflow over < 1 vessel • Manifest hyperthyroidism • Renal insufficiency (creatinine > 2.0 mg/dL) • Major gastrointestinal bleeding within the last 6 months • Intolerance to study medications or contrast dye • Life expectancy < 2 years • Conditions requiring different treatment • Serious safety concerns regarding the procedure • Doubtful willingness or capability of the people to undergo 6-month follow-up
Interventions	Uncoated balloon angioplasty: 42 participants Uncoated balloon angioplasty device: Bavaria Medizin Technologie GmbH (Oberpfaffenhofen, Germany) DEB: 45 participants DEB device: Bavaria Medizin Technologie GmbH (Oberpfaffenhofen, Germany)

FemPac 2008 *(Continued)*

	Drug used: paclitaxel 3 µg/mm^2 balloon surface (mean ± SD: 3.7 ± 2.5 µg per participant) Vessels treated: femoropopliteal arteries Anticoagulation/platelets: clopidogrel 75 mg/day and ASA 100 mg/day were started as long-term medication on the day of angioplasty. After common femoral sheath placement, all participants received an initial bolus of heparin 2500 IU to 5000 IU. Further concomitant medication was documented by the investigator Predilation before DEB: no
Outcomes	Primary: • Late lumen loss at 6 months Secondary: • Restenosis rate (defined as incidence of stenosis > 50%) in the treated lesion at the 6-month follow-up angiography • TLR • Change in mean ABI • Rutherford class at baseline and 6-month visit • Amputation • Thrombotic complications of the target vessel • Clinical adverse events
Notes	Stents were placed in 6 PTA and 4 DEB participants (overall 11%) Late lumen loss defined as the difference between the minimal luminal diameter after the procedure and at 6 months by quantitative angiography Sponsor: balloon catheters provided by Bavaria Medizin Technologie (Oberpfaffenhofen, Germany) and financial support for the study provided by Bayer-Schering-Pharma AG (Berlin, Germany)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done centrally in advance for all patients without any stratification. Portions of the random list (eg, numbers 1 to 30) were assigned to a centre that enrolled the patients in the sequence of the randomization list"
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided in the study to assess allocation concealment bias adequately
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Blinding of the investigators was attempted but not guaranteed because of differences in the appearance of coated and uncoated balloons"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Quantitative evaluation of six-month angiographic control was performed by an independent core laboratory blinded to the type of treatment"
Incomplete outcome data (attrition bias) All outcomes	High risk	6-month primary outcome data available on 73% of participants in intervention arm and 83% in control arm

FemPac 2008 *(Continued)*

Selective reporting (reporting bias)	High risk	"No Doppler or angiographic information was obtained from 7 patients in the control and 9 patients in the coated balloon group"
Other bias	Unclear risk	11% of participants received a stent but clinical outcomes of those participants not reported separately

IN.PACT DEEP 2014

Methods	Study design: randomized-controlled trial Method of randomization: performed using blocks of sealed envelopes Blinding: participant-blinded Exclusions postrandomization: 0 Losses to follow-up: 4 (3 in DEB arm, 1 in PTA arm) Study enrollment period: September 2009 to July 2012 Cross-over: 0
Participants	Country: 13 European centers Setting: hospital, multicenter Number of participants: 358 (DEB 239, PTA 119) Age (mean ± SD): 73.3 ± 8.2 years (DEB), 71.7 ± 9.9 years (PTA) Gender: male 74% Rutherford class: DEB: class 3: 0%, class 4: 14.2%, class 5: 84.1%, class 6: 1.7%; PTA: class 3: 0.8%, class 4: 17.6%, class 5: 77.3%, class 6: 4.2% ABI: DEB: 0.75 ± 0.4, PTA: 0.81 ± 0.44 Inclusion criteria: • Age ≥ 18 years and ≤ 85 years • Women of childbearing potential have a negative pregnancy test ≤ 7 days before the procedure and were willing to use a reliable method of birth control for the duration of study participation • Rutherford category ≥ 4 • Life expectancy > 1 year Exclusion criteria: • Planned amputation • Acute thrombosis • Previously placed stents
Interventions	Uncoated balloon angioplasty: 119 participants Uncoated balloon angioplasty device: standard PTA, unspecified DEB: 239 participants DEB device: IN.PACT Amphirion (Medtronic) Drug used: paclitaxel (dose unknown)

IN.PACT DEEP 2014 *(Continued)*

	Vessels treated: infrapopliteal arteries Anticoagulation/platelets: preprocedure: ASA 100 mg at least 4 days prior to the index intervention, alternatively at least 500 mg loading dose prior to or within 2 hours postprocedure; clopidogrel 75 mg/day at least 4 days prior to the index intervention, alternatively at least 300 mg loading dose prior to or within 2 hours postprocedure (or ticlopidine, if required); the use of bivalirudin was allowed as an alternative to heparin Postprocedure: ASA 100 mg indefinitely and daily clopidogrel 75 mg (or ticlopidine, if required) for at least 1 month following the procedure. Prolonged antiplatelet therapy could be given at the discretion of the physician and should be considered after placement of stents Predilation before DEB: yes: 90.5% of procedures
Outcomes	Primary: • TVR and late lumen loss at 12 months, composite end-point of all-cause death, major amputation and clinically driven TLV Secondary: • Amputation-free survival at 30 days, 3 and 6 months, 1, 2, 3, 4, and 5 years • Rate of wound healing at 30 days, 6 months, 1 and 2 years • Amputation-free survival and wound healing at 6 months, 1 and 2 years • Amputation-free survival and resolved CLI at 6 months, 1 and 2 years • Death, amputation, and clinically driven TLR at 30 days, 6 months, 1 and 2 years • Primary sustained clinical improvement: an improvement shift in the Rutherford classification of 1 class in amputation-free, clinically driven TLR-free surviving participants at 1 year • Secondary sustained clinical improvement: an improvement shift in the Rutherford classification of 1 class including the need for clinically driven TLR in amputation-free surviving participants at 1 year • QoL assessment by EQ-5D at 6 months, 1 and 2 years vs. baseline • Walking capacity assessment by WIQ at 6 months, 1 and 2 years, MAE at 30 days, 6 months, 1, 2, 3, 4, and 5 years • Device success defined as the exact deployment of the device according to the instructions for use as documented with suitable imaging modalities and, in the case of digital subtraction angiography, in at least 2 different imaging projections • Technical success defined as successful vascular access and completion of the endovascular procedure and immediate morphologic success with ≤ 50% residual diameter reduction of the treated lesion on completion angiography • Procedural success defined as combination of technical success, device success, and absence of procedural complications • For the angio cohort: improvement in 12 months of % DS of the target lesion assessed by QVA • Days of hospitalization
Notes	It is unclear which vessels were treated and whether any participants required more than 1 treatment per limb Sponsor: Medtronic, Santa Rosa California

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomization process was performed using blocks of sealed envelopes". The methodology for generating those randomization blocks was not specified
Allocation concealment (selection bias)	Low risk	"The randomization process was performed using blocks of sealed envelopes"

IN.PACT DEEP 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"This trial is a 2:1 randomized, controlled, patient-blinded multicentre trial". This implies that the operators were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Both wound and angiographic core laboratories were blinded to the assigned treatment"
Incomplete outcome data (attrition bias) All outcomes	High risk	"The low angiographic and wound imaging compliance may have limited the full assessment of this therapy"
Selective reporting (reporting bias)	High risk	The published protocol listed several unreported outcomes such as change in Rutherford category and QoL scores. The number of inflow lesions treated and how those lesions were managed not reported
Other bias	Low risk	The outcomes of the 5% of participants who received a stent not reported

IN.PACT SFA 2015

Methods	Study design: randomized controlled trial Method of randomization: participants were randomly assigned by an Interactive Voice Response System with the use of a method of permuted blocks to ensure that a 2:1 ratio was maintained across sites Blinding: single-blinded Exclusions postrandomization: DEB: 13 participants, PTA: 4 participants Losses to follow-up: DEB: 3 participants, PTA: 3 participants Study enrollment period: September 2010 to April 2011 and April 2012 to January 2013 Cross-over: 0 The trial included 2 cohorts: European (IN.PACT SFA I) and North American (IN.PACT SFA II)
Participants	Country: Europe, USA, and Canada Setting: hospital (13 sites in Europe, 44 in the USA and Canada) Number of participants: 331 Age (mean ± SD): 67.5 ± 9.5 years (DEB), 68.0 ± 9.2 years (PTA) Gender: males: DEB 65%, PTA: 67.6% Rutherford class: DEB: class 2: 37.7%, class 3: 57.3%, class 4: 5%, class 5: 0%; PTA: class 2: 37.8%, class 3: 55.9%, class 4: 5.4%, class 5: 0.9% ABI: DEB: 0.769 ± 0.228, PTA: 0.744 ± 0.189 Inclusion criteria: • Moderate to severe intermittent claudication or ischemic rest pain (Rutherford class 2 to 4) and stenosis of 70% to 99% with lesion lengths between 4 and 18 cm or occlusion with lengths of ≤ 10 cm involving the superficial femoral and proximal popliteal arteries Exclusion criteria:

IN.PACT SFA 2015 *(Continued)*

- Unwilling or unlikely to comply with follow-up schedule
- Stroke or STEMI within 3 months prior to enrolment
- Acute or subacute thrombus in the target vessel

Interventions	Uncoated balloon angioplasty: 111 Uncoated balloon angioplasty device: unspecified "standard PTA balloon" DEB: 220 DEB device: IN.PACT Admiral (Medtronic, Santa Rosa, CA) Drug used: paclitaxel 3.5 µg/mm^2 balloon surface Vessels treated: femoropopliteal arteries Anticoagulation/platelets: periprocedural: loading dose of ASA 300 mg to 325 mg and clopidogrel 300 mg within 24 hours of the index procedure or 2 hours postprocedure. Heparin administered at the time of the procedure to maintain an activated clotting time ≥ 250 seconds Postprocedural: ASA 81 mg/day to 325 mg/day (for a minimum of 6 months) and clopidogrel 75 mg/day for a minimum duration of 1 month for nonstented participants and 3 months for participants who received stents Predilation before DEB: yes
Outcomes	Primary: • Primary patency at 12 months following the index procedure (defined as freedom from clinically driven TLV and restenosis (defined as peak velocity ratio ≤ 2.4) Secondary: • 30-day device- and procedure-related mortality • All-cause mortality • Major target limb amputation • Target vessel thrombosis • Acute procedural success • TVR at 12 months • Primary sustained clinical improvement (defined as freedom from target limb amputation, TVR, and increase in Rutherford class at 12 months) • QoL outcomes (using the EQ-5D and the WIQ)
Notes	Primary patency defined as freedom from clinically driven TLV and restenosis as determined by a duplex ultrasonography-derived peak systolic velocity ratio of ≤ 2.4 Participants were followed by the treating physician at 30 days, 6 months, and 12 months, including office visits with duplex ultrasonography functional testing and adverse event assessment Sponsor: Medtronic, Santa Rosa, CA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were randomly assigned by an Interactive Voice Response System with the use of a method of permuted blocks to ensure that a 2:1 ratio was maintained across sites"

IN.PACT SFA 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Subjects were randomly assigned by an Interactive Voice Response System with the use of a method of permuted blocks to ensure that a 2:1 ratio was maintained across sites"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Because of the visual difference between the IN.PACT DCB and standard PTA balloon, treating physicians, research coordinators, and catheterization laboratory staff were not blinded to the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Independent core laboratories analyzed all images, including duplex ultrasonography", "Each component of the primary efficacy end point was independently adjudicated by the blinded Clinical Events Committee"
Incomplete outcome data (attrition bias) All outcomes	Low risk	94% of DEB participants and 96% of PTA participants analyzed at 1 year. "Multiple imputation was performed by using the logistic regression approach for patients with missing primary end point data (29 DCB, 7 PTA)"
Selective reporting (reporting bias)	Low risk	Restenosis rate not reported. While this omission was concerning, the remaining outcomes were reported and as such this single omission does not, in our opinion, place the study at a high risk of reporting bias
Other bias	Unclear risk	The outcomes of the 9% of stented participants were not reported. However, the authors stated that, "when stented patients were excluded from the analysis, there were no changes in any of the conclusions". The majority of study authors declared a financial relationship with the study sponsor

LEVANT I 2014

Methods	Study design: randomized controlled trial Method of randomization: sequentially numbered sealed envelopes in blocks of 4 via computer-generated random numbers Blinding: single-blind (participants) Exclusions postrandomization: 0 Losses to follow-up: 5 (at 6-month follow-up) Study enrollment period: June 2009 to December 2009 Cross-over: 0
Participants	Country: Europe and USA Setting: 9 hospitals Number of participants: 101 Age (mean ± SD): 67 ± 8 (DEB), 70 ± 10 (PTA) Gender: male: DEB 34 (69%), PTA 30 (58%) Rutherford class: DEB: class 2: 22%, class 3: 72%, class 4: 2%, class 5: 4%; PTA: class 2: 21%, class 3: 71%, class 4: 4%, class 5: 4% ABI (± SD): DEB: 0.69 ± 0.23, PTA: 0.60 ± 0.36 Inclusion criteria:

LEVANT I 2014 *(Continued)*

	• Single de novo or (non-instent) restenotic lesions (operator-determined > 70% stenosis; length ≥ 4 cm and ≤ 15 cm) • RVD ≥ 4 mm and ≤ 6 mm) • ≥ 18 years old with Rutherford clinical category 2 to 5 • Claudication or CLI Exclusion criteria: • Life expectancy ≤ 2 years • Creatinine > 2.5 mg/dL • History of hemorrhagic stroke ≤ 3 months • Previous surgery of the target lesion • Previous or planned intervention ≤ 30 days • Use of adjunctive therapies (including glycoprotein IIb/IIIa inhibitors) • Severe lesion calcification • Sudden symptom onset • Acute or subacute target vessel thrombus or occlusion • Absence of ≥ 1 patent untreated runoff vessel • Significant inflow disease
Interventions	Uncoated balloon angioplasty: 52 (of whom 38 did not receive a stent) Uncoated balloon angioplasty device: unspecified "standard PTA balloon" DEB: 49 (of whom 37 did not receive a stent) DEB device: Lutonix DEB (C.R. Bard, New Hope, MN) Drug used: paclitaxel 2 µg/mm^2 balloon surface Vessels treated: femoropopliteal arteries Anticoagulation/platelets: according to local clinical practice. ASA 100 mg/day to 325 mg/day indefinitely and clopidogrel loading dose (75 mg or 300 mg) with maintenance for 1 month in balloon-only participants and 3 months in stented participants Predilation before DEB: yes
Outcomes	Primary: • Angiographic late lumen loss at 6 months Secondary: • Device-related adverse events • Primary patency of treated segment • TLR • TVR • Device success • Successful delivery and deployment of the first inserted study device • Procedural success • Completion of the procedure with < 30% residual stenosis • Change in ABI • Change in WIQ • Change in Rutherford class • Serum paclitaxel levels - in subsets of participants
Notes	25% of enrolled participants received a stent

LEVANT I 2014 *(Continued)*

	Clinical follow-up at 1, 6, 12, and 24 months after the procedure
	Angiography of the treated limb performed at 6 months
	Duplex ultrasound, Rutherford classification, ABI, and WIQ evaluated at baseline, 6, 12, and 24 months
	Sponsor: C.R. Bard (New Hope, MN)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects in each stratum (intended balloon-only or intended stenting) were randomized 1:1 to Lutonix DCB or uncoated balloon (control group) using sequentially numbered sealed envelopes in blocks of 4 via computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	"Subjects in each stratum (intended balloon-only or intended stenting) were randomized 1:1 to Lutonix DCB or uncoated balloon (control group) using sequentially numbered sealed envelopes in blocks of 4 via computer-generated random numbers"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was "single blind" (to participant)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome assessed by "independent, blinded angiographic core lab analysis". "Major adverse events were independently adjudicated by a Clinical events committee"
Incomplete outcome data (attrition bias) All outcomes	High risk	"Six-month angiographic follow-up for the primary endpoint was available for 39 patients (80%) in the Lutonix DCB group and 36 (69%) in the uncoated balloon group, due in part to 4 deaths and 5 withdrawals"
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoint data reported
Other bias	High risk	8 DEB devices (16%) malfunctioned and failed to deploy properly. Antiplatelet therapy regimens varied across sites and anticoagulation protocol with heparin not specified

LEVANT II 2015

Methods	Study design: randomized controlled trial
	Method of randomization: 2:1 randomization
	Blinding: single-blind (participants)
	Exclusions postrandomization: 0
	Losses to follow-up: 74 of 476 participants (16%) at 12 months
	Study enrollment period: July 2011 to July 2012
	Cross-over: 0
Participants	Country: Europe and USA

LEVANT II 2015 *(Continued)*

Setting: 54 hospitals

Number of participants: 476

Age (mean ± SD): 68 ± 10 years (DEB), 69 ± 9 years (PTA)

Gender: male: DEB 193 (61%), PTA 107 (67%)

Rutherford class: DEB: class 2: 29% class 3: 63%, class 4: 8%; PTA: class 2: 34%, class 3: 58%, class 4: 8%

ABI (± SD): DEB: 0.74 ± 0.20, PTA: 0.73 ± 0.18

Inclusion criteria:

- Male or nonpregnant female aged ≥ 18 years
- Rutherford clinical category 2 to 4
- Willing to provide informed consent, is geographically stable and comply with the required follow-up visits, testing schedule, and medication regimen.
- Lesion length ≤ 15 cm
- Up to 2 focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. 2 discrete segments, separated by several cm, but both falling within a composite length of ≤ 15 cm)
- ≥ 70% stenosis by visual estimate
- Lesion location starts ≥ 1 cm below the common femoral bifurcation and terminates distally ≤ 2 cm below the tibial plateau AND ≥ 1 cm above the origin of the tibial plateau trunk
- De novo lesion(s) or nonstented restenotic lesion(s) > 90 days from prior angioplasty procedure
- Lesion located at least 3 cm from any stent, if target vessel was previously stented
- Target vessel diameter between ≥ 4 mm and ≤ 6 mm and able to be treated with available device size matrix
- Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion
- A patent inflow artery free from significant lesion (≥ 50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions)
- At least 1 patent native outflow artery to the ankle, free from significant (≥ 50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure)
- Contralateral limb lesion(s) cannot be treated within 2 weeks before or planned 30 days after the protocol treatment (or both) in order to avoid confounding complications
- No other prior vascular interventions within 2 weeks before or planned 30 days after the protocol treatment (or both)

Exclusion criteria:

- Pregnant or planning on becoming pregnant or men intending to father children
- Life expectancy < 5 years
- Currently participating in an investigational drug or other device study or previously enrolled in this study
- History of hemorrhagic stroke within 3 months
- Previous or planned surgical or intervention procedure within 2 weeks before or within 30 days after the index procedure
- History of MI, thrombolysis, or angina within 2 weeks of enrolment
- Rutherford class 0, 1, 5, or 6
- Renal failure or chronic kidney disease with MDRD glomerular filtration rate ≤ 30 mL/minute/1.73 m^2 (or serum creatinine ≥ 2.5 mg/L within 30 days of index procedure or treated with dialysis)
- Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion
- Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and postprocedure medication
- Anticipated use of class IIb/IIIa inhibitor prior to randomization
- Ipsilateral retrograde access

LEVANT II 2015 *(Continued)*

	• Composite lesion length > 15 cm or no normal proximal arterial segment in which duplex flow velocity could be measured • Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment • Known inadequate distal outflow (> 50% stenosis of distal popliteal or all 3 tibial vessels, or both), or planned future treatment of vascular disease distal to the target lesion • Sudden symptom onset, acute vessel occlusion, or acute or subacute thrombus in target vessel • Severe calcification that renders the lesion undilatable • Use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.)
Interventions	Uncoated balloon angioplasty: 160 Uncoated balloon angioplasty device: unspecified "standard PTA balloon" DEB: 316 DEB device: Lutonix DEB (C.R. Bard, New Hope, MN) Drug used: paclitaxel 2 µg/mm^2 balloon surface Vessels treated: femoropopliteal arteries Anticoagulation/platelets: according to local clinical practice ASA loading dose 75 mg to 325 mg before the procedure and 75 mg/day to 100 mg/day indefinitely, and clopidogrel or prasugrel loading dose (clopidogrel 75 mg or 300 mg and prasugrel 10 mg or 60 mg) before the procedure and clopidogrel 75 mg/day or prasugrel 5 mg to 10 mg (depending on bodyweight) for at least 1 month postoperatively Predilation before DEB: yes
Outcomes	Primary: • Primary effectiveness measure: primary patency of the target lesion at 12 months • Primary safety measure: composite of freedom from perioperative death from any cause (≤ 30 days after the procedure) and freedom at 12 months from index-limb amputation, index limb revascularization, and index-limb-related death (i.e. death from a medical complication related to a limb) Secondary: • Procedural success • Clinically driven TLR • Changes from baseline in the Rutherford classification • WIQ scores • QoL measures (the EQ-5D and SF-36 scores) • All-cause mortality rate • Amputation-free survival • TVR • Reintervention for thrombosis
Notes	Primary patency defined as the absence of evidence of binary restenosis and freedom from TLR Procedural success defined as technical success without periprocedural complications Participants were followed up at 1, 3, and 12 months postoperatively Sponsor: C.R. Bard (New Hope, MN)

Risk of bias

LEVANT II 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized 2:1 to the intervention and control arms, but the methodology of randomization not explained in the manuscript, supplementary materials, or study protocol
Allocation concealment (selection bias)	Unclear risk	Methodology of allocation not explained in the manuscript, supplementary materials, or study protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The clinician was aware of the index treatment because the drug-coated balloon looked different from a standard balloon"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators who completed follow-up, vascular-laboratory personnel, core laboratory evaluators, and members of the clinical-events committee were unaware of the treatment received"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 16% of participants were lost to follow-up over the 12-month study period
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoint data reported
Other bias	Low risk	Participants randomized after a lesion was predilated so people requiring stent placement were excluded. More challenging or dissection-prone lesions were thus excluded from this study, which may not be reflective of existing clinical practices

PACIFIER 2012

Methods	Study design: randomized controlled trial Method of randomization: computer generated, in blocks of 10 participants Blinding: single-blind (participants) Exclusions postrandomization: 0 Losses to follow-up: 4 participants at 6 months, 10 participants at 12 months Study enrollment period: 2010 to 2011 Cross-over: 0
Participants	Country: Germany Setting: hospital (3 centers) Number of participants: 85 (91 intervention procedures, 1 target lesion per procedure) Age (mean ± SD): 71 ± 7 years (DEB), 71 ± 9 years (PTA) Gender: males: DEB 26 (59%), PTA 30 (64%) Rutherford class: DEB: class 2: 9.1%, class 3: 86.4%, class 4: 0%, class 5: 4.5%; PTA: class 2: 12.8%, class 3: 83%, class 4: 4.3%, class 5: 0%

PACIFIER 2012 *(Continued)*

	ABI: DEB: 0.73 ± 0.30, PTA: 0.65 ± 0.26 Inclusion criteria: • Claudication or CLI (Rutherford class 2, 3, 4, or 5) • Atherosclerotic disease involving the SFA or the popliteal artery • Lesion length 3 cm to 30 cm • An occlusion or a grade of stenosis ≥ 70% • Absence of contraindications to dual antiplatelet therapy • Written informed consent Exclusion criteria: • Acute thrombus or aneurysm in the target vessel • Failure to cross the target lesion with a guidewire • Inflow lesions that could not be successfully pretreated • Significant disease of all 3 infrapopliteal vessels • Renal failure (serum creatinine > 2.0 mg/dL) • Known intolerance or allergy to study medications • Life expectancy < 2 years
Interventions	Uncoated balloon angioplasty: 47 procedures in 44 participants Uncoated balloon angioplasty device: Pacific Xtreme (Medtronic, Santa Rosa, CA) DEB: 44 procedures in 41 participants DEB device: IN.PACT Pacific (Medtronic, Santa Rosa, CA) Drug used: paclitaxel 3 µg/mm^2 balloon surface Vessels treated: femoropopliteal arteries Anticoagulation/platelets: all participants were pretreated with ASA and thienopyridines, which were continued for > 2 months after PTA Predilation before DEB: yes: DEB 6 cases (13.6%), PTA 3 cases (6.4%)
Outcomes	Primary: • Late lumen loss at 6 months Secondary: • Binary restenosis at 6 months • Rutherford class change at 6 months • TLR at 6 and 12 months • Major adverse clinical events (death, target limb amputation, or TLV) at 6 and 12 months
Notes	Follow-up to 24 months reported Stents provisionally implanted in 9 (20.5%) DEB cases and 16 (34%) PTA cases Sponsor: Medtronic (Santa Rosa, CA)

