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[Intervention Review]

Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for the treatment of in-stent restenosis of the femoropopliteal arteries

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ABSTRACT

Background

Stents are placed in the femoropopliteal arteries for numerous reasons, such as atherosclerotic disease, the need for dissection, and perforation of the arteries, and can become stenosed with the passage of time. When a stent develops a flow-limiting stenosis, this process is known as "in-stent stenosis." It is thought that in-stent restenosis is caused by a process known as "intimal hyperplasia" rather than by the progression of atherosclerotic disease. Management of in-stent restenosis may include performing balloon angioplasty, deploying another stent within the stenosed stent to force it open, and creating a bypass to deliver blood around the stent. The role of drug-eluting technologies, such as drug-eluting balloons (DEBs), in the management of in-stent restenosis is unclear. Drug-eluting balloons might function by coating the inside of stenosed stents with cytotoxic chemicals such as paclitaxel and by inhibiting the hyperplastic processes responsible for in-stent restenosis. It is important to perform this systematic review to evaluate the efficacy of DEB because of the potential for increased expenses associated with DEBs over uncoated balloon angioplasty, also known as plain old balloon angioplasty (POBA).

Objectives

To assess the safety and efficacy of DEBs compared with uncoated balloon angioplasty in people with in-stent restenosis of the femoropopliteal arteries as assessed by criteria such as amputation-free survival, vessel patency, target lesion revascularization, binary restenosis rate, and death. We define "in-stent restenosis" as 50% or greater narrowing of a previously stented vessel by duplex ultrasound or angiography.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to November 28, 2017. Review authors also undertook reference checking to identify additional studies.

Selection criteria

We included all randomized controlled trials that compared DEBs versus uncoated balloon angioplasty for treatment of in-stent restenosis in the femoropopliteal arteries.

Data collection and analysis

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

Main results

Three trials that randomized a combined total of 263 participants met the review inclusion criteria. All three trials examined the treatment of symptomatic in-stent restenosis within the femoropopliteal arteries. These trials were carried out in Germany and Austria and used paclitaxel as the agent in the drug-eluting balloons. Two of the three trials were industry sponsored. Two companies manufactured the drug-eluting balloons (Eurocor, Bonn, Germany; Medtronic, Fridley, Minnesota, USA). The trials examined both anatomical and clinical endpoints. We noted heterogeneity in the frequency of bailout stenting deployment between studies as well as in the dosage of paclitaxel applied by the DEBs. Using GRADE assessment criteria, we determined that the certainty of evidence presented was very low for the outcomes of amputation, target lesion revascularization, binary restenosis, death, and improvement of one or more Rutherford categories. Most participants were followed up to 12 months, but one trial followed participants for up to 24 months.

Trial results show no difference in the incidence of amputation between DEBs and uncoated balloon angioplasty. DEBs showed better outcomes for up to 24 months for target lesion revascularization (odds ratio (OR) 0.05, 95% confidence interval (CI) 0.00 to 0.92 at six months; OR 0.24, 95% CI 0.08 to 0.70 at 24 months) and at six and 12 months for binary restenosis (OR 0.28, 95% CI 0.14 to 0.56 at six months; OR 0.34, 95% CI 0.15 to 0.76 at 12 months). Participants treated with DEBs also showed improvement of one or more Rutherford categories at six and 12 months (OR 1.81, 95% CI 1.02 to 3.21 at six months; OR 2.08, 95% CI 1.13 to 3.83 at 12 months). Data show no clear differences in death between DEBs and uncoated balloon angioplasty. Data were insufficient for subgroup or sensitivity analyses to be conducted.

Authors' conclusions

Based on a meta-analysis of three trials with 263 participants, evidence suggests an advantage for DEBs compared with uncoated balloon angioplasty for anatomical endpoints such as target lesion revascularization (TLR) and binary restenosis, and for one clinical endpoint - improvement in Rutherford category post intervention for up to 24 months. However, the certainty of evidence for all these outcomes is very low due to the small number of included studies and participants and the high risk of bias in study design. Adequately powered and carefully constructed randomized controlled trials are needed to adequately investigate the role of drug-eluting technologies in the management of in-stent restenosis.