Risk of bias

Bias	Authors' judgement	Support for judgement

PACIFIER 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	"The randomization sequence was computer generated, in blocks of 10 patients each"
Allocation concealment (selection bias)	Low risk	"Allocation concealment was guaranteed by the use of numbered, opaque, sealed envelopes, which were only opened after the decision was made that the patient had to be treated according to the protocol"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Blinding of investigators after assignment of a patient to a treatment is not possible due to differences in the appearance of coated and uncoated catheters"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary endpoint "assessed by blinded angiographic core lab quantitative analyses"
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing primary outcome data on 20.5% of DEB arm and 27.3% of control arm
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoint data reported
Other bias	High risk	21% of DEB and 34% of control participants were stented but little discussion of outcomes in those participants. Baseline risk characteristics such as smoking and diabetes were unevenly distributed between DEB and control arms. Dosing and duration of antiplatelet therapies were unclear

THUNDER 2008

Methods	Study design: randomized controlled trial Method of randomization: participants were assigned to different treatment groups according to a lot-generated random list Blinding: participant blinded Exclusions postrandomization: 0 Losses to follow-up: 3 Study enrollment period: June 2004 to June 2005 Cross-over: 0
Participants	Country: Germany Setting: 3 hospitals Number of participants: 154 Age (mean ± SD): 69 ± 8 years (DEB), 68 ± 9 years (PTA) Gender: males: DEB 31 (65%), PTA 34 (63%) Rutherford class (mean ± SD): DEB: 3.4 ± 0.8, PTA 3.1 ± 0.8 ABI (± SD): DEB: 0.5 ± 0.3, PTA 0.5 ± 0.3 Inclusion criteria:

THUNDER 2008 *(Continued)*

- Age 18 to 95 years
- Rutherford class 1 to 5
- ≥ 1 obstructive lesions or new lesions or restenoses ≥ 70% of vessel diameter and ≥ 2 cm in length, in the SFA, the popliteal artery, or both

Exclusion criteria:

- Poor inflow
- Absence of a patent crural artery
- Acute onset of symptoms
- Pregnancy
- Life expectancy < 1 year
- Contraindications to required medications

Interventions	Uncoated balloon angioplasty: 54 Uncoated balloon angioplasty device: Bavaria Medizintechnologie DEB: 48 DEB device: Bavaria Medizintechnologie Drug used: paclitaxel 3 µg/mm^2 balloon surface, mean dose (± SD) 4.7 ± 3.µg Vessels treated: femoropopliteal arteries Anticoagulation/platelets: participants not already taking ASA and clopidogrel were administered loading doses of 300 mg of each drug 12 hours before the procedure. All participants received ASA 100 mg/day indefinitely and clopidogrel 75 mg/day for 4 weeks after the intervention. In addition, participants were given an intra-arterial bolus of heparin 3000 U to 5000 U) at the time of the procedure Predilation before DEB: yes
Outcomes	Primary: • Late lumen loss at 6 months Secondary: • The secondary efficacy endpoints were the technical success of the intervention • 6-month angiographic restenosis rate (i.e. incidence of stenosis of ≥ 50% of the diameter of the reference-vessel segment) • Change in Rutherford class • ABI • Patency rate • Incidence of TLR
Notes	Study had 3 arms: balloons coated with paclitaxel, uncoated balloons with paclitaxel dissolved in the contrast medium, and uncoated balloons Clinical evaluations were performed at baseline, at 24 to 72 hours after intervention, and at 6 months after intervention Angiographic evaluation of restenosis was performed at 6 months with the same projections as those used during intervention Sponsor: Bavaria Medizintechnologie and Schering, Germany
Risk of bias	

THUNDER 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to different treatment groups according to a lot-generated random list
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment strategy
Blinding of participants and personnel (performance bias) All outcomes	High risk	The paclitaxel-coated balloons had a distinctive appearance that could be recognized by the investigators, who also performed some of the poststudy evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The paclitaxel-coated balloons had a distinctive appearance that could be recognized by the investigators, who also performed some of the poststudy evaluations". "All angiograms were assessed in a blinded fashion by an independent angiographic core laboratory (C2RM, Lille, France)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 DEB participants and 1 PTA participant did not undergo clinical follow-up and angiography at 6 months
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoint data reported
Other bias	High risk	4% of the intervention and 22% of control participants were stented but little discussion was provided of the outcomes in those participants

ABI: ankle-brachial index; ASA: acetylsalicylic acid (aspirin); BTHC: n-butyryl tri-nhexyl citrate; BTK: below the knee; CLI: critical limb ischemia; DCB: drug-coated balloon; DEB: drug-eluting balloon; DES: drug-eluting stent; DS: diameter stenosis; EQ-5D: Euro-Qol Group 5-Dimension Self-Report Questionnaire; IU: international unit; MAE: major adverse events; MDRD: modification of diet in renal disease; MI: myocardial infarction; MLD: minimum lumen diameter; PTA: percutaneous transluminal angioplasty; QoL: quality of life; QVA: quantitative vascular angiography; RVD: reference vessel diameter; SD: standard deviation; SFA: superficial femoral artery; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; TASC: Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease; TLR: target lesion revascularization; TVR: target vessel revascularization; U: unit; WIQ: Walking Impairment Questionnaire.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
COPA CABANA	Randomized controlled trial comparing DEB with uncoated balloon angioplasty for the treatment of instent restenosis
DEBATE SFA	Randomized controlled trial comparing stenting and DEB with stenting and uncoated balloon angioplasty for the treatment of peripheral arterial disease
DEBATE-ISR	Randomized controlled trial comparing DEB with uncoated balloon angioplasty for the prevention of instent restenosis in people with diabetes
DEFINITIVE AR	Randomized controlled trial comparing atherectomy and DEB angioplasty with DEB angioplasty alone for the treatment of peripheral arterial disease
EURO CANAL	The trial was terminated early by the DEB manufacturer before any data were collected. The reason for early termination was that the manufacturer withdrew the DEB from the market

Study	Reason for exclusion
FAIR	Randomized controlled trial comparing DEB with uncoated balloon angioplasty for the prevention of instent restenosis
Freeway Stent Study	Randomized controlled trial of primary nitinol stenting followed by DEB or uncoated balloon angioplasty for the prevention of instent restenosis
IDEAS	Randomized controlled trial comparing DEB angioplasty with drug-eluting stenting for the treatment of peripheral arterial disease
ISAR-PEBIS	Randomized controlled trial comparing drug-eluting with uncoated balloon angioplasty for the prevention of instent restenosis
ISAR-STATH	Randomized controlled trial comparing DEB angioplasty, stenting, and atherectomy for the treatment of lower-extremity peripheral arterial disease
PACUBA 1	Randomized controlled trial comparing DEB with uncoated balloon angioplasty for the treatment of instent restenosis
PHOTOPAC	Randomized controlled trial comparing photoablation and DEB angioplasty with DEB angioplasty alone for the prevention of instent restenosis
RAPID	Randomized controlled trial comparing stenting and DEB with stenting and uncoated balloon angioplasty for the treatment of peripheral arterial disease
SWEDEPAD	Randomized controlled trial comparing drug-eluting technologies (DEB or drug-eluting stenting) with nondrug-eluting technologies (uncoated balloon angioplasty or stenting) for the treatment of peripheral arterial disease

DEB: drug-eluting balloon.

Characteristics of ongoing studies *[ordered by study ID]*

AcoArt I

Trial name or title	Prospective, Multi-center and Randomized Controlled Clinical Study to Verify Effectiveness and Safety of Drug-Eluting Balloon in PTA Procedure (AcoArt I Study)
Methods	Randomized controlled trial
Participants	Country: China Setting: 7 hospitals Number of participants: 200 Inclusion criteria: • Age 18 to 80 years • Have PAD, with Rutherford classification between 2 and 5 • An occlusion or a minimum grade of stenosis > 70% in the SFA, PA, or both • Total length of treat lesion(s) ≤ 40 cm • Signed informed consent form Exclusion criteria: • Plasma creatinine > 150 µmol/L • Acute thrombosis requiring lysis or thrombectomy

AcoArt I *(Continued)*

	• Lysis or any lower limb intervention as a therapy within the last 6 weeks • Requiring intervention in both lower limbs at the same time • Target lesion cannot be crossed by the guidewire • Distal outflow through less than one lower leg vessel. • Known hypersensitivity to acetylsalicylic acid (aspirin), heparin, clopidogrel, paclitaxel, or contrast medium • Participating in another clinical trial with interfere with this trial in the past 3 months • Pregnancy and lactating woman • Untreatable bleeding diseases • Other diseases, such as cancer, liver disease, or cardiac insufficiency, which may lead to protocol violations or markedly shorten a person's life expectancy (< 2 years) • Unable or unwilling to participate in trial
Interventions	Uncoated balloon angioplasty device: Orchid catheter DEB device: Admiral catheter Vessels treated: femoropopliteal vessels
Outcomes	Primary: • Late lumen loss at 6 months Secondary: • Change in minimal lumen diameter • Target vessel restenosis • TLR • Change in Rutherford classification • Change in ABI • Major amputation • Death
Starting date	April 2013
Contact information	Acotec Scientific Company, China
Notes	Sponsor: Acotec Scientific Company

AcoArt II

Trial name or title	Prospective, Multi-center and Randomized Controlled Clinical Study to Verify Effectiveness and Safety of Drug-Eluting Balloon in PTA Procedure of the Infrapopliteal Artery
Methods	Randomized controlled trial
Participants	Country: China Setting: single hospital Number of participants: 180 Inclusion criteria: • Age 18 to 85 years • PAD, with Rutherford classification between 4 and 6

AcoArt II *(Continued)*

	• An occlusion or a minimum grade of stenosis > 70% in the below-PA vessels • Expected survival time ≥ 1 year • Signed participant informed consent form Exclusion criteria: • Serum creatinine clearance rate < 30 mL/minute • Acute thrombosis requiring lysis or thrombectomy • Lysis or a lower limb intervention as a therapy within the last 6 weeks • Requiring intervention in both lower limbs at the same time • Instent restenosis in the blow-knee PA • Target lesion cannot be cross by the guidewire • Stenosis rate of proximal outflow > 30% with or without intervention • Length of the stenosis or occlusion in proximal outflow (including the Iliac artery, the SFA, the PA) > 150 mm before intervention • Stenosis or occlusion of distal outflow for below-the-ankle artery • Expected major amputations at the index limb before intervention • Known hypersensitivity to acetylsalicylic acid (aspirin), heparin, clopidogrel, paclitaxel, or contrast medium • Participating in another clinical trials with interfere with this trial in the same time • Pregnancy and lactating women • Untreatable bleeding diatheses
Interventions	Uncoated balloon angioplasty device: Lotus/Tulip catheter DEB device: Amphirion Deep catheter Vessels treated: below-knee vessels
Outcomes	Primary: • Late lumen loss Secondary: • Device success rate • Technical success rates • Operation success rate • TLR • Major amputation • Ulcer healing rate • Change in Rutherford classification
Starting date	May 2014
Contact information	Qianqian Wei, weiqianqian@mrbc-nccd.com
Notes	Sponsor: Acotec Scientific Company

ACOART-BTK

Trial name or title	Evaluation of the Use of ACOTEC Drug-Eluting Balloon Litos in Below-The-Knee Arteries to Treat Critical Limb Ischemia (ACOART-BTK).

ACOART-BTK *(Continued)*

Methods	Randomized controlled trial
Participants	Country: Italy Setting: single hospital Number of participants: 140 Inclusion Criteria: • Age > 18 years • CLI (Rutherford class 4 to 6) • Angiographic stenosis > 50% or occlusion of at least 1 tibial vessel of at least 40 mm for which an intervention treatment is scheduled Exclusion criteria: • Need for major amputation known before intervention • Allergy to paclitaxel • Contraindication for combined antiplatelet treatment • Life expectancy < 1 year • Hypersensitivity or contraindication to 1 of the study drugs • Lack of consent
Interventions	Uncoated balloon angioplasty device: unspecified conventional balloon catheter DEB device: Litos drug-eluting balloon catheter Vessels treated: infrapopliteal arteries
Outcomes	Primary: • Angiographic late lumen loss at 6 months Secondary: • Angiographic binary restenosis at 12 months • TLR at 12 months
Starting date	September 2015
Contact information	Dr Leonardo Bolognese, l.bolognese@usl8.toscana.it
Notes	Sponsor: Ospedale San Donato No industry support declared

Advance 18PTX Balloon Catheter Study

Trial name or title	Advance® 18PTX® Balloon Catheter Study: Treatment of Lesions in Superficial Femoral Artery/ Popliteal Artery with a Paclitaxel-coated Balloon.
Methods	Randomized controlled trial
Participants	Country: Germany and Russia Setting: 3 hospitals in Germany and 1 hospital in Russia

Advance 18PTX Balloon Catheter Study *(Continued)*

	Number of participants: 150 Inclusion criteria: • Age > 18 years • Able to provide informed consent • Has at least 1 de novo or restenotic lesion(s) with > 70% stenosis documented angiographically of the SFA or PA. If > 1 lesion requires intervention, only 1 should be treated as a study lesion Exclusion criteria: • Significant stenosis (> 50%) or occlusion of inflow tract (proximal ipsilateral, iliofemoral, or aortic lesions) not successfully treated before this procedure • Lack of at least 1 patent runoff vessel with < 50% stenosis throughout its course • Lesions in target area requiring atherectomy (or ablative devices), cutting balloons, cryoplasty balloons, or any other advanced device to facilitate angioplasty balloon or stent delivery
Interventions	Uncoated balloon angioplasty device: Advance® 18LP catheter DEB device: Advance 18PTX catheter Drug used: paclitaxel
Outcomes	Primary: Late lumen loss. Secondary: No information provided on secondary outcomes
Starting date	October 2008
Contact information	None provided
Notes	Sponsor: Cook

EFFPac

Trial name or title	Phase III Multicenter Randomized Controlled Trial to Assess the Effectiveness of Paclitaxel-coated Luminor Balloon Catheter versus Uncoated Balloon Catheter in the Superficial Femoral and Popliteal Arteries to Prevent Vessel Restenosis or Reocclusion
Methods	Randomized controlled trial
Participants	Country: Germany Setting: 9 German hospitals Number of participants: 172 Inclusion criteria: • Age ≥ 18 years • Must agree to undergo the 6-month angiographic and clinical follow-up at 12 months postprocedure • Rutherford classification 2 to 4 • De novo stenotic or restenotic lesion or occlusive lesions in the SFA, PA, or both • ≥ 70% DS or occlusion

EFFPac *(Continued)*

	• Target lesion length: ≤ 15 cm (TASC II A and B) • ≥ 1 patent infrapopliteal runoff artery to the foot • If the index lesion is restenotic, the prior PTA must have been > 30 days prior to treatment in the current study Exclusion criteria: • Severely calcified target lesions in the SFA/PA resistant to PTA • Previous intervention or surgery in the target vessel • Major amputation in the same limb as the target lesion • Acute MI within 30 days before the intervention • Renal insufficiency with a serum creatinine > 2.0 mg/dL at baseline • Platelet count < 50 g/L or > 600 g/L at baseline
Interventions	Uncoated balloon angioplasty device: unspecified DEB device: Luminor 35 Paclitaxel Eluting Peripheral Balloon catheter Drug used: paclitaxel Vessels treated: femoropopliteal arteries
Outcomes	Primary: • Late lumen loss Secondary: • Incidence of ≥ 50% restenosis • Freedom from TLR and TVR • Rutherford class • ABI • Change in walking distance from baseline • QoL, measured using the WIQ and the EQ-5D
Starting date	April 2015
Contact information	Dr Ulf Teichgräber, Jena University Hospital, Germany Sponsor: University of Jena, Germany
Notes	-

FREERIDE Study

Trial name or title	Phase III FREERIDE STUDY Freeway Randomized Angioplasty Study
Methods	Randomized controlled trial
Participants	Country: Europe and Colombia Setting: 16 European hospitals and 1 Colombian hospital Number of participants: 280 Inclusion criteria:

FREERIDE Study *(Continued)*

	• Male or nonpregnant female (> 18 years of age) with symptomatic ischemia, requiring treatment of SFA or PA segment (Rutherford classification 2 to 5). • Single, multiple, or both de novo occluded, stenotic or reoccluded, restenotic lesion(s) of > 70%, ≤ 15 cm in total length and vessel diameter ≥ 4 mm and ≤ 7 mm (by visual estimation) • Signed informed consent and complies with the follow-up visits • Successful wire crossing of lesion • At least 1 patent (< 50% stenosis) tibioperoneal runoff vessel Exclusion criteria: • Gastrointestinal bleeding or coagulopathy contraindicating use of antiplatelet therapy • Known intolerance contraindications to study medications and contrast agents, noncontrollable with medication • Actively participating in another device or drug study • History of hemorrhagic stroke within 3 months • Previous or planned surgical or intervention procedure within 30 days of index procedure • Significant untreated inflow disease or no normal arterial segment proximal of lesion in which duplex ultrasound velocity ratios can be measured • Acute or subacute thrombus in target vessel • Use of adjunctive therapies (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon) • Instent restenosis or prior surgery of the target lesion • Abdominal aortic aneurysm ≥ 4 cm diameter
Interventions	Uncoated balloon angioplasty device: unspecified DEB device: Freeway balloon catheter Drug used: paclitaxel 3 µg/mm^2 Vessels treated: femoropopliteal arteries
Outcomes	Primary: • Rate of clinically driven TLR Secondary: • Technical success • Clinical success • Procedural success • ABI improvement • Change in Rutherford classification • Walking improvement • Rate of minor and major complications • Rate of TLR • Late lumen loss • Patency rate
Starting date	May 2011
Contact information	Beatriz Fernandez, fernandez@eurocor.de Rembert Pogge von Strandmann, pogge@eurocor.de
Notes	Sponsor: Eurocor GmbH

ILLUMENATE

Trial name or title	Pivotal Trial of a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon
Methods	Randomized controlled trial
Participants	Country: USA and Austria Setting: 44 hospitals and endovascular centers Number of participants: 360 Inclusion criteria: • Age > 18 years • Symptomatic leg ischemia, requiring treatment of the SFA or PA Exclusion criteria: • Known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator cannot be adequately pretreated
Interventions	Uncoated balloon angioplasty device: EverCross catheter DEB device: Cardiovascular Ingenuity (CVI) catheter Vessels treated: femoropopliteal vessels
Outcomes	Primary: • Patency at 12 months postprocedure, defined as the absence of target lesion restenosis as determined by duplex ultrasound (PSVR ≤ 2.5) and freedom from clinically driven TLR • Freedom from device and procedure-related death through 30 days postprocedure and freedom from target limb major amputation and clinically driven TLR through 12 months postprocedure Secondary: • MAE rate in the hospital and at 1, 6, 12, 24, 36, 48, and 60 months postprocedure, defined as a composite rate of cardiovascular death, target limb major amputation and clinically driven TLR • Rate of vascular access and bleeding complications in the hospital and at 1, 6, 12, and 24 months • Rate of clinically driven TLR at 6, 12, 24, 36, 48, and 60 months • Rate of TLR at 6, 12, 24, 36, 48, and 60 months • Rate of target limb major amputation at 1, 6, 12, 24, 36, 48, and 60 months • Mortality rate at 6, 12, 24, 36, 48, and 60 months • Rate of occurrence of arterial thrombosis of the treated segment at 1, 6, 12, 24, 36, 48, and 60 months • Patency rate and freedom from clinically driven TLR at 6, 24, and 36 months • Lesion success, defined as achievement of a final inlesion residual diameter stenosis of ≤ 50% (as determined by the angiographic core lab), using any device after wire passage through the lesion • Technical success, defined as achievement of a final inlesion residual diameter stenosis of ≤ 50% (as determined by the angiographic core lab), using the CVI Paclitaxel-coated PTA Catheter or bare balloon catheter without a device malfunction after wire passage through the lesion • Clinical success (per participant) defined as technical success without the occurrence of MAEs during the procedure • Procedural success (per participant) defined as lesion success without the occurrence of MAEs during the procedure • Change in ABI from preprocedure at 6, 12, 24, and 36 months • Change in WIQ from preprocedure at 6, 12, 24, and 36 months • Change in Rutherford-Becker classification of chronic limb ischemia from preprocedure at 6, 12, 24, and 36 months

ILLUMENATE *(Continued)*

	• Change in EQ-5D from preprocedure at 6, 12, 24, and 36 months
Starting date	June 2013
Contact information	Dr Prakash Krishnan, prakash.krishnan@mssm.edu Dr Sean Lyden, lydens@ccf.org
Notes	Sponsor: Spectranetics Corporation

LEVANT Japan

Trial name or title	A Prospective, Multicenter, Single Blind, Randomized, Controlled Japanese Population Trial Comparing MD02-LDCB Versus Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries
Methods	Randomized controlled trial
Participants	Country: Japan Setting: single hospital Number of participants: 150 Inclusion criteria: • Male or nonpregnant female ≥ 20 years of age • Rutherford classification 2 to 4 • Length ≤ 15 cm • ≥ 70% stenosis • Lesion location starts ≥ 1 cm below the common femoral bifurcation and terminates distally ≤ 2 cm below the tibial plateau and ≥ 1 cm above the origin of the tibioperoneal trunk • A patent inflow artery as confirmed by angiography • ≥ 1 patent native outflow artery to the ankle Exclusion criteria: • Life expectancy of < 2 years • History of hemorrhagic stroke within 3 months • Previous or planned surgical or intervention procedure within 2 weeks before or within 30 days after the index procedure • History of MI, thrombolysis, or angina within 2 weeks of enrolment • Renal failure or chronic kidney disease • Severe calcification that renders the lesion undilatable
Interventions	Uncoated balloon angioplasty device: unspecified DEB device: MD02-LDCB balloon catheter Drug used: paclitaxel Vessels treated: femoropopliteal arteries
Outcomes	Primary: • Composite of freedom from all-cause perioperative (≤ 30 day) death and freedom at 6 months from the following: index limb amputation (above or below the ankle), index limb reintervention, and index-limb-related death

LEVANT Japan *(Continued)*

	Secondary: • Primary patency of the target lesion at 6 months. Primary patency is defined as the absence of target lesion restenosis (defined by Doppler ultrasound PSVR ≥ 2.5) and freedom from TLR
Starting date	March 2013
Contact information	Dr Osamu Iida, Kansai Rosai Hospital Cardiovascular Internal Medicine
Notes	Sponsors: C.R. Bard and Medicon, Inc

Lutonix BTK

Trial name or title	A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Lutonix Drug Coated Balloon Versus Standard Balloon Angioplasty for Treatment of Below-the-Knee (BTK) Arteries (Lutonix BTK Trial)
Methods	Randomized controlled trial
Participants	Country: Europe, Japan, and North America Setting: 59 hospitals in Europe, USA, Canada, and Japan Number of participants: 480 Inclusion criteria: • Male or nonpregnant female ≥ 18 years of age • Rutherford clinical category 4 or 5 • Life expectancy ≥ 1 year • Significant stenosis (≥ 70%) • A patent inflow artery • Target vessel(s) diameter between 2 mm and 4 mm • Target vessel(s) reconstitute(s) at or above the ankle Exclusion criteria: • Pregnant or planning on becoming pregnant • History of stroke within 3 months • History of MI, thrombolysis, or angina within 30 days of enrolment • Prior or planned major amputation • Glomerular filtration rate ≤ 30 mL/minute per 1.73 m^2 • Acute limb ischemia • Instent restenosis of target lesion
Interventions	Uncoated balloon angioplasty device: unspecified DEB device: Lutonix drug-coated balloon catheter Drug used: paclitaxel Vessels treated: below-the-knee arteries
Outcomes	Primary: • Composite of all-cause death, above-ankle amputation, or major re-intervention • Freedom from the composite of above-ankle amputation

Lutonix BTK *(Continued)*

	• Freedom from target vessel occlusion and clinically driven target lesion reintervention Secondary: • Wound healing • Primary patency: freedom from occlusion without clinically driven TLR • Change in toe and ankle pressures • Revascularization performed on all randomized participants who returned with clinical symptoms, and if the participant has a target lesion diameter stenosis ≥ 50% • Limb salvage in surviving participants
Starting date	May 2013
Contact information	Robert M Jardin, lutonixresearch@crbard.com
Notes	Sponsor: C.R. Bard

MDT-2113 SFA

Trial name or title	Randomized Trial of MDT-2113 Drug-Eluting Balloon (DEB) vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery
Methods	Randomized controlled trial

Participants	Country: Japan
	
	Setting: single hospital
	
	Number of participants: 100
	
	Inclusion criteria:
	
	• Age: ≥ 20 to ≤ 85 years
	• Documented ischemia with Rutherford classification 2, 3, or 4
	• Able to walk without assistive devices
	• Target lesion is in the SFA or the PA (or both) above the knee
	• Target lesion consists of a single de novo or nonstented restenotic lesion (or tandem lesions) or is a combination lesion that meets the following criteria:
	  ◦ ≥ 70% and < 100% occluded with total lesion length ≥ 40 mm and ≤ 200 mm
	  ◦ 100% occluded with total lesion length ≤ 100 mm
	  ◦ Combination lesions must have total lesion length ≥ 40 mm and ≤ 200 mm with an occluded segment that is ≤ 100 mm in length (by visual estimates)
	• Reference vessel diameter ≥ 4 mm and ≤ 7 mm (by visual estimate)
	• Angiographic evidence of adequate distal runoff through the foot
	
	Exclusion criteria:
	
	• Stroke or STEMI within the 3 months prior to enrolment
	• Either local or systemic thrombolytic therapy within the 48 hours prior to the index procedure
	• Inability to tolerate oral anticoagulation therapy (blood thinners such as warfarin) while on concomitant dual antiplatelet therapy
	• Known allergies or sensitivities to heparin, acetylsalicylic acid (aspirin), other anticoagulant/antiplatelet therapies or to paclitaxel, or an allergy to contrast media that cannot be adequately pretreated prior to the index procedure
	• Chronic renal insufficiency
	• Person is enrolled in another investigational device, drug, or biologic study

MDT-2113 SFA *(Continued)*

	• Any major surgical procedure or intervention performed within the 30-day period prior to or post index procedure • Contralateral SFA/proximal PA disease requiring treatment in the same setting as index procedure • Failure to successfully cross the target lesion • Angiographic evidence of severe calcification • Target lesion known in advance of enrolment to require treatment with alternative therapy such as stenting, laser, atherectomy, cryoplasty, brachytherapy, re-entry devices, cutting balloons, scoring balloons; use of embolic protection devices is also prohibited
Interventions	Uncoated balloon angioplasty device: unspecified DEB device: MDT-2113 drug-eluting balloon catheter Drug used: paclitaxel Vessels treated: femoropopliteal arteries
Outcomes	Primary: Freedom from clinically driven TLR and freedom from restenosis as determined by duplex ultrasound Secondary: Freedom from device- and procedure-related death through 30 days postprocedure, and freedom from target limb major amputation and clinically driven TVR
Starting date	September 2013
Contact information	Unspecified
Notes	Sponsor: Medtronic Endovascular

PICCOLO

Trial name or title	Paclitaxel Coated Balloons for Prevention of Restenosis in Small Arteries Below the Knee Compared to Angioplasty Using Uncoated Balloons
Methods	Randomized controlled trial
Participants	Country: Germany Setting: 5 hospitals Number of participants: 114 Inclusion criteria: • Age 18 to 95 years • Rutherford classification 3 to 5 • Diameter stenosis ≥ 70%, ≥ 15 mm to 150 mm length, up to 2 vessels to be treated Exclusion criteria: • Disease associated with life-expectancy < 18 months • Acute thrombus or aneurysm in the index limb/ vessel • Doubts in the willingness or capability of the person to allow follow-up exam

PICCOLO *(Continued)*

Interventions	Uncoated balloon angioplasty device: Submarine, Ampherion Deep by Invatec DEB device: Submarine, Ampherion Deep by Invatec coated with paclitaxel 3 µg/mm^2 Drug used: paclitaxel Vessels treated: below-knee arteries
Outcomes	Primary: • Late lumen loss of the target lesion after 6 months Secondary: • Intervention success rate (defined as restenosis < 50%) • Restenosis rate (diameter stenosis of ≥ 50% of reference diameter) • MLD at 6 months • TLR • TVR • Target limb revascularization • Change in Rutherford classification • Change in ABI compared to pretreatment if vessels are compressible • Hospitalization (extra days due to complications of the index procedure) and hospitalization between the follow-up visits due to the index leg • Major amputations at the index limb • Mortality
Starting date	April 2008
Contact information	Dr Gunnar Tepe, gunnar.tepe@med.uni-tuebingen.de
Notes	Sponsor: University of Tuebingen, Germany. Industrial support unspecified The status of this trial is unclear. The trial information has not been updated on ClinicalTrials.gov since 2008. Attempts to reach the trial researchers have not been successful

RANGER-SFA

Trial name or title	Prospective, Randomized, Multicentre Clinical Study of the Hemoteq Ranger™ Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) in Comparison to Uncoated PTA Balloons in Femoropopliteal Lesions
Methods	Randomized controlled trial
Participants	Country: Europe Setting: 2 hospitals in Austria, 7 in Germany, 4 in France Number of participants: 105 Inclusion criteria: • Age ≥ 18 years • Willing and able to provide informed consent • Available to attend all required follow-up visits • Has a clinically significant symptomatic leg ischemia requiring treatment • Rutherford clinical category 2 to 4

RANGER-SFA *(Continued)*

- If the index lesion is restenotic, the prior PTA must have been > 30 days prior to treatment in the current study
- Only 1 lesion per limb can be treated under this protocol
- Successful intraluminal wire crossing of the target lesion
- Index lesion is a clinically and hemodynamically significant stenotic or restenotic lesion located in the native nonstented SFA or proximal PA
- Degree of stenosis ≥ 70%, by visual assessment
- Lesion length 20 mm to 150 mm
- At least 1 patent infrapopliteal artery to the foot of the index limb

Exclusion criteria:

- People who have undergone prior vascular surgery of the femoropopliteal artery in the index limb to treat atherosclerotic disease
- History of major amputation in the same limb as the target lesion
- Presence of aneurysm in the target vessel
- Acute ischemia or acute thrombosis (or both) in any artery of the lower limbs
- Acute MI within 30 days before the index procedure
- Persistent, intraluminal thrombus of the proposed target lesion post-thrombolytic therapy
- Known hypersensitivity or contraindication to contrast dye that cannot be adequately premedicated
- Known allergies against paclitaxel or other components of the used medical devices
- Intolerance to antiplatelet, anticoagulant, or thrombolytic medications that would be administered during the trial
- Platelet count < 100,000 mm^3 or > 600,000 mm^3
- Concomitant renal failure with a serum creatinine > 2.0 mg/dL
- Receiving dialysis or immunosuppressant therapy
- Life expectancy of < 1 year
- Women of childbearing potential must agree to use a reliable method of birth control from the time of screening through 12 months after the index procedure
- Pregnant or nursing woman
- Previously planned stenting of the index lesion
- Use of adjunctive therapies (debulking, laser, cryoplasty, re-entry devices)
- Planned or expected procedures (cardiac, aorta, peripheral) within 30 days after the index procedure
- Presence of outflow lesions requiring intervention within 30 days of the index procedure
- Perforated vessel as evidenced by extravasation of contrast media
- Heavily calcified target lesions resistant to PTA
- Current participation in another drug or device trial that has not completed the primary endpoint, that may potentially confound the results of this trial, or that would limit the person's compliance with the follow-up requirements
- Current participation in any study using drug-coated/drug-eluting technologies
- Target lesion with instent restenosis (any stent or stent-graft)

Interventions	Uncoated balloon angioplasty device: unspecified DEB device: Ranger drug-coated balloon Drug used: paclitaxel Vessels treated: femoropopliteal arteries
Outcomes	Primary: • In-segment late lumen loss

RANGER-SFA *(Continued)*

	Secondary: • Technical success • Procedural success • Primary patency: percentage of lesions that reach endpoint without a hemodynamically significant stenosis on duplex ultrasound and without TLR or bypass of the target lesion to maintain or restore patency • Assisted primary patency: percentage of lesions without TLR and those with TLR (not due to complete occlusion or bypass) that reach endpoint without restenosis • Secondary patency: percentage of lesions with TLR for occlusion that reach endpoint without restenosis • Binary restenosis: defined as > 50% diameter stenosis via PSVR > 2.4 via duplex ultrasound and assessed by the core lab • Clinical success: positive change (by ≥ +1) of Rutherford category at predischarge post-index-procedure as compared to baseline • Hemodynamic success: positive change in ABI at predischarge as compared to baseline • Change in QoL
Starting date	January 2014
Contact information	Dr Dierk Scheinert, Park-Krankenhaus Leipzig GmbH
Notes	Sponsor: Hemoteq AG, Ceres GmbH Evaluation and Research, CoreLab Bad Krozingen GmbH

SINGA-PACLI

Trial name or title	Singapore INfra-Genicular Angioplasty with PAclitaxel-eluting Balloon for Critical Limb Ischaemia (SINGA-PACLI) Trial
Methods	Randomized controlled trial
Participants	Country: Singapore Setting: 2 hospitals Number of participants: 136 Inclusion criteria: • Written informed consent • Age > 21 years • If female with childbearing potential, woman may not be pregnant at the study entry and must utilize reliable birth control for the duration of her participation into the study • Willing and able to comply with the specified follow-up evaluation • Critical limb ischemia, Rutherford category 4 to 6 • Stenosis (> 50% luminal loss) or occlusion of infragenicular arteries (defined as: distal to the infrapopliteal artery), including the tibiofibular trunk, anterior tibial artery, posterior tibial artery, and peroneal artery • Infragenicular arterial lesions with length of < 20 cm • At least 1 crural (anterior tibial, posterior tibial, or peroneal) artery with expected unobstructed runoff to ankle level after treatment • Successful guidewire crossing of the trial lesion Exclusion criteria: • Acute limb ischemia

SINGA-PACLI *(Continued)*

- Subacute limb ischemia that requires thrombolysis as first treatment modality
- Previous major amputation of the affected limb (at or above the level of the ankle)
- Concurrent iliac or femoropopliteal artery disease not suitable for endovascular or surgical revascularization
- Concurrent iliac or femoropopliteal artery occlusion of > 10 cm, even if suitable for surgical or endovascular revascularization
- People without (expected) distal runoff to the index site
- Revascularization involving the same site within 30 days prior to the index procedure or planned revascularization of the same limb within 30 days of the index procedure
- Previous implanted stent at the index site
- Life expectancy < 6 months
- Factors making clinical follow-up very difficult or impossible
- Known allergy to paclitaxel
- Known allergy to contrast media
- People taking warfarin or any other anticoagulants
- Known allergy to antiplatelet drugs or unable to tolerate dual antiplatelet therapy
- Active history of gastritis and other bleeding tendencies precluding use of dual antiplatelet therapy
- Known heparin-induced thrombocytopenia (HIT type 2)
- Person unable or unwilling to tolerate contrast media
- Estimated glomerular filtration rate < 60 mL/minute/1.73 m^2 unless person is receiving dialysis
- Left ventricular ejection fraction percentage < 35% (person may be at risk of life-threatening irregular heartbeats)
- Either prothrombin time/partial thromboplastin time of > 1.5 times the median of normal that cannot be corrected for the time of the procedure or international normalized ratio > 1.6 that cannot be corrected for the time of the procedure
- Thrombocytopenia of platelet count < 50,000 /µL (50 x 10^9/L) that cannot be corrected for the time of the procedure

Interventions	Uncoated balloon angioplasty device: unspecified DEB device: unspecified Drug used: paclitaxel Vessels treated: infrapopliteal arteries
Outcomes	Primary: • Primary patency of the treated (index) site at 6 months Secondary: • Limb-salvage rate • Clinical categorization of the treated ischemic leg by means of the Rutherford classification • Minor amputation • Infrapopliteal surgical bypass of the trial leg • Infrapopliteal endovascular reintervention of the trial leg • Primary patency of treated femoropopliteal sites • Periprocedural complications • Death • Incremental cost-effectiveness ratio
Starting date	December 2013
Contact information	Dr Bien Soo Tan, tan.bien.soo@sgh.com.sg

SINGA-PACLI *(Continued)*	Dr Farah Gillan Irani, farah.gillan.irani@sgh.com.sg
Notes	Sponsor: Singapore General Hospital No industrial support has been specified

ABI: ankle-brachial index; CLI: critical limb ischemia; DEB: drug-eluting balloon; DES: drug-eluting stent; DS: diameter stenosis; EQ-5D: Euro-Qol Group 5-Dimension Self-Report Questionnaire; PA: popliteal artery; PAD: peripheral arterial disease; PSVR: peak systolic velocity ratio; PTA: percutaneous transluminal angioplasty; QoL: quality of life; MAE: major adverse events; MI: myocardial infarction; SFA: superficial femoral artery; STEMI: ST-elevation myocardial infarction; TLR: target lesion revascularization; TVR: target vessel revascularization; WIQ: Walking Impairment Questionnaire.

DATA AND ANALYSES

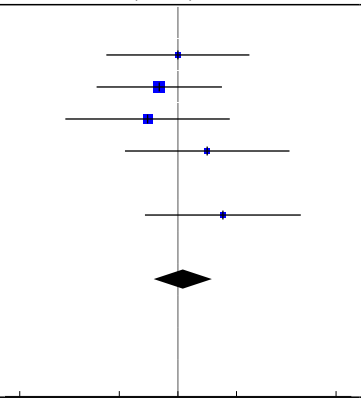
Comparison 1. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	7	541	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.39, 3.80]
2 Primary vessel patency	2	162	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.22, 9.57]
3 Late lumen loss	7	603	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.00, -0.28]
4 Target lesion revascularization	7	603	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.17, 0.47]
5 Binary restenosis	6	528	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.29, 0.67]
6 Death	7	541	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.31, 2.14]
7 Change in Rutherford category	3	249	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.49, 0.36]
8 Change in ankle-brachial index	4	369	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.19, 0.18]
9 Change in quality of life (EQ-5D)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Change in walking impairment score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Amputation (sensitivity analysis)	4	322	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [0.42, 7.54]
12 Primary vessel patency (sensitivity analysis)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Late lumen loss (sensitivity analysis)	4	343	Mean Difference (IV, Random, 95% CI)	-0.96 [-1.21, -0.71]
14 Target lesion revascularization (sensitivity analysis)	4	343	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.44]
15 Binary restenosis (sensitivity analysis)	3	268	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.13, 0.50]
16 Death (sensitivity analysis)	4	322	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.11]
17 Change in Rutherford category (sensitivity analysis)	2	177	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.42, 0.50]
18 Change in ankle-brachial index (sensitivity analysis)	2	177	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.09, 0.08]

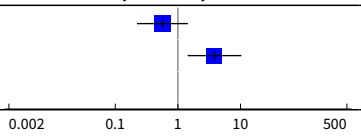
Analysis 1.1. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 1 Amputation.

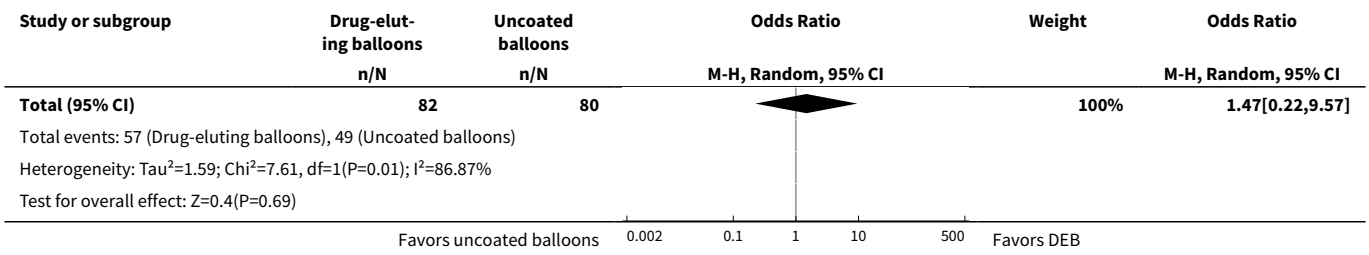
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
BIOLUX P-I	0/30	0/30			Not estimable
BIOLUX P-II	1/36	1/36		18.16%	1[0.06,16.63]
DEBELLUM 2012	1/27	2/27		35.98%	0.48[0.04,5.64]
FemPac 2008	0/45	1/42		28.65%	0.3[0.01,7.67]
LEVANT I 2014	1/37	0/38		8.86%	3.16[0.12,80.19]
PACIFIER 2012	0/44	0/47			Not estimable
THUNDER 2008	2/48	0/54		8.35%	5.86[0.27,125.17]
Total (95% CI)	**267**	**274**		**100%**	**1.21[0.39,3.8]**
Total events: 5 (Drug-eluting balloons), 4 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=2.62, df=4(P=0.62); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					



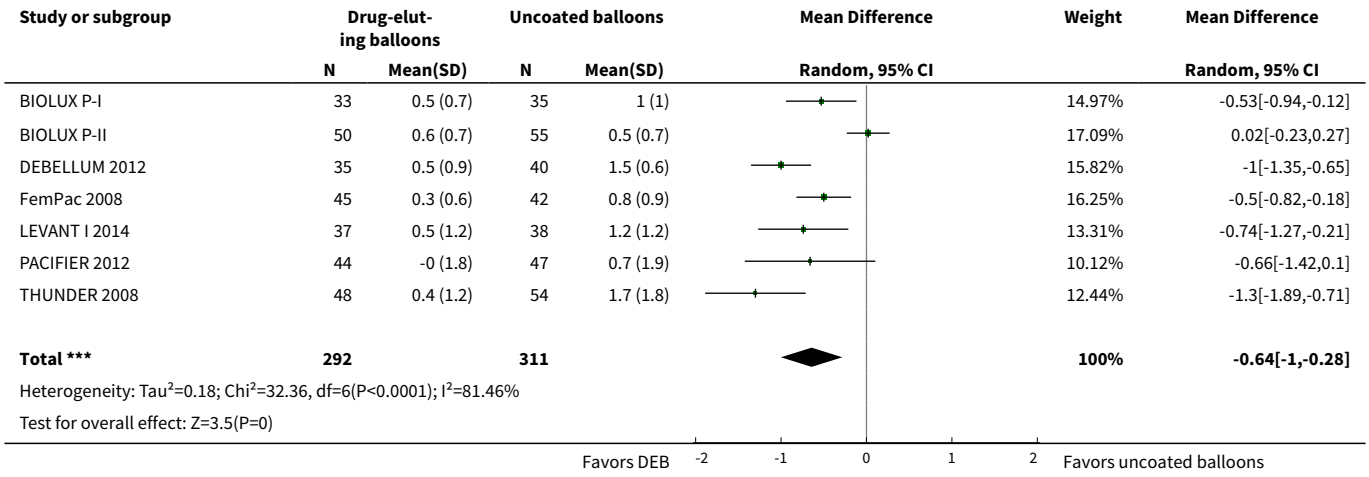
Analysis 1.2. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 2 Primary vessel patency.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
FemPac 2008	29/45	32/42		50.34%	0.57[0.22,1.44]
LEVANT I 2014	28/37	17/38		49.66%	3.84[1.43,10.31]

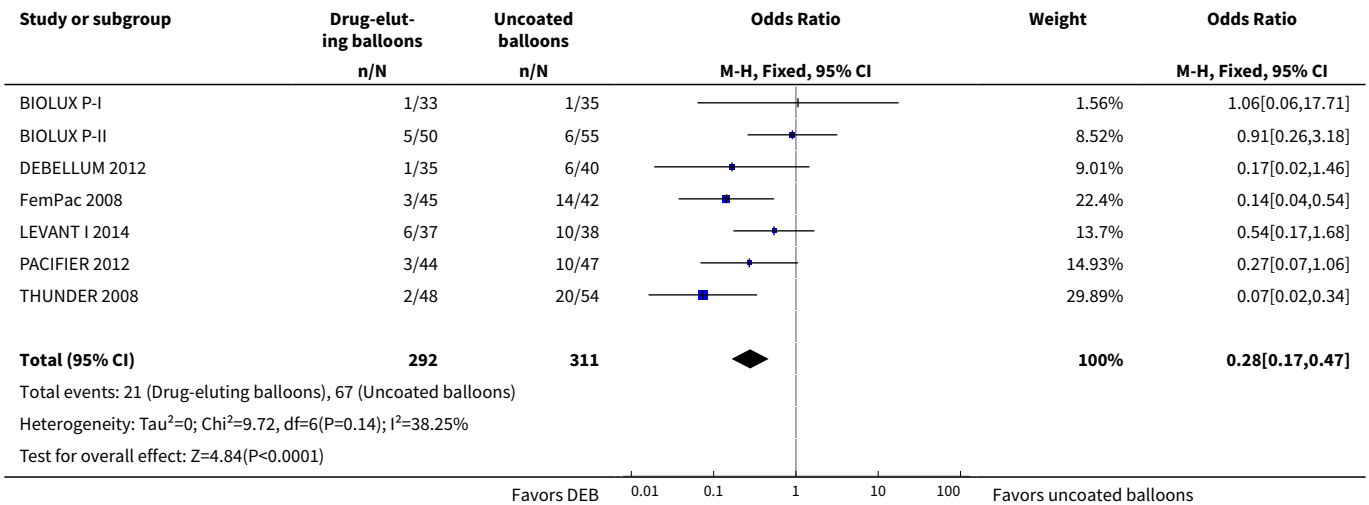




Analysis 1.3. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 3 Late lumen loss.

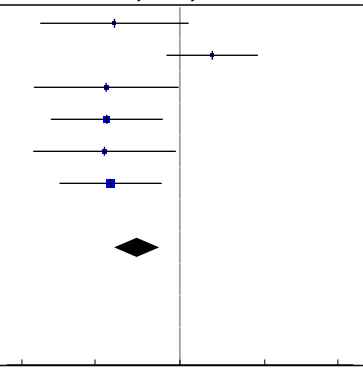


Analysis 1.4. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 4 Target lesion revascularization.



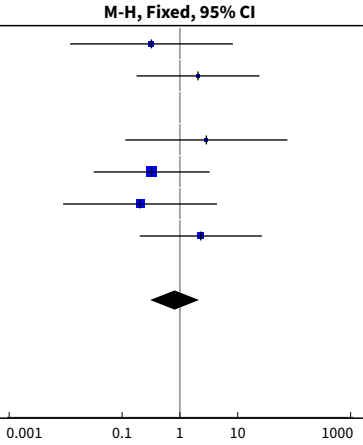
Analysis 1.5. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 5 Binary restenosis.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
BIOLUX P-I	3/33	9/35		12.03%	0.29[0.07,1.18]
BIOLUX P-II	17/50	12/55		11.43%	1.85[0.78,4.39]
DEBELLUM 2012	3/35	11/40		14.22%	0.25[0.06,0.97]
FemPac 2008	6/45	16/42		21.73%	0.25[0.09,0.72]
PACIFIER 2012	3/44	11/47		15.02%	0.24[0.06,0.93]
THUNDER 2008	7/48	21/54		25.58%	0.27[0.1,0.71]
Total (95% CI)	**255**	**273**		**100%**	**0.44[0.29,0.67]**
Total events: 39 (Drug-eluting balloons), 80 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=14.39, df=5(P=0.01); I^2=65.26%					
Test for overall effect: Z=3.76(P=0)					



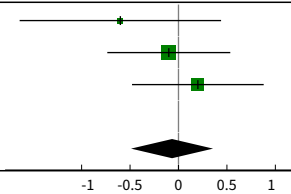
Analysis 1.6. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 6 Death.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
BIOLUX P-I	0/30	1/30		16.23%	0.32[0.01,8.24]
BIOLUX P-II	2/36	1/36		10.38%	2.06[0.18,23.77]
DEBELLUM 2012	0/27	0/27			Not estimable
FemPac 2008	1/45	0/42		5.5%	2.87[0.11,72.29]
LEVANT I 2014	1/37	3/38		31.67%	0.32[0.03,3.27]
PACIFIER 2012	0/44	2/47		26.31%	0.2[0.01,4.38]
THUNDER 2008	2/48	1/54		9.92%	2.3[0.2,26.25]
Total (95% CI)	**267**	**274**		**100%**	**0.81[0.31,2.14]**
Total events: 6 (Drug-eluting balloons), 8 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=3.55, df=5(P=0.62); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					

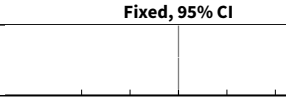


Analysis 1.7. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 7 Change in Rutherford category.

Study or subgroup	Drug-eluting balloons N	Mean(SD)	Uncoated balloons N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
BIOLUX P-II	36	-2.2 (2.2)	36	-1.6 (2.3)		16.6%	-0.6[-1.64,0.44]
LEVANT I 2014	37	-1.7 (1.3)	38	-1.6 (1.5)		44.54%	-0.1[-0.73,0.53]
THUNDER 2008	48	-0.1 (1.7)	54	-0.3 (1.8)		38.86%	0.2[-0.48,0.88]
Total ***	**121**		**128**			**100%**	**-0.07[-0.49,0.36]**

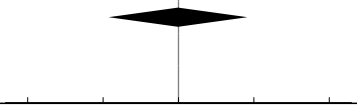


Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.61, df=2(P=0.45); I²=0%							
Test for overall effect: Z=0.31(P=0.76)							



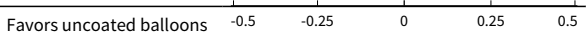
Analysis 1.8. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 8 Change in ankle-brachial index.

Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
BIOLUX P-II	50	0 (0.3)	55	0.2 (0.3)		24.85%	-0.2[-0.31,-0.09]
FemPac 2008	45	0.1 (0.2)	42	-0.1 (0.1)		26.52%	0.2[0.13,0.27]
LEVANT I 2014	37	0.2 (0.3)	38	0.2 (0.3)		23.19%	-0.02[-0.17,0.13]
THUNDER 2008	48	-0.1 (0.3)	54	-0.1 (0.2)		25.44%	0[-0.1,0.1]
Total ***	**180**		**189**			**100%**	**-0[-0.19,0.18]**
Heterogeneity: Tau²=0.03; Chi²=38.54, df=3(P<0.0001); I²=92.22%							
Test for overall effect: Z=0.01(P=0.99)							



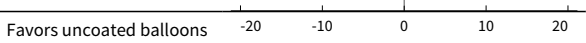
Analysis 1.9. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 9 Change in quality of life (EQ-5D).

Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
BIOLUX P-II	36	0.7 (0.3)	36	0.8 (0.2)		-0.1[-0.22,0.02]



Analysis 1.10. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 10 Change in walking impairment score.

Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
LEVANT I 2014	37	35.3 (32.5)	38	36 (35.1)		-0.7[-16,14.6]

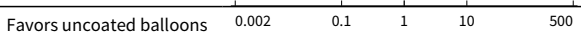


Analysis 1.11. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 11 Amputation (sensitivity analysis).

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
DEBELLUM 2012	1/27	2/27		67.65%	0.48[0.04,5.64]
LEVANT I 2014	1/37	0/38		16.65%	3.16[0.12,80.19]
PACIFIER 2012	0/44	0/47			Not estimable
THUNDER 2008	2/48	0/54		15.7%	5.86[0.27,125.17]
Total (95% CI)	**156**	**166**		**100%**	**1.77[0.42,7.54]**
Total events: 4 (Drug-eluting balloons), 2 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=1.79, df=2(P=0.41); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					

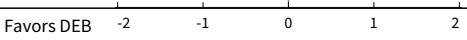
Analysis 1.12. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 12 Primary vessel patency (sensitivity analysis).

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
LEVANT I 2014	28/37	17/38		3.84[1.43,10.31]



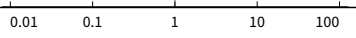
Analysis 1.13. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 13 Late lumen loss (sensitivity analysis).

Study or subgroup	Drug-eluting balloons N	Mean(SD)	Uncoated balloons N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DEBELLUM 2012	35	0.5 (0.9)	40	1.5 (0.6)		49.7%	-1[-1.35,-0.65]
LEVANT I 2014	37	0.5 (1.2)	38	1.2 (1.2)		22.05%	-0.74[-1.27,-0.21]
PACIFIER 2012	44	-0 (1.8)	47	0.7 (1.9)		10.5%	-0.66[-1.42,0.1]
THUNDER 2008	48	0.4 (1.2)	54	1.7 (1.8)		17.75%	-1.3[-1.89,-0.71]
Total ***	**164**		**179**			**100%**	**-0.96[-1.21,-0.71]**
Heterogeneity: Tau^2=0; Chi^2=2.59, df=3(P=0.46); I^2=0%							
Test for overall effect: Z=7.6(P<0.0001)							



Analysis 1.14. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 14 Target lesion revascularization (sensitivity analysis).

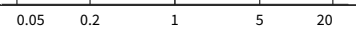
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
DEBELLUM 2012	1/35	6/40		13.35%	0.17[0.02,1.46]
LEVANT I 2014	6/37	10/38		20.28%	0.54[0.17,1.68]
PACIFIER 2012	3/44	10/47		22.11%	0.27[0.07,1.06]
THUNDER 2008	2/48	20/54		44.26%	0.07[0.02,0.34]
Total (95% CI)	**164**	**179**		**100%**	**0.22[0.11,0.44]**
Total events: 12 (Drug-eluting balloons), 46 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=4.52, df=3(P=0.21); I^2=33.58%					
Test for overall effect: Z=4.3(P<0.0001)					



Favors DEB — Favors uncoated balloons

Analysis 1.15. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 15 Binary restenosis (sensitivity analysis).

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
DEBELLUM 2012	3/35	11/40		25.94%	0.25[0.06,0.97]
PACIFIER 2012	3/44	11/47		27.4%	0.24[0.06,0.93]
THUNDER 2008	7/48	21/54		46.66%	0.27[0.1,0.71]
Total (95% CI)	**127**	**141**		**100%**	**0.25[0.13,0.5]**
Total events: 13 (Drug-eluting balloons), 43 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=2(P=0.99); I^2=0%					
Test for overall effect: Z=3.92(P<0.0001)					



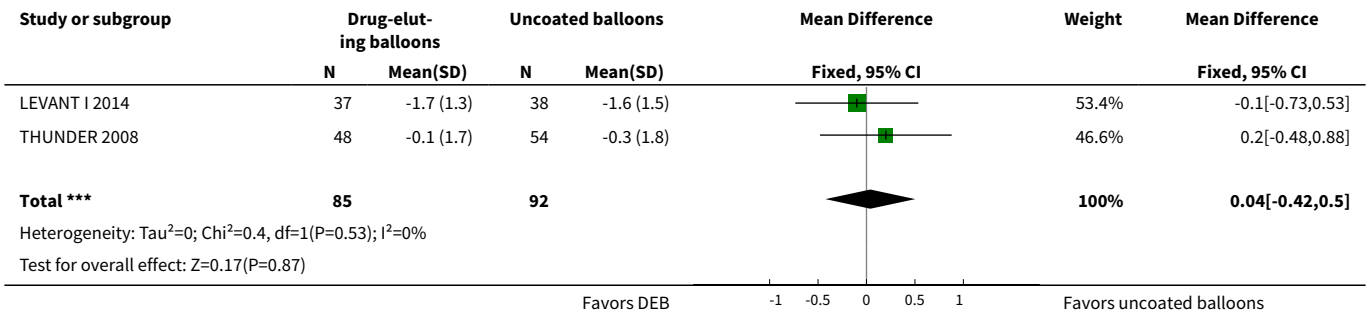
Favors DEB — Favors uncoated balloons

Analysis 1.16. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 16 Death (sensitivity analysis).

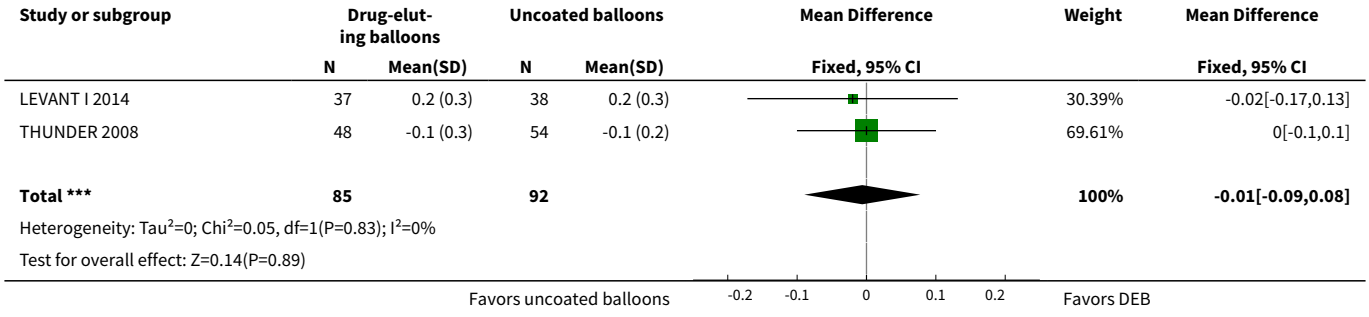
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
DEBELLUM 2012	0/27	0/27			Not estimable
LEVANT I 2014	1/37	3/38		46.64%	0.32[0.03,3.27]
PACIFIER 2012	0/44	2/47		38.75%	0.2[0.01,4.38]
THUNDER 2008	2/48	1/54		14.61%	2.3[0.2,26.25]
Total (95% CI)	**156**	**166**		**100%**	**0.57[0.15,2.11]**
Total events: 3 (Drug-eluting balloons), 6 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=0.85(P=0.4)					

Favors DEB — Favors uncoated balloons

Analysis 1.17. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 17 Change in Rutherford category (sensitivity analysis).



Analysis 1.18. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months, Outcome 18 Change in ankle-brachial index (sensitivity analysis).



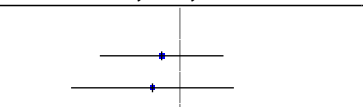
Comparison 2. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months

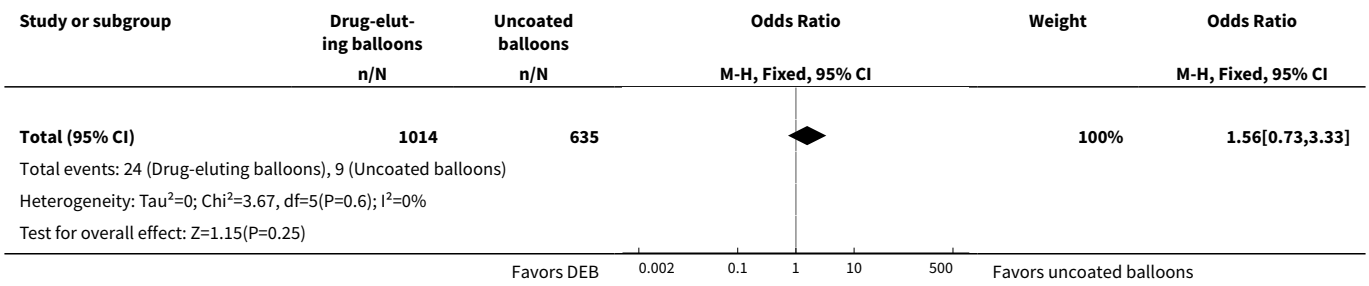
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	9	1649	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.73, 3.33]
2 Amputation-free survival	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Primary vessel patency	3	882	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [1.45, 2.56]
4 Late lumen loss	3	535	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.59, 0.13]
5 Target lesion revascularization	11	1900	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.31, 0.51]
6 Binary restenosis	4	1094	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.15, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Death	9	1649	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.64, 1.71]
8 Change in Rutherford category	3	623	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.29, 0.10]
9 Change in ankle-brachial index	3	656	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.07, 0.01]
10 Change in Quality of Life (EQ-5D)	3	879	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.02, 0.04]
11 Change in walking impairment score	2	551	Mean Difference (IV, Fixed, 95% CI)	3.57 [-1.23, 8.38]
12 Amputation (sensitivity analysis)	7	1517	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.79, 4.04]
13 Target lesion revascularization (sensitivity analysis)	8	1640	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.18, 0.61]
14 Death (sensitivity analysis)	7	1517	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.64, 1.85]
15 Late lumen loss (sensitivity analysis)	2	177	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.41, -0.79]
16 Change in Rutherford category (sensitivity analysis)	2	551	Mean Difference (IV, Random, 95% CI)	0.09 [-0.58, 0.77]
17 Change in ankle-brachial index (sensitivity analysis)	2	551	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.03]
18 Change in quality of life (EQ-5D) (sensitivity analysis)	2	807	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.05]

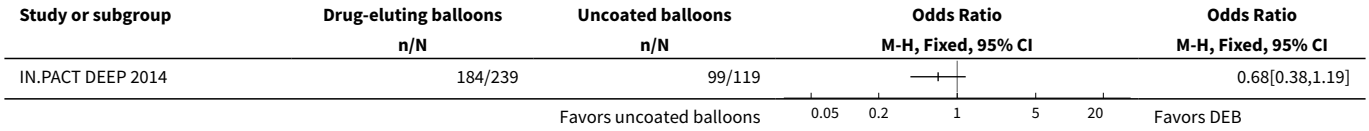
Analysis 2.1. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 1 Amputation.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
BIOLUX P-I	0/30	0/30			Not estimable
BIOLUX P-II	1/36	2/36		17.11%	0.49[0.04,5.61]
DEBATE-BTK 2013	0/65	1/67		12.9%	0.34[0.01,8.46]
DEBELLUM 2012	1/27	2/27		16.95%	0.48[0.04,5.64]
IN.PACT DEEP 2014	20/239	4/119		43.06%	2.63[0.88,7.86]
IN.PACT SFA 2015	0/220	0/111			Not estimable
LEVANT I 2014	1/37	0/38		4.17%	3.16[0.12,80.19]
LEVANT II 2015	1/316	0/160		5.81%	1.53[0.06,37.67]
PACIFIER 2012	0/44	0/47			Not estimable

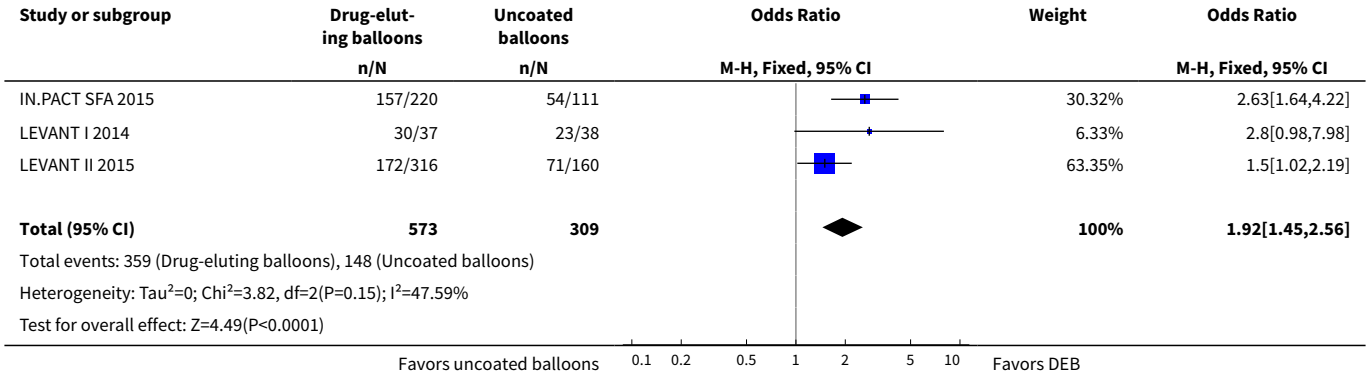




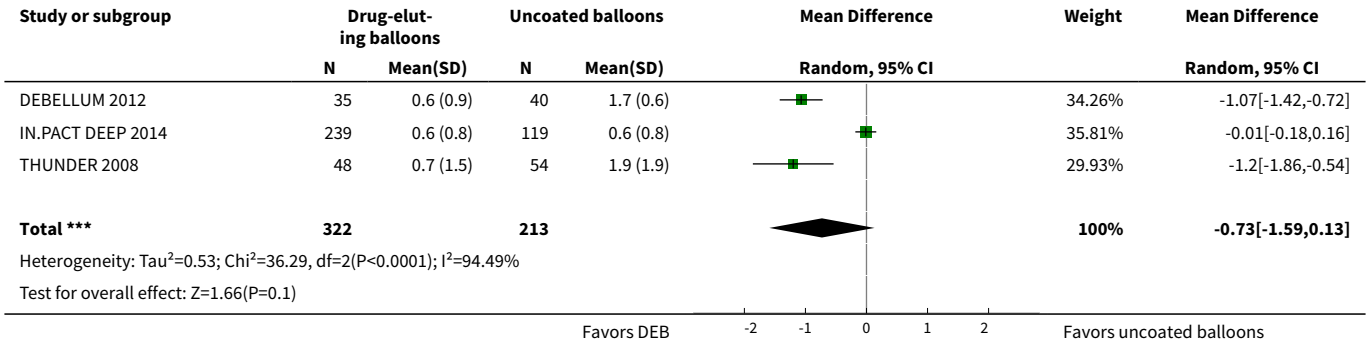
Analysis 2.2. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 2 Amputation-free survival.



Analysis 2.3. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 3 Primary vessel patency.

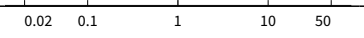


Analysis 2.4. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 4 Late lumen loss.



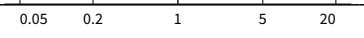
Analysis 2.5. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 5 Target lesion revascularization.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
BIOLUX P-I	4/33	10/35		4.47%	0.34[0.1,1.24]
BIOLUX P-II	10/50	10/55		3.99%	1.13[0.42,2.98]
DEBATE-BTK 2013	12/65	29/67		12.2%	0.3[0.13,0.65]
DEBELLUM 2012	5/35	17/40		7.12%	0.23[0.07,0.7]
FemPac 2008	6/45	21/42		9.86%	0.15[0.05,0.44]
IN.PACT DEEP 2014	27/239	15/119		9.3%	0.88[0.45,1.73]
IN.PACT SFA 2015	5/220	22/111		14.97%	0.09[0.03,0.26]
LEVANT I 2014	13/37	14/38		4.69%	0.93[0.36,2.39]
LEVANT II 2015	35/316	24/160		14.84%	0.71[0.4,1.23]
PACIFIER 2012	3/44	15/47		7.08%	0.16[0.04,0.59]
THUNDER 2008	5/48	26/54		11.48%	0.13[0.04,0.36]
Total (95% CI)	**1132**	**768**		**100%**	**0.4[0.31,0.51]**
Total events: 125 (Drug-eluting balloons), 203 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=35.95, df=10(P<0.0001); I^2=72.19%					
Test for overall effect: Z=7.19(P<0.0001)					



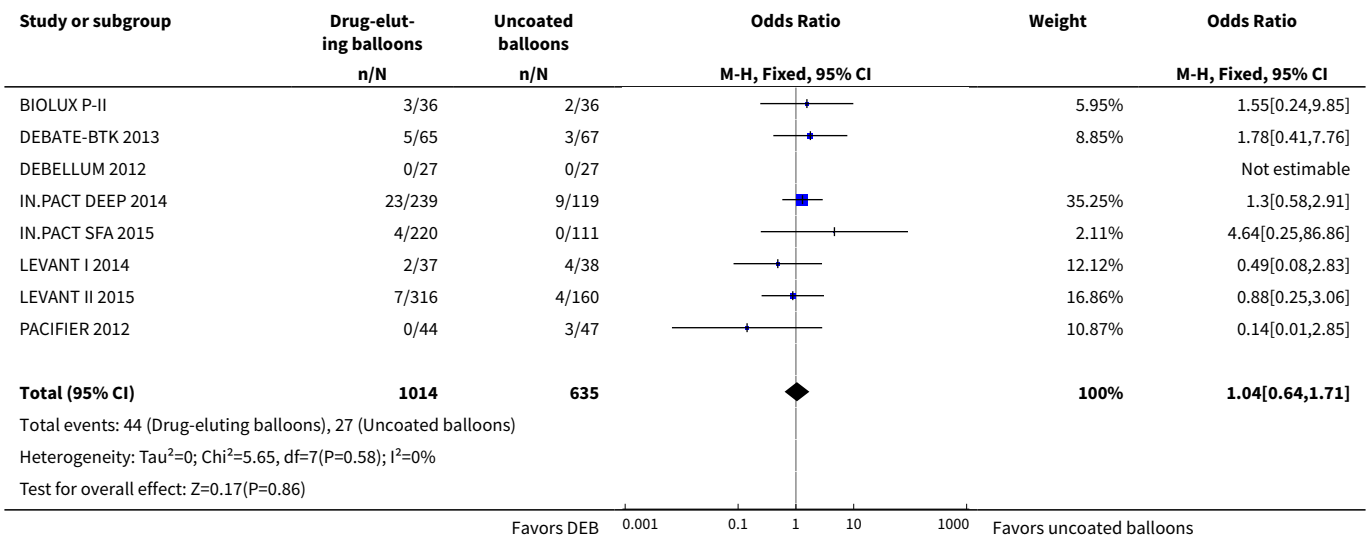
Analysis 2.6. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 6 Binary restenosis.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
DEBATE-BTK 2013	20/80	55/78		24.93%	0.14[0.07,0.28]
IN.PACT DEEP 2014	25/239	11/119		24.49%	1.15[0.54,2.42]
LEVANT II 2015	57/316	40/160		27.13%	0.66[0.42,1.04]
THUNDER 2008	15/48	38/54		23.45%	0.19[0.08,0.45]
Total (95% CI)	**683**	**411**		**100%**	**0.38[0.15,0.98]**
Total events: 117 (Drug-eluting balloons), 144 (Uncoated balloons)					
Heterogeneity: Tau^2=0.78; Chi^2=23.37, df=3(P<0.0001); I^2=87.16%					
Test for overall effect: Z=2.01(P=0.04)					

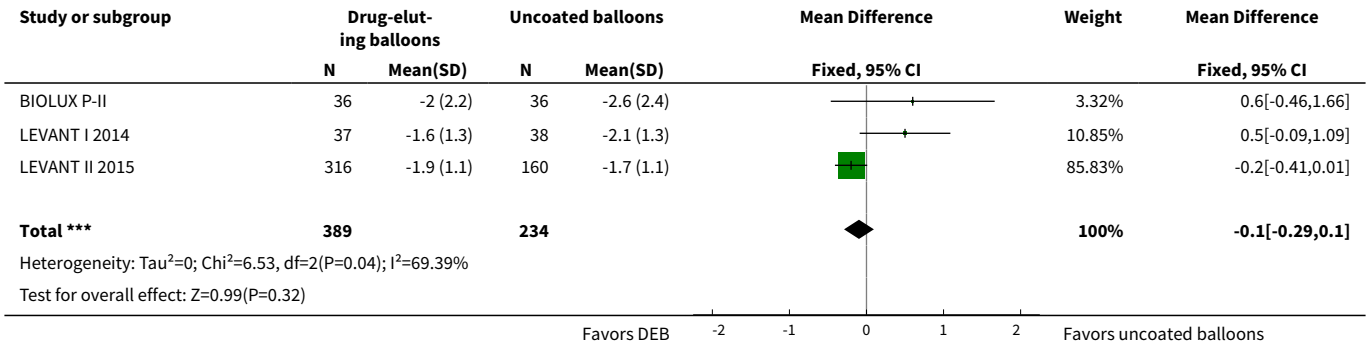


Analysis 2.7. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 7 Death.

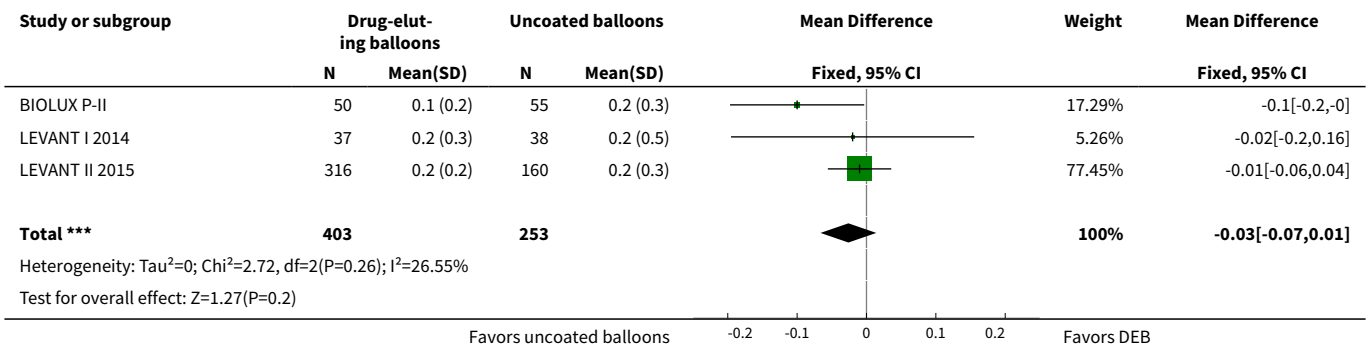
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
BIOLUX P-I	0/30	2/30		7.98%	0.19[0.01,4.06]



Analysis 2.8. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 8 Change in Rutherford category.

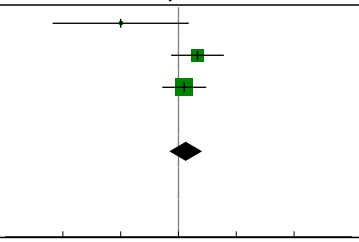


Analysis 2.9. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 9 Change in ankle-brachial index.



Analysis 2.10. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 10 Change in Quality of Life (EQ-5D).

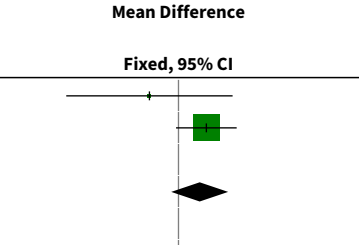
Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
BIOLUX P-II	36	0.7 (0.3)	36	0.8 (0.2)		5.79%	-0.1[-0.22,0.02]
IN.PACT SFA 2015	220	0.1 (0.2)	111	0.1 (0.2)		38.65%	0.03[-0.01,0.08]
LEVANT II 2015	316	0.1 (0.2)	160	0.1 (0.2)		55.56%	0.01[-0.03,0.05]
Total ***	**572**		**307**			**100%**	**0.01[-0.02,0.04]**
Heterogeneity: Tau^2=0; Chi^2=4.29, df=2(P=0.12); I^2=53.38%							
Test for overall effect: Z=0.86(P=0.39)							



Favors uncoated balloons — Favors DEB

Analysis 2.11. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 11 Change in walking impairment score.

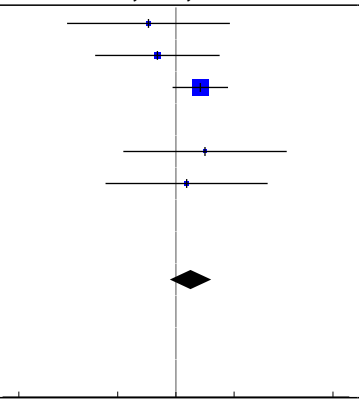
Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
LEVANT I 2014	37	29.7 (26.1)	38	34.6 (35.3)		11.72%	-4.9[-18.92,9.12]
LEVANT II 2015	316	23.9 (27.6)	160	19.2 (26.5)		88.28%	4.7[-0.41,9.81]
Total ***	**353**		**198**			**100%**	**3.57[-1.23,8.38]**
Heterogeneity: Tau^2=0; Chi^2=1.59, df=1(P=0.21); I^2=37.06%							
Test for overall effect: Z=1.46(P=0.14)							



Favors uncoated balloons — Favors DEB

Analysis 2.12. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 12 Amputation (sensitivity analysis).

Study or subgroup	Drug-eluting balloons	Uncoated balloons	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
DEBATE-BTK 2013	0/65	1/67		15.57%	0.34[0.01,8.46]
DEBELLUM 2012	1/27	2/27		20.44%	0.48[0.04,5.64]
IN.PACT DEEP 2014	20/239	4/119		51.95%	2.63[0.88,7.86]
IN.PACT SFA 2015	0/220	0/111			Not estimable
LEVANT I 2014	1/37	0/38		5.03%	3.16[0.12,80.19]
LEVANT II 2015	1/316	0/160		7.01%	1.53[0.06,37.67]
PACIFIER 2012	0/44	0/47			Not estimable
Total (95% CI)	**948**	**569**		**100%**	**1.78[0.79,4.04]**
Total events: 23 (Drug-eluting balloons), 7 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=2.72, df=4(P=0.61); I^2=0%					
Test for overall effect: Z=1.38(P=0.17)					



Favors DEB — Favors uncoated balloons

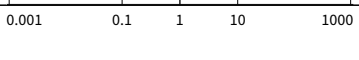
Analysis 2.13. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 13 Target lesion revascularization (sensitivity analysis).

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
DEBATE-BTK 2013	12/65	29/67		13.57%	0.3[0.13,0.65]
DEBELLUM 2012	5/35	17/40		11.04%	0.23[0.07,0.7]
IN.PACT DEEP 2014	27/239	15/119		14.43%	0.88[0.45,1.73]
IN.PACT SFA 2015	5/220	22/111		12%	0.09[0.03,0.26]
LEVANT I 2014	13/37	14/38		12.44%	0.93[0.36,2.39]
LEVANT II 2015	35/316	24/160		15.22%	0.71[0.4,1.23]
PACIFIER 2012	3/44	15/47		9.78%	0.16[0.04,0.59]
THUNDER 2008	5/48	26/54		11.52%	0.13[0.04,0.36]
Total (95% CI)	**1004**	**636**		**100%**	**0.33[0.18,0.61]**
Total events: 105 (Drug-eluting balloons), 162 (Uncoated balloons)					
Heterogeneity: Tau^2=0.59; Chi^2=28.44, df=7(P=0); I^2=75.39%					
Test for overall effect: Z=3.48(P=0)					

Favors DEB — Favors uncoated balloons

Analysis 2.14. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 14 Death (sensitivity analysis).

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
DEBATE-BTK 2013	5/65	3/67		10.29%	1.78[0.41,7.76]
DEBELLUM 2012	0/27	0/27			Not estimable
IN.PACT DEEP 2014	23/239	9/119		40.96%	1.3[0.58,2.91]
IN.PACT SFA 2015	4/220	0/111		2.45%	4.64[0.25,86.86]
LEVANT I 2014	2/37	4/38		14.08%	0.49[0.08,2.83]
LEVANT II 2015	7/316	4/160		19.59%	0.88[0.25,3.06]
PACIFIER 2012	0/44	3/47		12.63%	0.14[0.01,2.85]
Total (95% CI)	**948**	**569**		**100%**	**1.09[0.64,1.85]**
Total events: 41 (Drug-eluting balloons), 23 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=4.24, df=5(P=0.52); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					

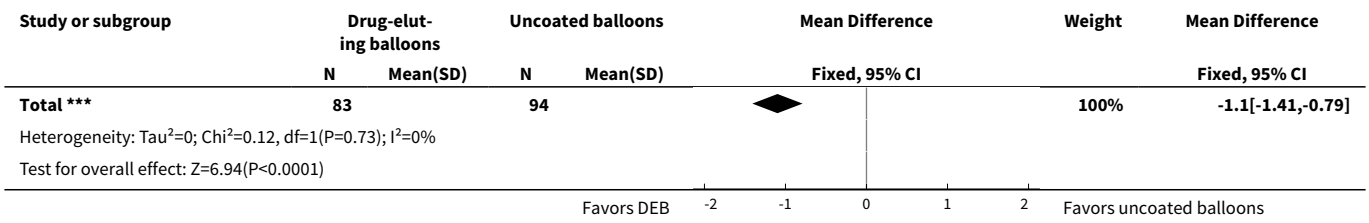


Favors DEB — Favors uncoated balloons

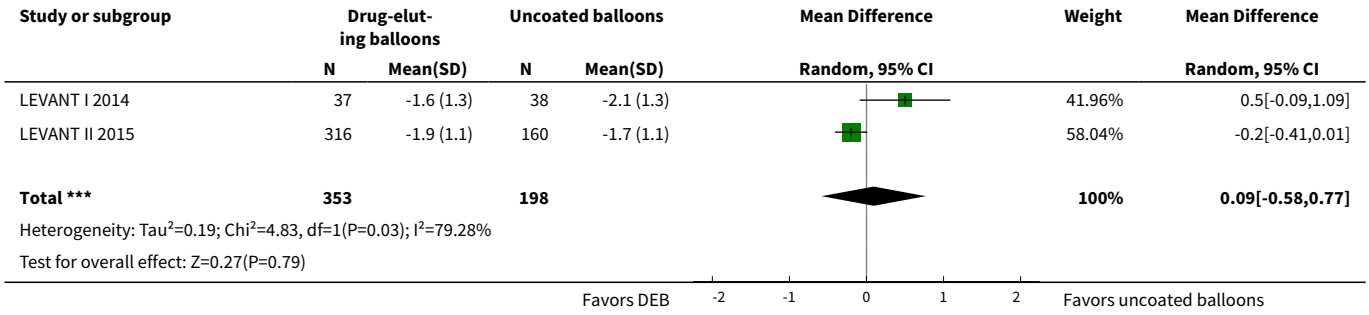
Analysis 2.15. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 15 Late lumen loss (sensitivity analysis).

Study or subgroup	Drug-eluting balloons N	Mean(SD)	Uncoated balloons N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
DEBELLUM 2012	35	0.6 (0.9)	40	1.7 (0.6)		77.96%	-1.07[-1.42,-0.72]
THUNDER 2008	48	0.7 (1.5)	54	1.9 (1.9)		22.04%	-1.2[-1.86,-0.54]

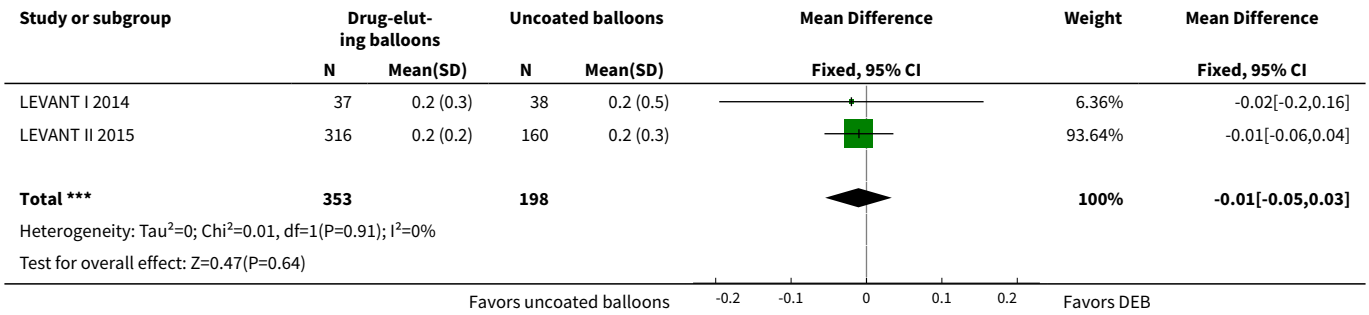
Favors DEB — Favors uncoated balloons



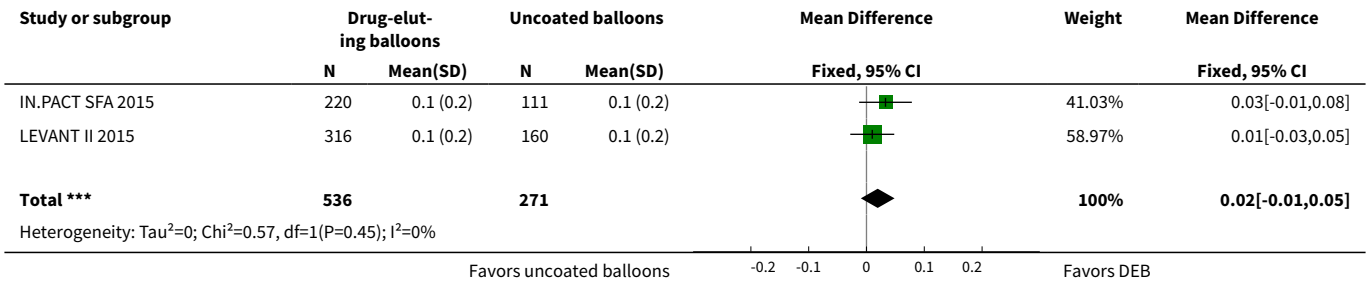
Analysis 2.16. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 16 Change in Rutherford category (sensitivity analysis).

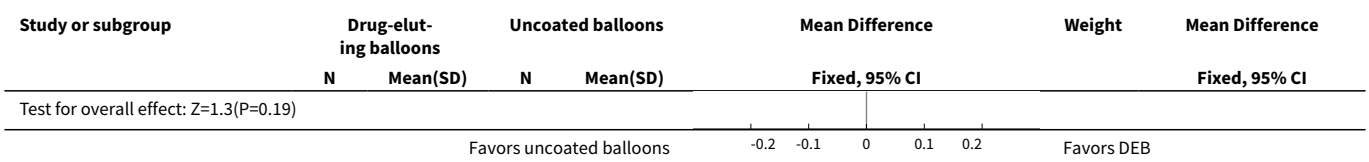


Analysis 2.17. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 17 Change in ankle-brachial index (sensitivity analysis).



Analysis 2.18. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months, Outcome 18 Change in quality of life (EQ-5D) (sensitivity analysis).

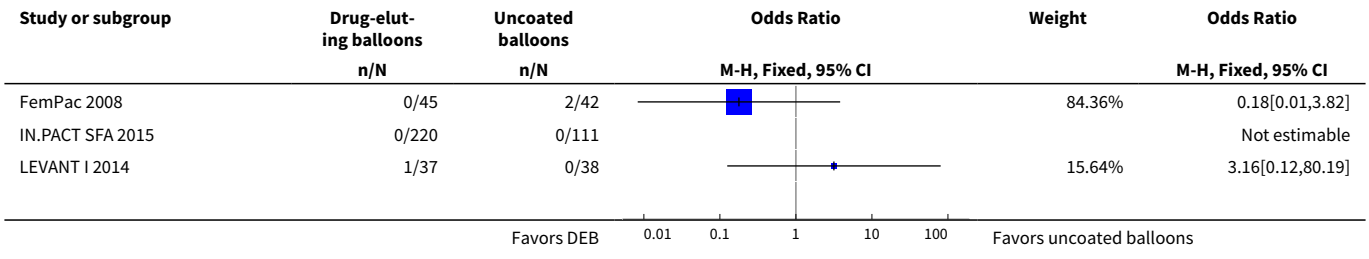


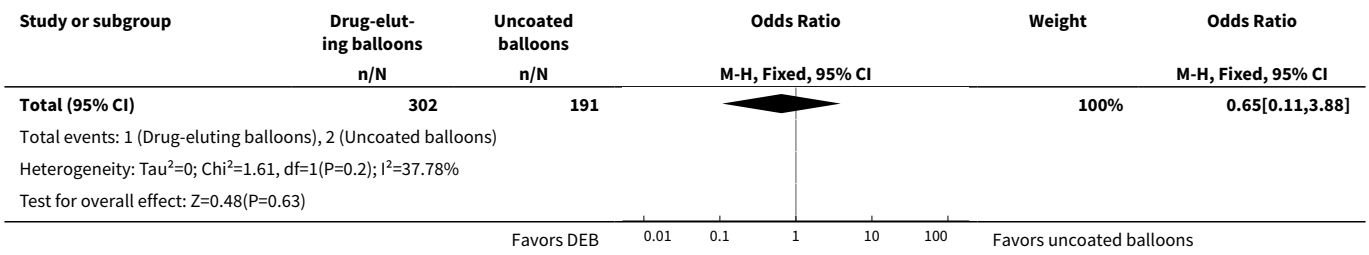


Comparison 3. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years

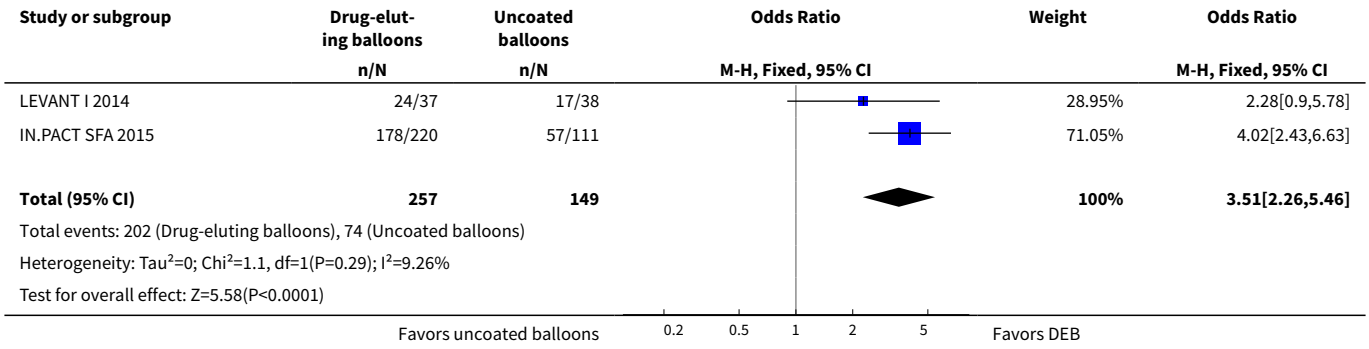
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	3	493	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.11, 3.88]
2 Primary vessel patency	2	406	Odds Ratio (M-H, Fixed, 95% CI)	3.51 [2.26, 5.46]
3 Late lumen loss	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Target lesion revascularization	3	508	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.18, 0.44]
5 Binary restenosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Death	4	595	Odds Ratio (M-H, Fixed, 95% CI)	2.13 [1.08, 4.20]
7 Change in Rutherford category	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Change in ankle-brachial index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Change in quality of life (EQ-5D)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Change in walking impairment score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Amputation (sensitivity analysis)	2	406	Odds Ratio (M-H, Fixed, 95% CI)	3.16 [0.12, 80.19]
12 Death (sensitivity analysis)	3	508	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [1.00, 4.67]

Analysis 3.1. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 1 Amputation.

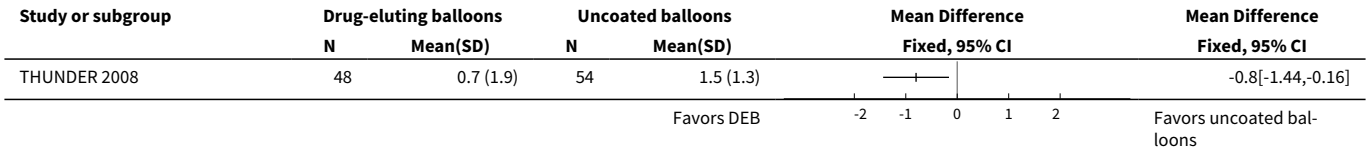




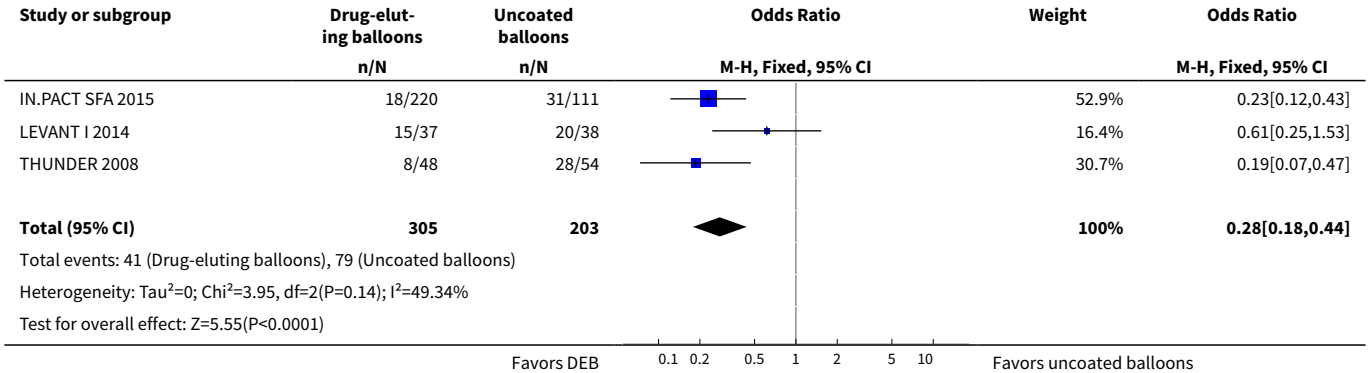
Analysis 3.2. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 2 Primary vessel patency.



Analysis 3.3. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 3 Late lumen loss.

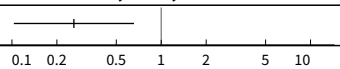


Analysis 3.4. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 4 Target lesion revascularization.



Analysis 3.5. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 5 Binary restenosis.

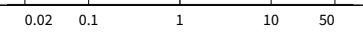
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
FemPac 2008	10/45	22/42		0.26[0.1,0.66]



Favors DEB | Favors uncoated balloons

Analysis 3.6. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 6 Death.

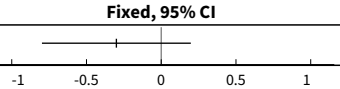
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
FemPac 2008	6/45	3/42		21.79%	2[0.47,8.57]
IN.PACT SFA 2015	16/220	1/111		9.99%	8.63[1.13,65.92]
LEVANT I 2014	4/37	5/38		35.65%	0.8[0.2,3.25]
THUNDER 2008	7/48	5/54		32.57%	1.67[0.49,5.67]
Total (95% CI)	**350**	**245**		**100%**	**2.13[1.08,4.2]**
Total events: 33 (Drug-eluting balloons), 14 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=3.85, df=3(P=0.28); I^2=22.08%					
Test for overall effect: Z=2.18(P=0.03)					



Favors DEB | Favors uncoated balloons

Analysis 3.7. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 7 Change in Rutherford category.

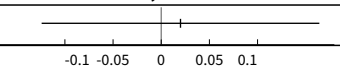
Study or subgroup	Drug-eluting balloons N	Mean(SD)	Uncoated balloons N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
LEVANT I 2014	37	-2.1 (1.1)	38	-1.8 (1.1)		-0.3[-0.8,0.2]



Favors DEB | Favors uncoated balloons

Analysis 3.8. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 8 Change in ankle-brachial index.

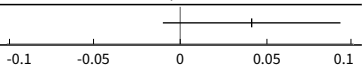
Study or subgroup	Drug-eluting balloons N	Mean(SD)	Uncoated balloons N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
LEVANT I 2014	42	0.2 (0.3)	41	0.2 (0.3)		0.02[-0.12,0.16]



Favors uncoated balloons | Favors DEB

Analysis 3.9. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 9 Change in quality of life (EQ-5D).

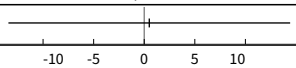
Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
IN.PACT SFA 2015	220	0.1 (0.2)	111	0.1 (0.2)		0.04[-0.01,0.09]



Favors uncoated balloons — Favors DEB

Analysis 3.10. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 10 Change in walking impairment score.

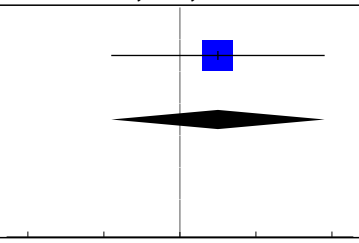
Study or subgroup	Drug-eluting balloons		Uncoated balloons		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
LEVANT I 2014	37	40.8 (29.5)	38	40.3 (32)		0.5[-13.42,14.42]



Favors uncoated balloons — Favors DEB

Analysis 3.11. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 11 Amputation (sensitivity analysis).

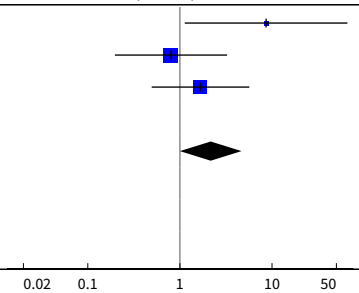
Study or subgroup	Drug-eluting balloons	Uncoated balloons	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
IN.PACT SFA 2015	0/220	0/111			Not estimable
LEVANT I 2014	1/37	0/38		100%	3.16[0.12,80.19]
Total (95% CI)	**257**	**149**		**100%**	**3.16[0.12,80.19]**
Total events: 1 (Drug-eluting balloons), 0 (Uncoated balloons)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					



Favors DEB — Favors uncoated balloons

Analysis 3.12. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at two years, Outcome 12 Death (sensitivity analysis).

Study or subgroup	Drug-eluting balloons	Uncoated balloons	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
IN.PACT SFA 2015	16/220	1/111		12.77%	8.63[1.13,65.92]
LEVANT I 2014	4/37	5/38		45.59%	0.8[0.2,3.25]
THUNDER 2008	7/48	5/54		41.64%	1.67[0.49,5.67]
Total (95% CI)	**305**	**203**		**100%**	**2.16[1,4.67]**
Total events: 27 (Drug-eluting balloons), 11 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=3.89, df=2(P=0.14); I^2=48.53%					
Test for overall effect: Z=1.97(P=0.05)					



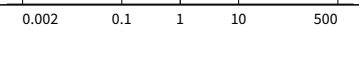
Favors DEB — Favors uncoated balloons

Comparison 4. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at five years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Target lesion revascularization	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Binary restenosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Death	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

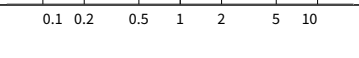
Analysis 4.1. Comparison 4 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at five years, Outcome 1 Amputation.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
THUNDER 2008	4/48	1/54		4.82[0.52,44.7]



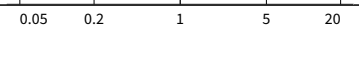
Analysis 4.2. Comparison 4 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at five years, Outcome 2 Target lesion revascularization.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
THUNDER 2008	10/48	30/54		0.21[0.09,0.51]



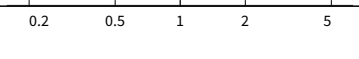
Analysis 4.3. Comparison 4 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at five years, Outcome 3 Binary restenosis.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
THUNDER 2008	18/48	45/54		0.12[0.05,0.3]



Analysis 4.4. Comparison 4 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at five years, Outcome 4 Death.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
THUNDER 2008	12/48	8/54		1.92[0.71,5.19]



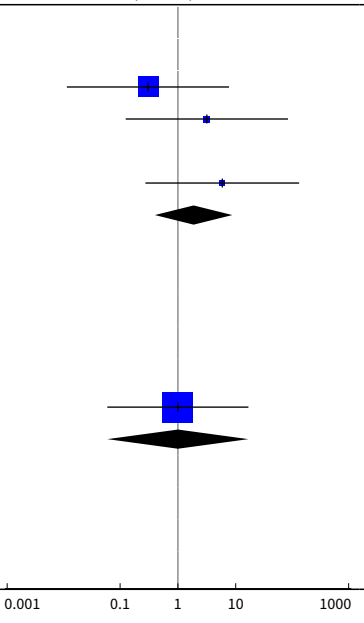
Comparison 5. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Femoropopliteal lesions	5	415	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [0.40, 8.75]
1.2 Tibial lesions	1	72	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.63]
2 Late lumen loss	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Femoropopliteal lesions	5	423	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-0.86, -0.45]
2.2 Tibial lesions	1	105	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.23, 0.27]
3 Target lesion revascularization	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Femoropopliteal lesions	5	423	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.12, 0.41]
3.2 Tibial lesions	1	105	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.26, 3.18]
4 Binary restenosis	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Femoropopliteal lesions	4	348	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.15, 0.46]
4.2 Tibial lesions	1	105	Odds Ratio (M-H, Fixed, 95% CI)	1.85 [0.78, 4.39]
5 Death	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Femoropopliteal lesions	5	415	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.22, 1.97]
5.2 Tibial lesions	1	72	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.18, 23.77]
6 Change in Rutherford category	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Femoropopliteal lesions	2	177	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.42, 0.50]
6.2 Tibial lesions	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.64, 0.44]
7 Change in ankle-brachial index	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Femoropopliteal lesions	3	264	Mean Difference (IV, Random, 95% CI)	0.07 [-0.09, 0.22]
7.2 Tibial lesions	1	105	Mean Difference (IV, Random, 95% CI)	-0.2 [-0.31, -0.09]
8 Amputation (sensitivity analysis)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Femoropopliteal lesions	3	268	Odds Ratio (M-H, Fixed, 95% CI)	4.47 [0.49, 40.67]
9 Late lumen loss (sensitivity analysis)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Femoropopliteal lesions	3	268	Mean Difference (IV, Fixed, 95% CI)	-0.92 [-1.27, -0.57]
10 Target lesion revascularization (sensitivity analysis)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Femoropopliteal lesions	3	268	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.11, 0.48]
11 Binary restenosis (sensitivity analysis)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Femoropopliteal lesions	2	193	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.12, 0.57]
12 Death (sensitivity analysis)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Femoropopliteal lesions	3	268	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.11]
13 Change in ankle-brachial index (sensitivity analysis)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Femoropopliteal lesions	2	177	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.09, 0.08]

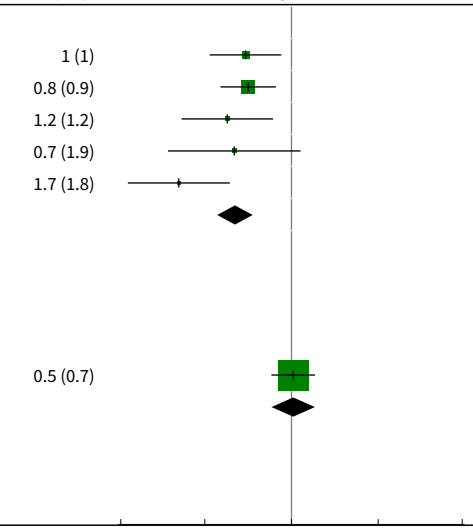
Analysis 5.1. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 1 Amputation.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Femoropopliteal lesions					
BIOLUX P-I	0/30	0/30			Not estimable
FemPac 2008	0/45	1/42		62.48%	0.3[0.01,7.67]
LEVANT I 2014	1/37	0/38		19.31%	3.16[0.12,80.19]
PACIFIER 2012	0/44	0/47			Not estimable
THUNDER 2008	2/48	0/54		18.21%	5.86[0.27,125.17]
Subtotal (95% CI)	**204**	**211**		**100%**	**1.87[0.4,8.75]**
Total events: 3 (Drug-eluting balloons), 1 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=1.85, df=2(P=0.4); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
5.1.2 Tibial lesions					
BIOLUX P-II	1/36	1/36		100%	1[0.06,16.63]
Subtotal (95% CI)	**36**	**36**		**100%**	**1[0.06,16.63]**
Total events: 1 (Drug-eluting balloons), 1 (Uncoated balloons)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					



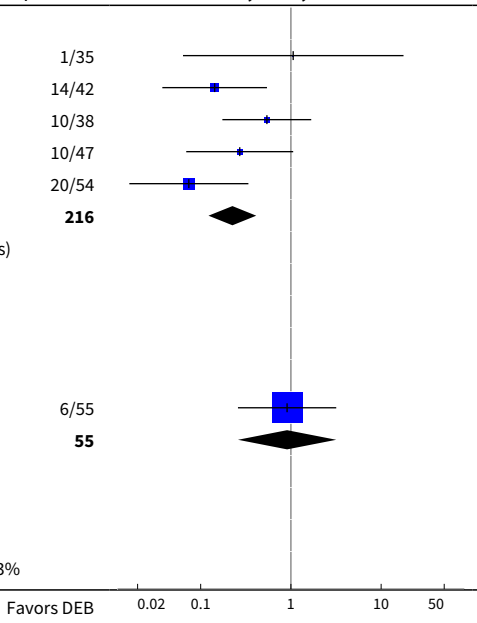
Analysis 5.2. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 2 Late lumen loss.

Study or subgroup	Drug-eluting balloons N	Drug-eluting balloons Mean(SD)	Uncoated balloons N	Uncoated balloons Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.2.1 Femoropopliteal lesions							
BIOLUX P-I	33	0.5 (0.7)	35	1 (1)		24.63%	-0.53[-0.94,-0.12]
FemPac 2008	45	0.3 (0.6)	42	0.8 (0.9)		41.01%	-0.5[-0.82,-0.18]
LEVANT I 2014	37	0.5 (1.2)	38	1.2 (1.2)		15.06%	-0.74[-1.27,-0.21]
PACIFIER 2012	44	-0 (1.8)	47	0.7 (1.9)		7.17%	-0.66[-1.42,0.1]
THUNDER 2008	48	0.4 (1.2)	54	1.7 (1.8)		12.12%	-1.3[-1.89,-0.71]
Subtotal ***	**207**		**216**			**100%**	**-0.65[-0.86,-0.45]**
Heterogeneity: Tau^2=0; Chi^2=5.98, df=4(P=0.2); I^2=33.09%							
Test for overall effect: Z=6.24(P<0.0001)							
5.2.2 Tibial lesions							
BIOLUX P-II	50	0.6 (0.7)	55	0.5 (0.7)		100%	0.02[-0.23,0.27]
Subtotal ***	**50**		**55**			**100%**	**0.02[-0.23,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.16(P=0.88)							
Test for subgroup differences: Chi^2=16.55, df=1 (P<0.0001), I^2=93.96%							



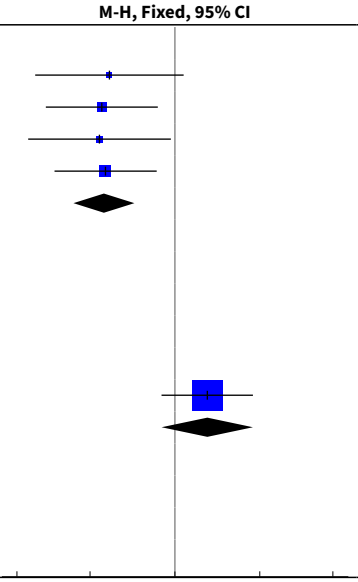
Analysis 5.3. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 3 Target lesion revascularization.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.3.1 Femoropopliteal lesions					
BIOLUX P-I	1/33	1/35		1.89%	1.06[0.06,17.71]
FemPac 2008	3/45	14/42		27.16%	0.14[0.04,0.54]
LEVANT I 2014	6/37	10/38		16.61%	0.54[0.17,1.68]
PACIFIER 2012	3/44	10/47		18.1%	0.27[0.07,1.06]
THUNDER 2008	2/48	20/54		36.24%	0.07[0.02,0.34]
Subtotal (95% CI)	**207**	**216**		**100%**	**0.22[0.12,0.41]**
Total events: 15 (Drug-eluting balloons), 55 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=6.06, df=4(P=0.19); I^2=33.97%					
Test for overall effect: Z=4.8(P<0.0001)					
5.3.2 Tibial lesions					
BIOLUX P-II	5/50	6/55		100%	0.91[0.26,3.18]
Subtotal (95% CI)	**50**	**55**		**100%**	**0.91[0.26,3.18]**
Total events: 5 (Drug-eluting balloons), 6 (Uncoated balloons)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					
Test for subgroup differences: Chi^2=3.85, df=1 (P=0.05), I^2=74.03%					



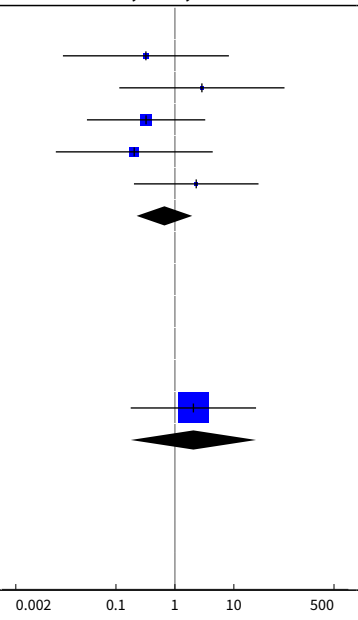
Analysis 5.4. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 4 Binary restenosis.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.4.1 Femoropopliteal lesions					
BIOLUX P-I	3/33	9/35		16.18%	0.29[0.07,1.18]
FemPac 2008	6/45	16/42		29.23%	0.25[0.09,0.72]
PACIFIER 2012	3/44	11/47		20.2%	0.24[0.06,0.93]
THUNDER 2008	7/48	21/54		34.4%	0.27[0.1,0.71]
Subtotal (95% CI)	**170**	**178**		**100%**	**0.26[0.15,0.46]**
Total events: 19 (Drug-eluting balloons), 57 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=3(P=1); I^2=0%					
Test for overall effect: Z=4.57(P<0.0001)					
5.4.2 Tibial lesions					
BIOLUX P-II	17/50	12/55		100%	1.85[0.78,4.39]
Subtotal (95% CI)	**50**	**55**		**100%**	**1.85[0.78,4.39]**
Total events: 17 (Drug-eluting balloons), 12 (Uncoated balloons)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.39(P=0.17)					
Test for subgroup differences: Chi^2=13.57, df=1 (P=0), I^2=92.63%					

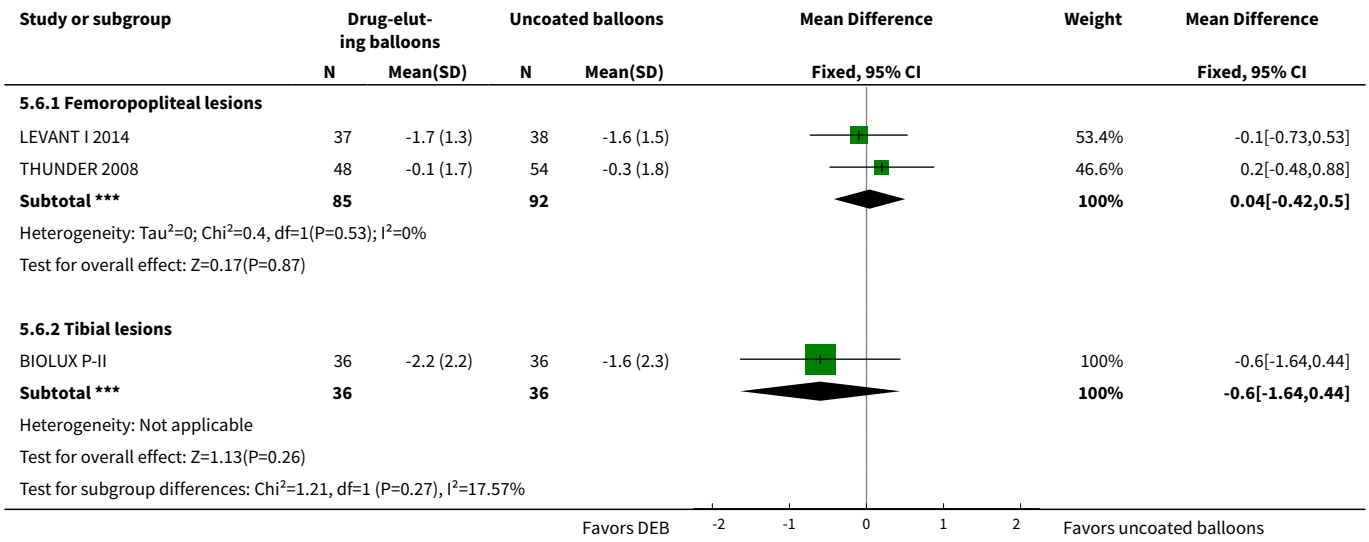


Analysis 5.5. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 5 Death.

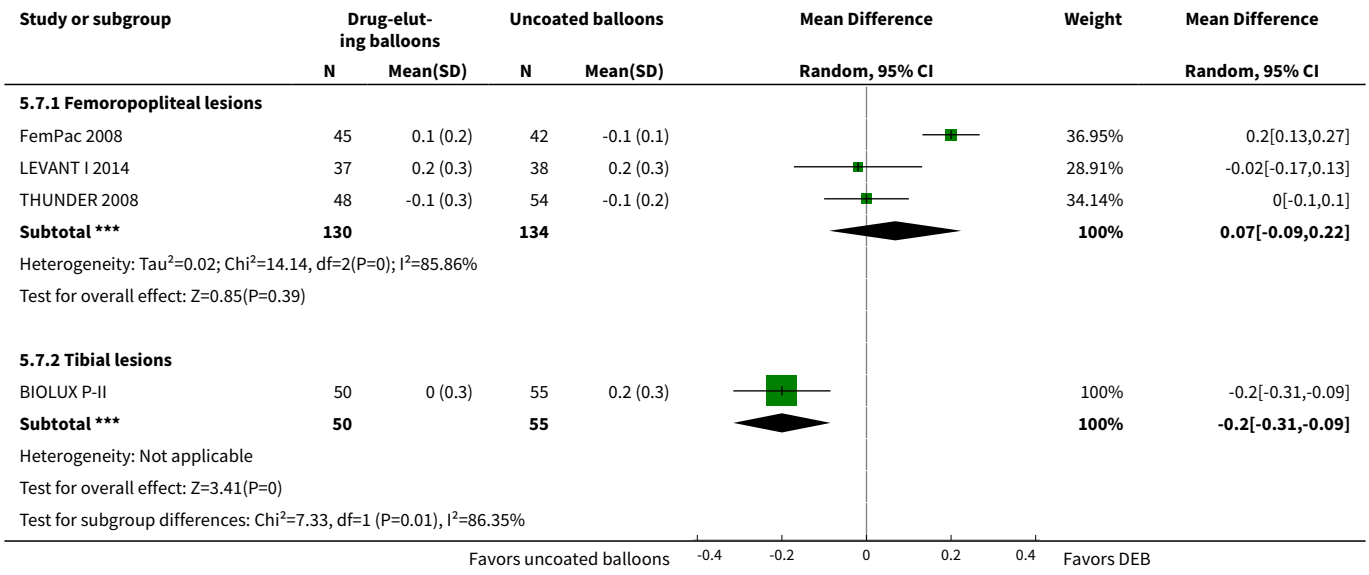
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.5.1 Femoropopliteal lesions					
BIOLUX P-I	0/30	1/30		18.11%	0.32[0.01,8.24]
FemPac 2008	1/45	0/42		6.13%	2.87[0.11,72.29]
LEVANT I 2014	1/37	3/38		35.34%	0.32[0.03,3.27]
PACIFIER 2012	0/44	2/47		29.35%	0.2[0.01,4.38]
THUNDER 2008	2/48	1/54		11.07%	2.3[0.2,26.25]
Subtotal (95% CI)	**204**	**211**		**100%**	**0.66[0.22,1.97]**
Total events: 4 (Drug-eluting balloons), 7 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=2.92, df=4(P=0.57); I^2=0%					
Test for overall effect: Z=0.74(P=0.46)					
5.5.2 Tibial lesions					
BIOLUX P-II	2/36	1/36		100%	2.06[0.18,23.77]
Subtotal (95% CI)	**36**	**36**		**100%**	**2.06[0.18,23.77]**
Total events: 2 (Drug-eluting balloons), 1 (Uncoated balloons)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					
Test for subgroup differences: Chi^2=0.69, df=1 (P=0.41), I^2=0%					



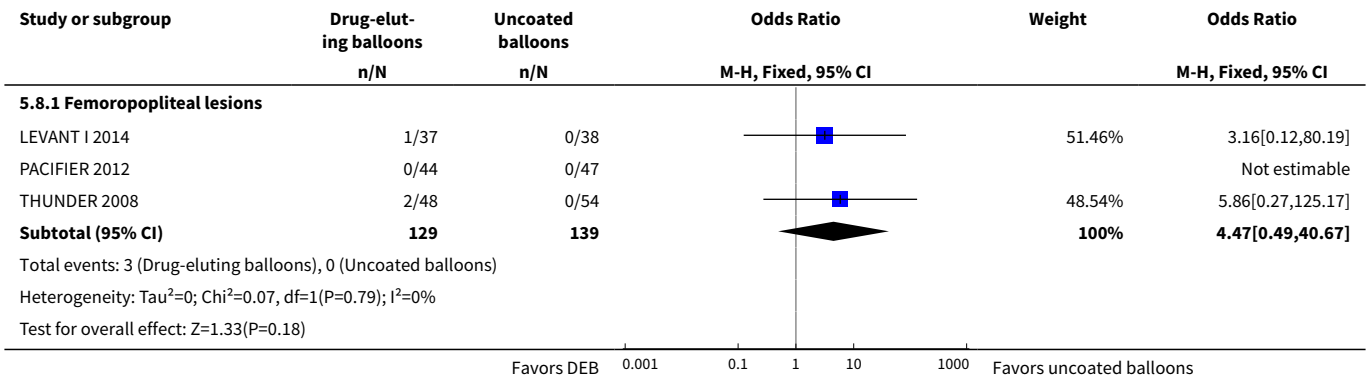
Analysis 5.6. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 6 Change in Rutherford category.



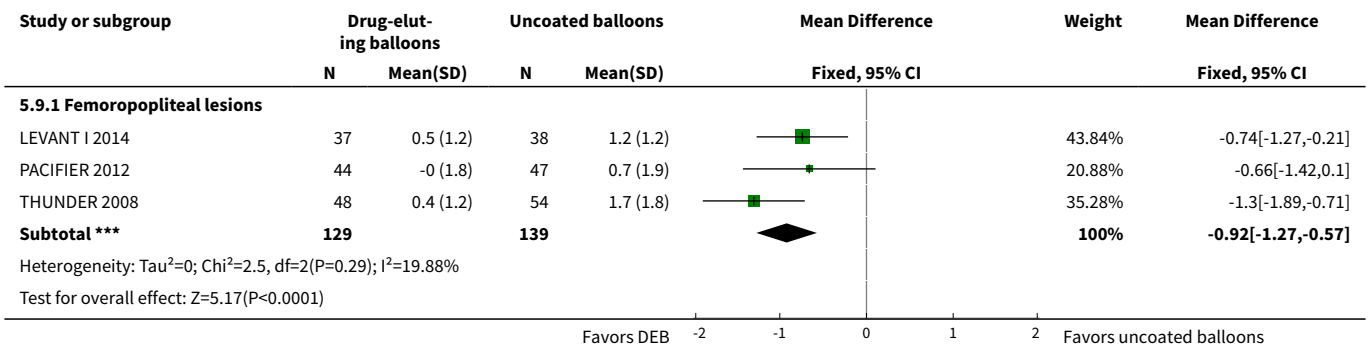
Analysis 5.7. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 7 Change in ankle-brachial index.



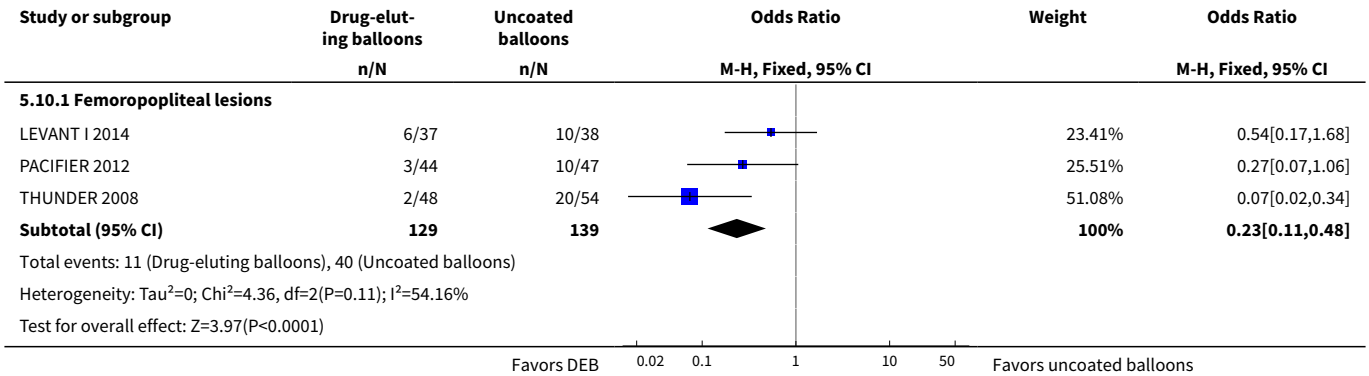
Analysis 5.8. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 8 Amputation (sensitivity analysis).



Analysis 5.9. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 9 Late lumen loss (sensitivity analysis).

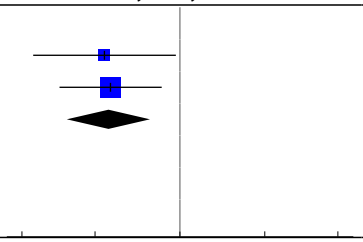


Analysis 5.10. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 10 Target lesion revascularization (sensitivity analysis).



Analysis 5.11. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 11 Binary restenosis (sensitivity analysis).

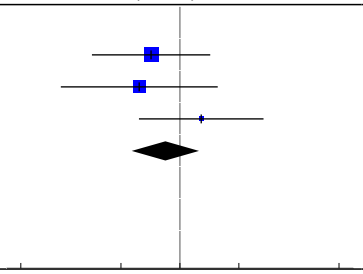
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.11.1 Femoropopliteal lesions					
PACIFIER 2012	3/44	11/47		36.99%	0.24[0.06,0.93]
THUNDER 2008	7/48	21/54		63.01%	0.27[0.1,0.71]
Subtotal (95% CI)	**92**	**101**		**100%**	**0.26[0.12,0.57]**
Total events: 10 (Drug-eluting balloons), 32 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=3.37(P=0)					



Favors DEB — Favors uncoated balloons

Analysis 5.12. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 12 Death (sensitivity analysis).

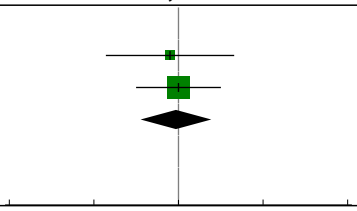
Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.12.1 Femoropopliteal lesions					
LEVANT I 2014	1/37	3/38		46.64%	0.32[0.03,3.27]
PACIFIER 2012	0/44	2/47		38.75%	0.2[0.01,4.38]
THUNDER 2008	2/48	1/54		14.61%	2.3[0.2,26.25]
Subtotal (95% CI)	**129**	**139**		**100%**	**0.57[0.15,2.11]**
Total events: 3 (Drug-eluting balloons), 6 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=0.85(P=0.4)					



Favors DEB — Favors uncoated balloons

Analysis 5.13. Comparison 5 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at six months: arterial segment subgroup analysis, Outcome 13 Change in ankle-brachial index (sensitivity analysis).

Study or subgroup	Drug-eluting balloons N	Mean(SD)	Uncoated balloons N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.13.1 Femoropopliteal lesions							
LEVANT I 2014	37	0.2 (0.3)	38	0.2 (0.3)		30.39%	-0.02[-0.17,0.13]
THUNDER 2008	48	-0.1 (0.3)	54	-0.1 (0.2)		69.61%	0[-0.1,0.1]
Subtotal ***	**85**		**92**			**100%**	**-0.01[-0.09,0.08]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%							
Test for overall effect: Z=0.14(P=0.89)							



Favors uncoated balloons — Favors DEB

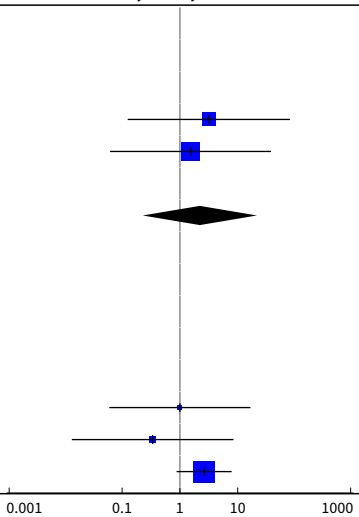
Comparison 6. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis

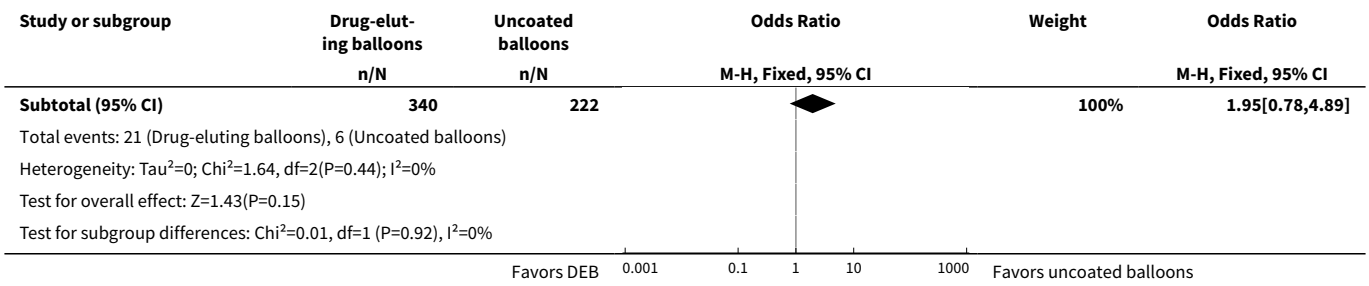
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Femoropopliteal lesions	5	1033	Odds Ratio (M-H, Fixed, 95% CI)	2.21 [0.23, 21.51]
1.2 Tibial lesions	3	562	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [0.78, 4.89]
2 Late lumen loss	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Femoropopliteal lesions	1	102	Mean Difference (IV, Random, 95% CI)	-1.2 [-1.86, -0.54]
2.2 Tibial lesions	1	358	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.18, 0.16]
3 Target lesion revascularization	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Femoropopliteal lesions	7	1230	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.56]
3.2 Tibial lesions	3	595	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.30, 1.44]
4 Binary restenosis	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Femoropopliteal lesions	2	578	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.11, 1.26]
4.2 Tibial lesions	2	516	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.05, 3.14]
5 Death	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Femoropopliteal lesions	5	1033	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.31, 1.46]
5.2 Tibial lesions	3	562	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.73, 2.74]
6 Change in Rutherford category	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Femoropopliteal lesions	2	551	Mean Difference (IV, Random, 95% CI)	0.09 [-0.58, 0.77]
6.2 Tibial lesions	1	72	Mean Difference (IV, Random, 95% CI)	0.60 [-0.46, 1.66]
7 Change in ankle-brachial index	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Femoropopliteal lesions	2	551	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.03]
7.2 Tibial lesions	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.2 [-0.31, -0.09]
8 Change in quality of life (EQ-5D)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Femoropopliteal lesions	2	807	Mean Difference (IV, Random, 95% CI)	0.02 [-0.01, 0.05]
8.2 Tibial lesions	1	72	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.22, 0.02]
9 Amputation (sensitivity analysis)	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Femoropopliteal lesions	4	973	Odds Ratio (M-H, Fixed, 95% CI)	2.21 [0.23, 21.51]
9.2 Tibial lesions	2	490	Odds Ratio (M-H, Fixed, 95% CI)	2.10 [0.79, 5.59]
10 Target lesion revascularization (sensitivity analysis)	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Femoropopliteal lesions	5	1075	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.73]
10.2 Tibial lesions	2	490	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.18, 1.52]
11 Death (sensitivity analysis)	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Femoropopliteal lesions	4	973	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.34, 1.73]
11.2 Tibial lesions	2	490	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.69, 2.83]

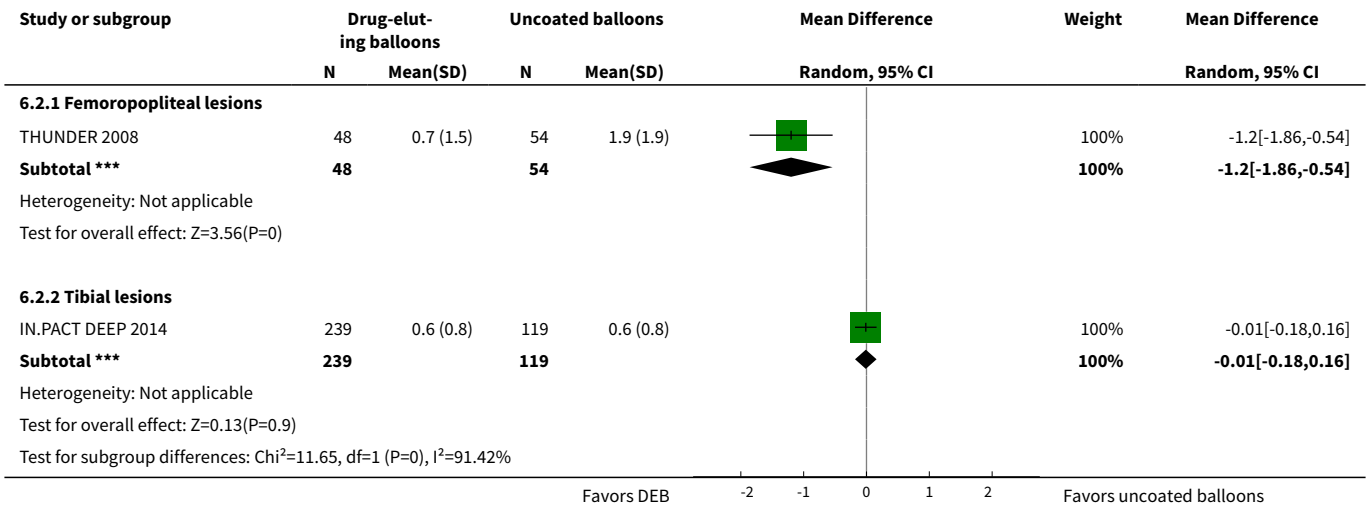
Analysis 6.1. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 1 Amputation.

Study or subgroup	Drug-eluting balloons n/N	Uncoated balloons n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Femoropopliteal lesions					
BIOLUX P-I	0/30	0/30			Not estimable
IN.PACT SFA 2015	0/220	0/111			Not estimable
LEVANT I 2014	1/37	0/38		41.8%	3.16[0.12,80.19]
LEVANT II 2015	1/316	0/160		58.2%	1.53[0.06,37.67]
PACIFIER 2012	0/44	0/47			Not estimable
Subtotal (95% CI)	**647**	**386**		**100%**	**2.21[0.23,21.51]**
Total events: 2 (Drug-eluting balloons), 0 (Uncoated balloons)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%					
Test for overall effect: Z=0.68(P=0.49)					
6.1.2 Tibial lesions					
BIOLUX P-II	1/36	1/36		13.26%	1[0.06,16.63]
DEBATE-BTK 2013	0/65	1/67		20%	0.34[0.01,8.46]
IN.PACT DEEP 2014	20/239	4/119		66.74%	2.63[0.88,7.86]

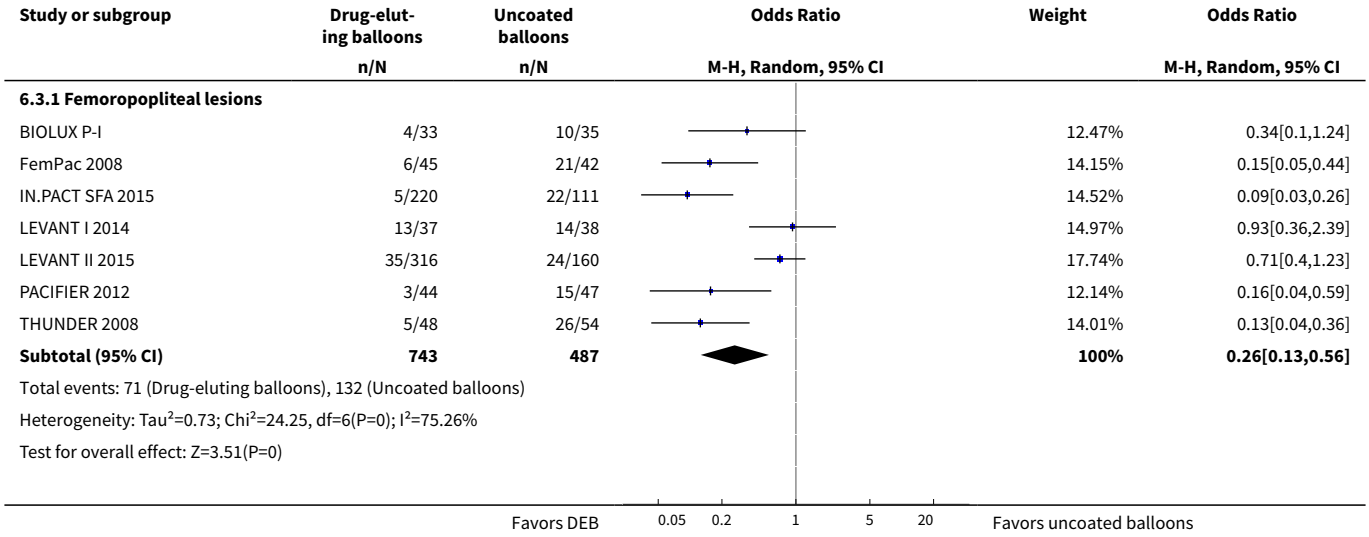


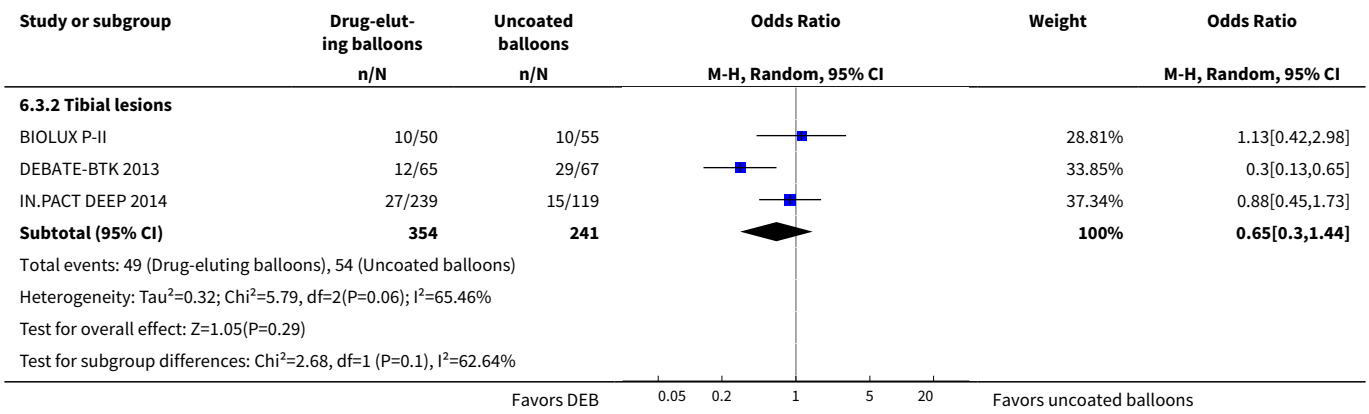


Analysis 6.2. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 2 Late lumen loss.

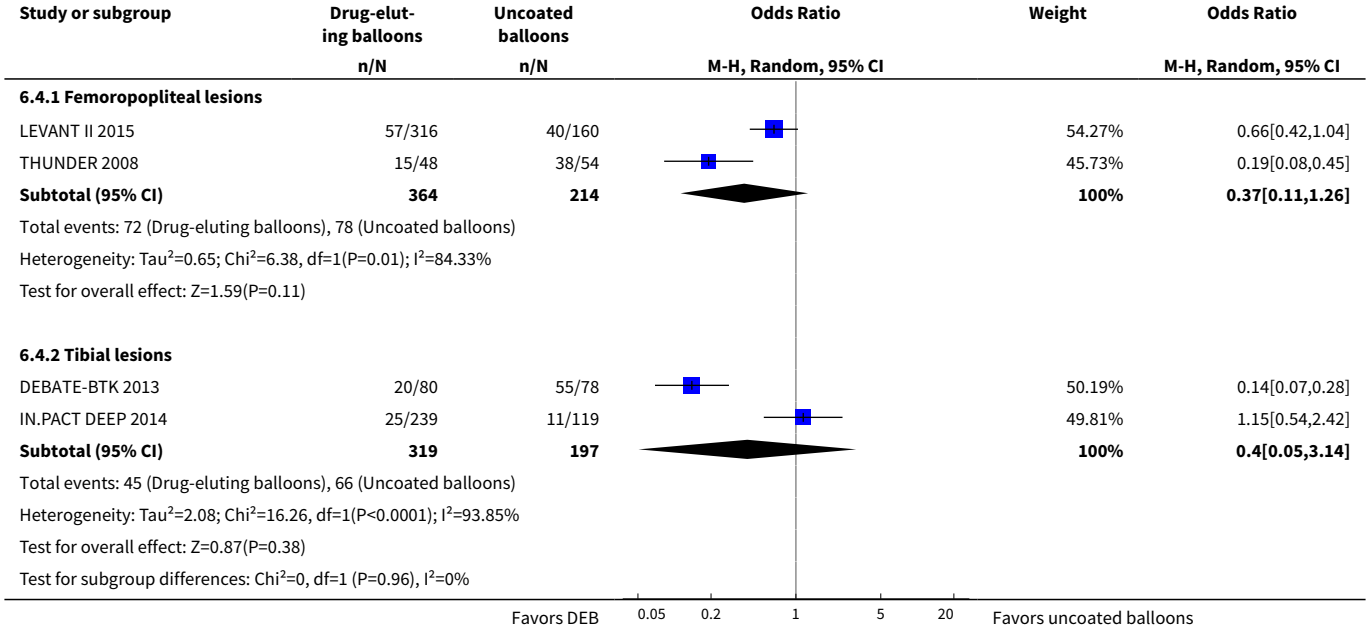


Analysis 6.3. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 3 Target lesion revascularization.

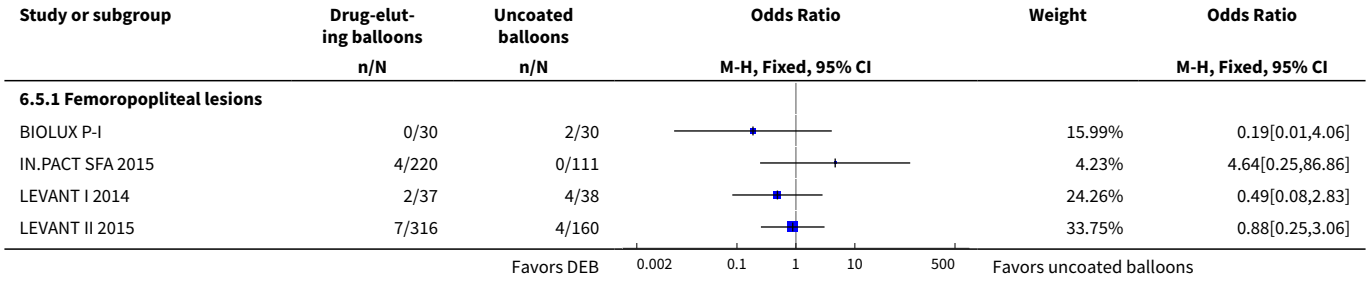


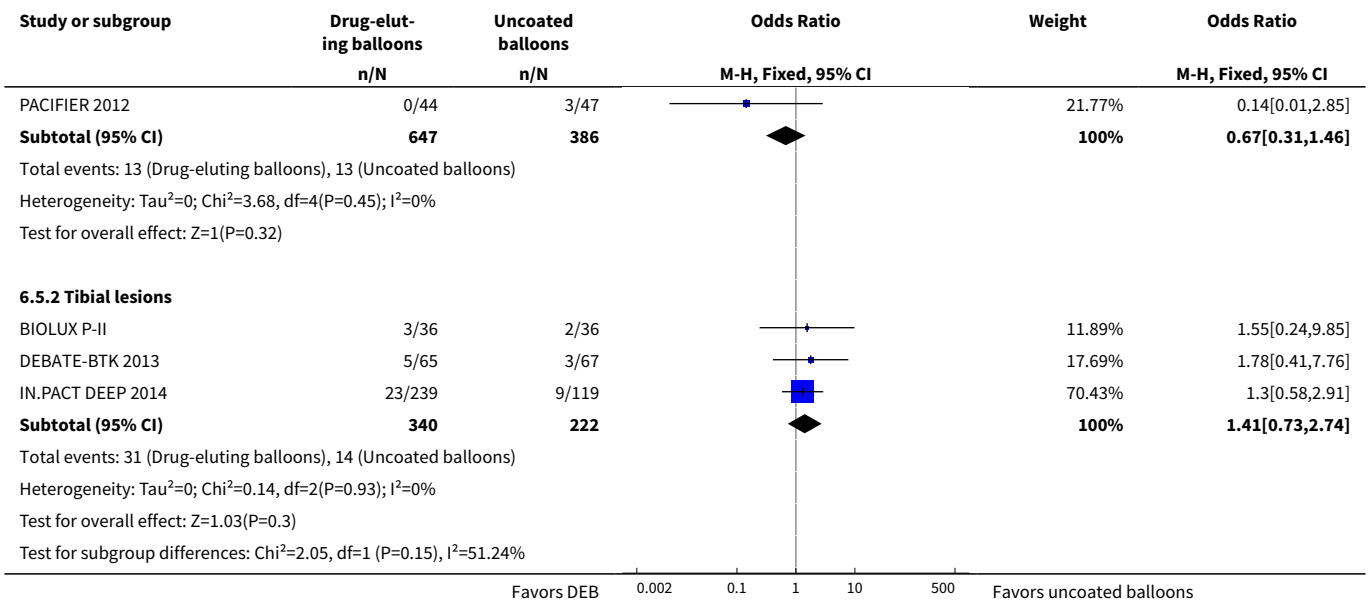


Analysis 6.4. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 4 Binary restenosis.

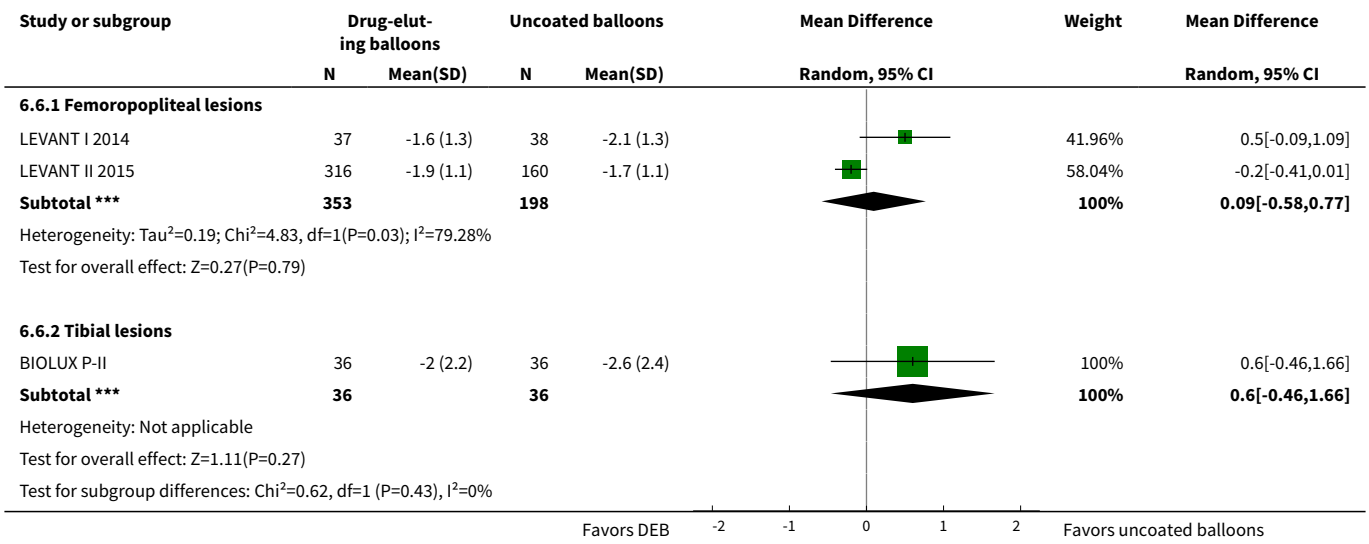


Analysis 6.5. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 5 Death.

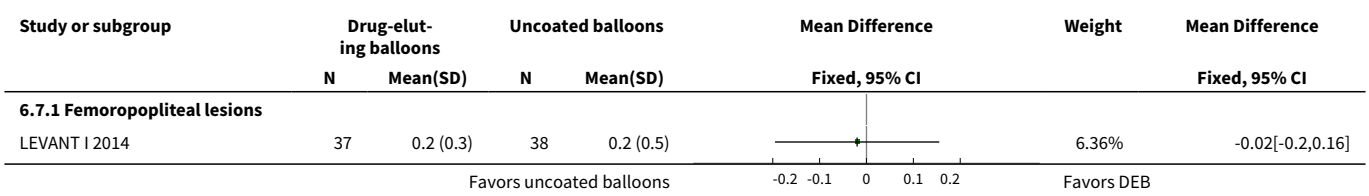


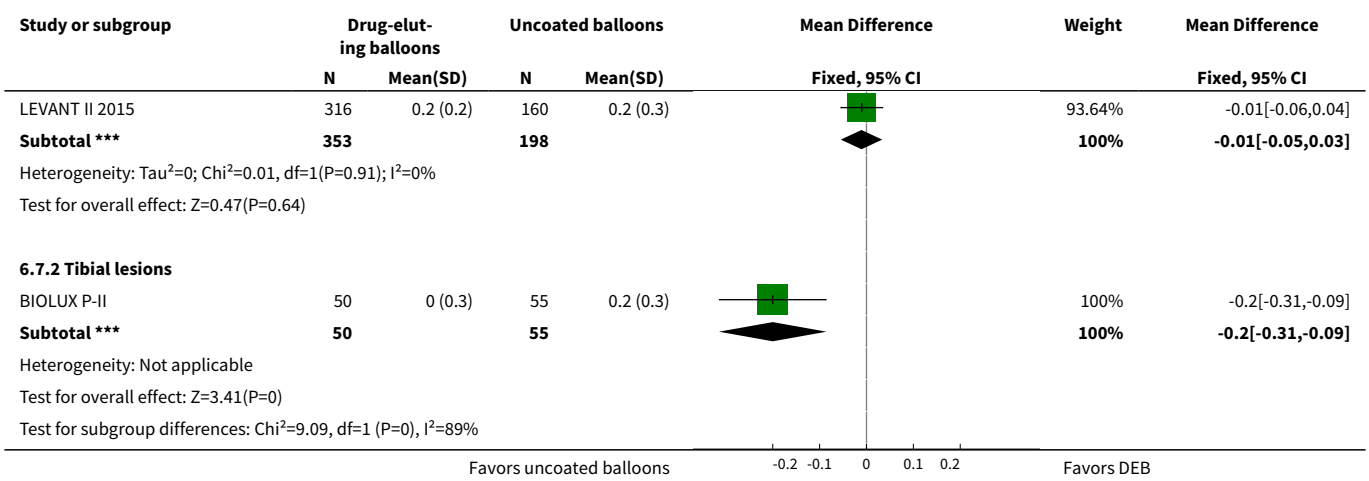


Analysis 6.6. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 6 Change in Rutherford category.

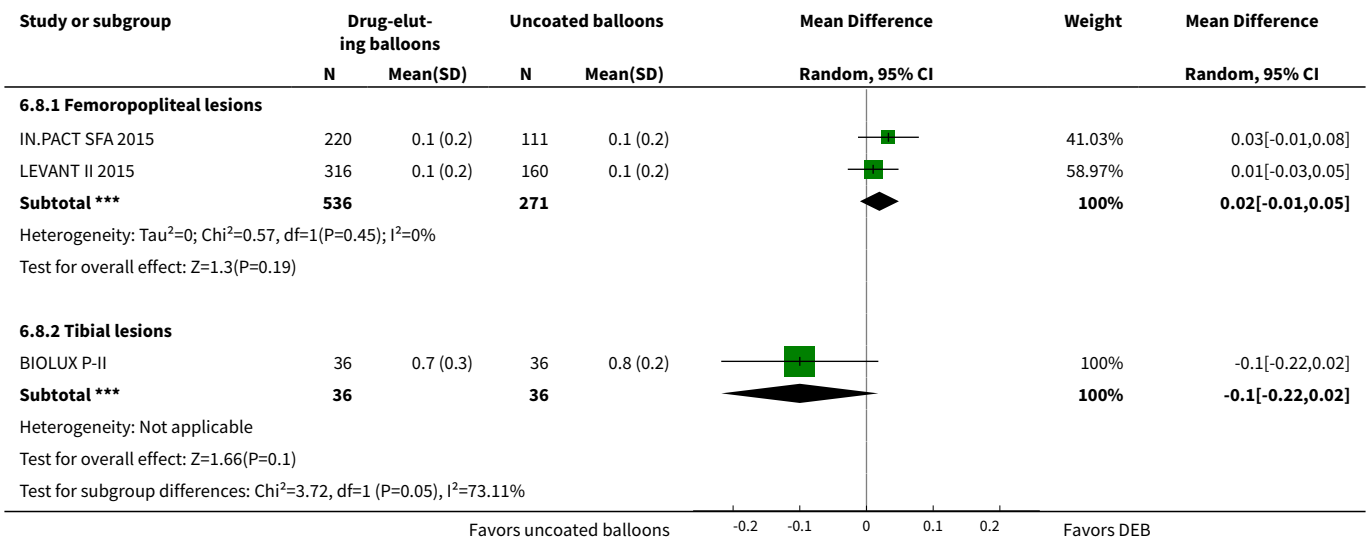


Analysis 6.7. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 7 Change in ankle-brachial index.

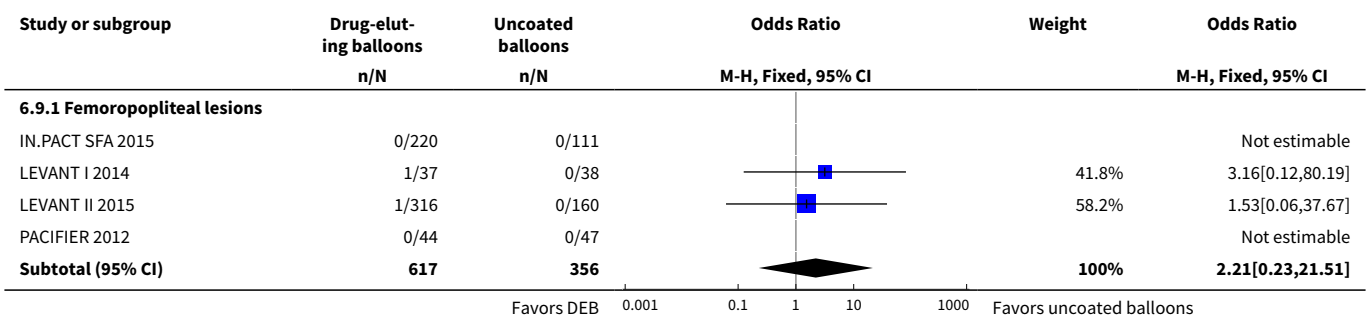


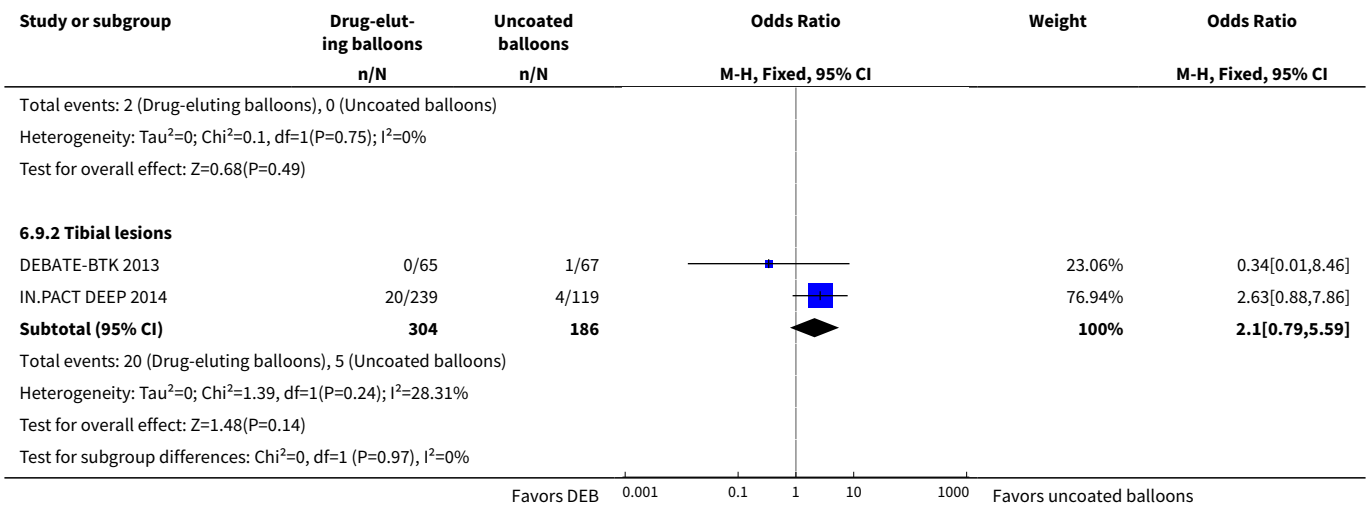


Analysis 6.8. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 8 Change in quality of life (EQ-5D).

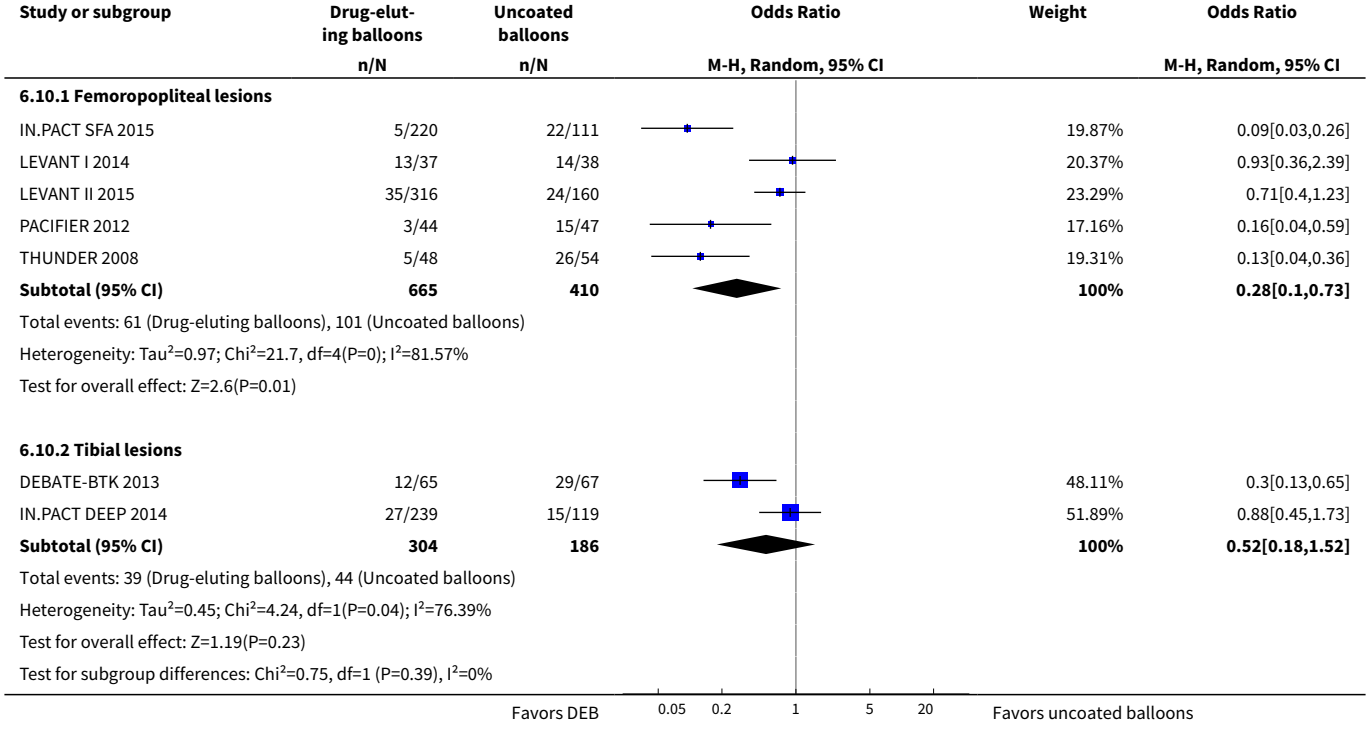


Analysis 6.9. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 9 Amputation (sensitivity analysis).

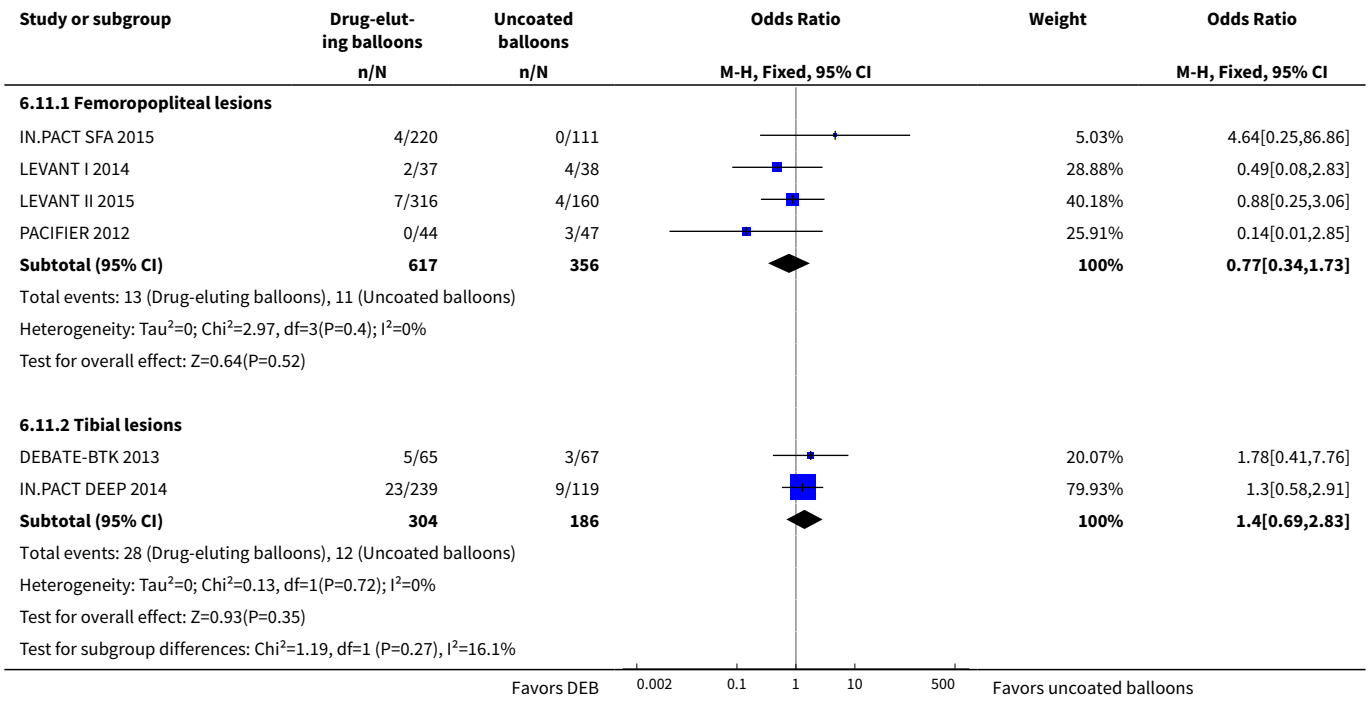




Analysis 6.10. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 10 Target lesion revascularization (sensitivity analysis).



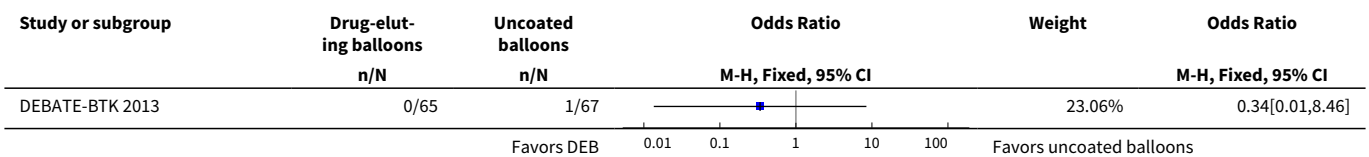
Analysis 6.11. Comparison 6 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: arterial segment subgroup analysis, Outcome 11 Death (sensitivity analysis).

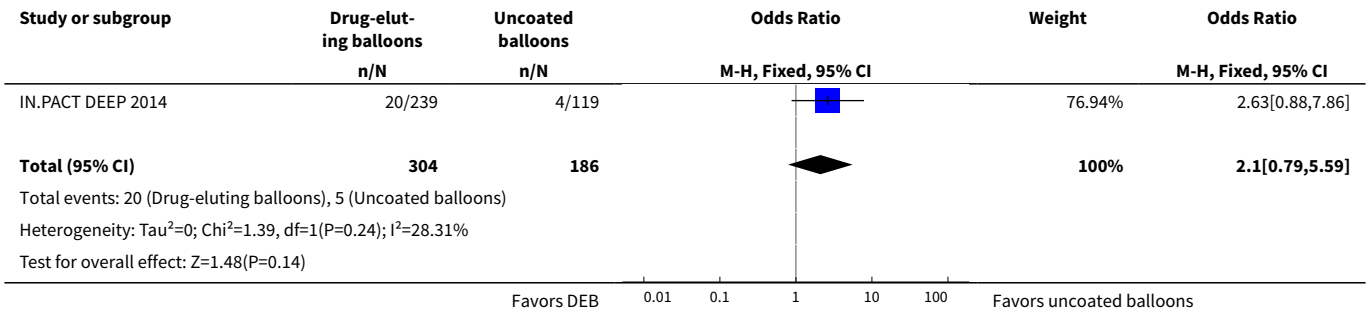


Comparison 7. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: severe peripheral arterial disease (PAD) subgroup analysis

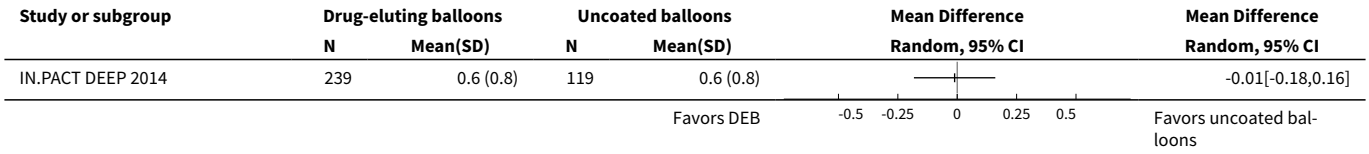
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation	2	490	Odds Ratio (M-H, Fixed, 95% CI)	2.10 [0.79, 5.59]
2 Late lumen loss	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Target lesion revascularization	2	490	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.18, 1.52]
4 Binary restenosis	2	516	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.05, 3.14]
5 Death	2	490	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.69, 2.83]

Analysis 7.1. Comparison 7 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: severe peripheral arterial disease (PAD) subgroup analysis, Outcome 1 Amputation.

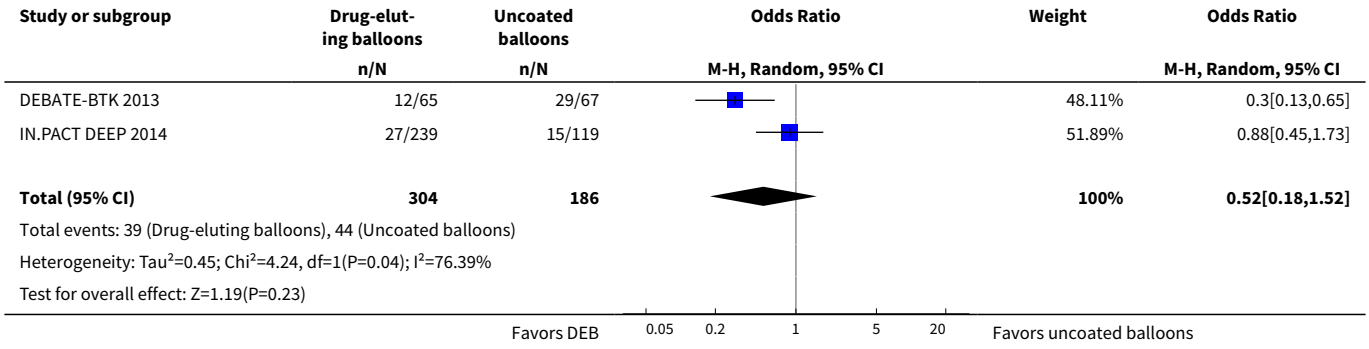




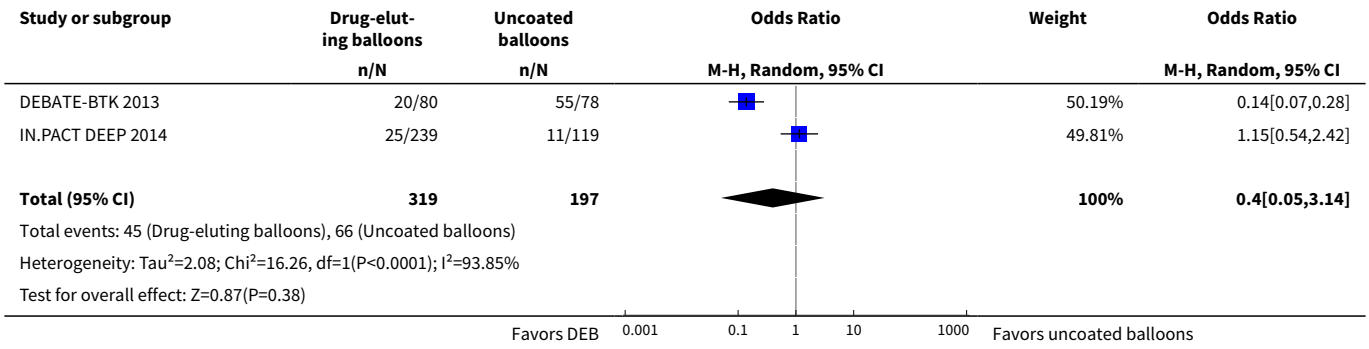
Analysis 7.2. Comparison 7 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: severe peripheral arterial disease (PAD) subgroup analysis, Outcome 2 Late lumen loss.



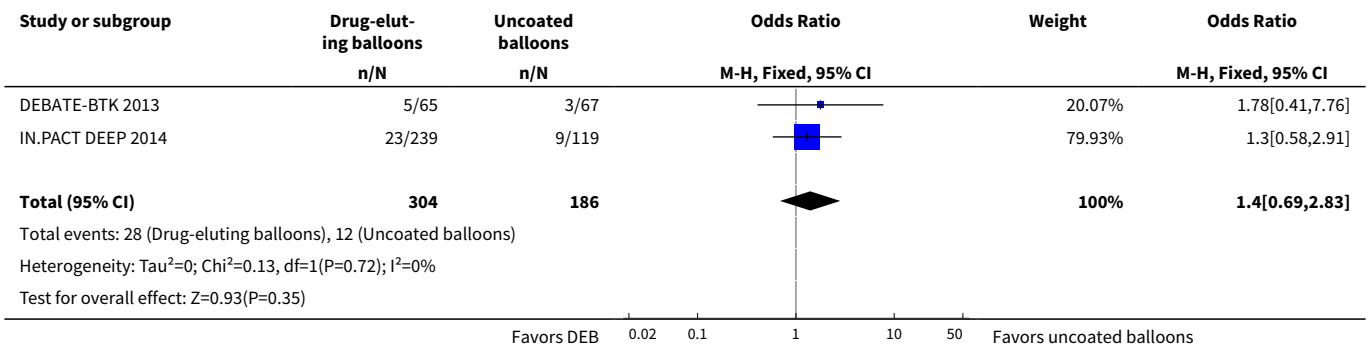
Analysis 7.3. Comparison 7 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: severe peripheral arterial disease (PAD) subgroup analysis, Outcome 3 Target lesion revascularization.



Analysis 7.4. Comparison 7 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: severe peripheral arterial disease (PAD) subgroup analysis, Outcome 4 Binary restenosis.



Analysis 7.5. Comparison 7 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months: severe peripheral arterial disease (PAD) subgroup analysis, Outcome 5 Death.



APPENDICES

Appendix 1. Cochrane Register of Studies (CRS) search strategy

#1	MESH DESCRIPTOR Arteriosclerosis	863
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	69
#4	MESH DESCRIPTOR Atherosclerosis	494
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	695
#6	MESH DESCRIPTOR Intermittent Claudication	669
#7	MESH DESCRIPTOR Ischemia	722
#8	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2085
#9	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	8107
#10	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	6888
#11	(peripheral near3 dis*):TI,AB,KY	2934
#12	(claudic* or IC):TI,AB,KY	2695
#13	(isch* or CLI):TI,AB,KY	20738
#14	arteriopathic:TI,AB,KY	7
#15	dysvascular*:TI,AB,KY	10

(Continued)

#16	(leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	82
#17	(limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	120
#18	((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	71
#19	((iliac or femoral or popliteal or femoro* or fempop* or crural) near3(occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	826
#20	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1062
#21	MESH DESCRIPTOR Iliac Artery	135
#22	MESH DESCRIPTOR Popliteal Artery	249
#23	MESH DESCRIPTOR Femoral Artery	728
#24	MESH DESCRIPTOR Tibial Arteries	30
#25	(((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	960
#26	restenosis:TI,AB,KY	2235
#27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	40028
#28	MESH DESCRIPTOR Angioplasty EXPLODE ALL TREES	3980
#29	MESH DESCRIPTOR Endovascular Procedures	101
#30	(angioplas* or percutan* or PTA):TI,AB,KY	11608
#31	valvuloplasty:TI,AB,KY	105
#32	(recanali* or revascular*):TI,AB,KY	6256
#33	dilat*:TI,AB,KY	6732
#34	(balloon or baloon):TI,AB,KY	6321
#35	endovascular:TI,AB,KY	1093
#36	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	23334
#37	MESH DESCRIPTOR Paclitaxel	1316
#38	(drug and (elut* or releas*)):TI,AB,KY	18150

(Continued)

#39	DEB:TI,AB,KY	68
#40	paclitax*:TI,AB,KY	3786
#41	sirolimus:TI,AB,KY	1746
#42	zotarolimus:TI,AB,KY	241
#43	rapalog:TI,AB,KY	0
#44	(IN.PACT or MOXY or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE):TI,AB,KY	61
#45	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	22498
#46	#27 AND #36 AND #45	1136

Appendix 2. Trials databases

Clinicaltrials.gov

82 studies found for: peripheral arterial disease and drug eluting | Interventional Studies

23 studies found for: drug eluting and ischemia and critical| Interventional Studies

47 studies found for: drug eluting and restenosis and peripheral| Interventional Studies

WHO

41 records for 40 trials found for: drug eluting and peripheral

31 records for 30 trials found for: drug eluting and ischemia

4 records for 4 trials found for: drug eluting and restenosis and peripheral

ISRCTN

drug eluting and peripheral 6

drug eluting and ischemia 4

drug eluting and restenosis 14

CONTRIBUTIONS OF AUTHORS

AK: drafting the proposal, study selection, data extraction and analysis, analysis interpretation, and final review drafting; will carry out updating.
TA: drafting the proposal, study selection, data extraction and analysis, analysis interpretation, and final review drafting.
GO: drafting the proposal, analysis interpretation, and final review drafting.
GR: drafting the proposal, analysis interpretation, and final review drafting.
KT: drafting the proposal, analysis interpretation, and final review drafting.
DR: drafting the proposal, analysis interpretation, and final review drafting; will carry out updating.

DECLARATIONS OF INTEREST

AK: none known.
TA: none known.
GO: reports having received consultancy fees from Cordis Medical (provision of services for lectures around abdominal aortic aneurysm (AAA) and peripheral vascular disease (PVD) with no requirement to endorse Cordis products).
GR: reports having received consultancy fees from Cordis Medical and Cook Medical related to giving lectures/proctoring on AAA and PVD with no exclusive relationship to promote their products.

KT: reports that his institution is involved in many multicenter clinical trials and he is a principal investigator for: The IN.PACT Global Clinical Study for the Treatment of Comprehensive Superficial Femoral and/or Popliteal Artery Lesions using Drug-Eluting Balloon; BIOFLEX-I clinical study: The Treatment of Iliac and Femoral Atherosclerotic Lesions Using the Self-expanding Astron and Astron Pulsar stents; Local Delivery of Paclitaxel for Prevention of Restenosis in Hemodialysis Access. Funds from Biotronic Inc and Medtronic Endovascular are managed independently by the department research board. KT declares payment for procuring and teaching of clinical specialists in advance aortic aneurysm stent graft (Cook Medical). Funds were also received by his institution for live course consultancy (Cordis), teaching and research activities from Cook Medical for the Advance EVAR [endovascular aneurysm repair] registry, Covidien grant for tumor ablation, and Gore Medical Teaching grants for fellows. These were also managed by the research department.
DR: reports having received consultancy fees from TVA Medical (no commercially available products and the startup company (percutaneous creation of dialysis fistulas) has no interests within peripheral arterial disease); and Cordis Medical (provision of services for lectures around AAA and PVD with no requirement to endorse Cordis products).

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- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not include trials that examined the use of DEB for the treatment of instent restenosis. Our team believes that the disease process underlying instent restenosis differs from stenosis in unstented vessels. Change in functional walking ability was assessed by the Walking Impairment Questionnaire rather than treadmill walking distance, which was not reported in any of the included trials. Finally, the incidence of amputation was added as an outcome and amputation-free rate was not used in the analysis because it was not reported by any of the included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Amputation, Surgical [statistics & numerical data]; Angioplasty, Balloon [*methods] [mortality]; Drug-Eluting Stents; Femoral Artery; Lower Extremity [*blood supply]; Paclitaxel [*therapeutic use]; Peripheral Arterial Disease [mortality] [*therapy]; Popliteal Artery; Randomized Controlled Trials as Topic; Tibial Arteries; Time Factors; Vascular Patency

MeSH check words

Humans