PLAIN LANGUAGE SUMMARY

Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for stenosis of stents in lower limb arteries

Background

Many people have disease in their leg arteries that may develop into a blockage and lead to loss of circulation and subsequent pain, skin ulcers, and amputation of the leg. In an effort to prevent lack of blood from harming the leg, procedures can be performed to bypass the blocked artery using a vein or an artificial graft, or to cross it with a wire and open it with a balloon, then place a stent to help prevent the blockage from happening again. Although stents are very strong and can last a long time, it is possible that a stent inside an artery might at times become narrower, and eventually can become blocked. This process is known as "in-stent restenosis." A blocked stent can be treated in several ways, such as sucking out the clot or ballooning it, or placing another stent inside the stent that failed. Although all treatment options offer advantages and disadvantages, there have been advancements in the technologies available to treat this problem. One of these advancements requires covering the balloon used to treat the stent blockage with a cytotoxic drug used in chemotherapy, to slow down the blockage process after the stent is treated. Such specially prepared balloons, known as "drug-eluting balloons," have shown encouraging results for treating patients with artery disease in the leg.

Review question

The goal of this review was to determine how drug-eluting balloon (DEB) angioplasty compares with traditional uncoated balloon angioplasty, also known as plain old balloon angioplasty (POBA), for the treatment of in-stent restenosis in stents placed in leg arteries.

Study characteristics

Our review included three clinical trials that randomized 263 participants (most recent search - November 28, 2017). Trials included leg arteries at and above the knee and were carried out in Europe; all used DEBs that contained the chemical known as "paclitaxel." Two companies manufactured the DEBs: Eurocor and Medtronic. Most study participants were followed for six or more months; this is called "follow-up."

Key results

Results showed that DEBs were not better for participants than uncoated balloon angioplasty with regard to the need for amputation. At 24 months of follow-up, DEBs were associated with fewer target lesion revascularizations, which refers to the need to perform a procedure on a stent that had already been treated with a DEB or an uncoated balloon angioplasty for in-stent restenosis. DEBs were also found to have better binary restenosis rates, which refers to the percentage of treated stents that develop new stenosis after they have been treated with a DEB or an uncoated balloon angioplasty. Finally, more people who were treated with DEBs described improvement in their leg

symptoms, as measured by a change in their Rutherford category. DEBs were not found to be better for participants than uncoated balloon angioplasty with regard to patient death.

Certainty of the evidence

The certainty of the evidence presented was very low because we identified only three studies with small numbers of participants, and because many participants in those studies were lost to follow-up. Furthermore, risk of performance and attrition bias was significant, as was risk of other biases, due to lack of accounting for the type of stent treated and the need for bailout stenting.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Drug-eluting balloon angioplasty at 6 months compared to uncoated balloon angioplasty at 6 months for in-stent restenosis of the femoropopliteal arteries

Drug-eluting balloon angioplasty at 6 months compared to uncoated balloon angioplasty at 6 months for in-stent restenosis of the femoropopliteal arteries

Patient or population: patients with in-stent restenosis of the femoropopliteal arteries

Setting: hospital

Intervention: drug-eluting balloon angioplasty at 6 months

Comparison: uncoated balloon angioplasty at 6 months

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with uncoated balloon angioplasty	Risk with drug-eluting balloon angioplasty				
Amputation Follow-up: 6 months	See comments	See comments	See comments	263 (3 RCTs)	⊕⊕⊕⊕ VERY LOW ^a	None of the 3 included studies reported any major or minor amputations during follow-up. Amputation-free survival was not an outcome in the included studies
Target lesion revascularization (TLR) Follow-up: 6 months	Study population 206 per 1000	13 per 1000 (0 to 193)	OR 0.05 (0.00 to 0.92)	70 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^a	
Binary restenosis Follow-up: 6 months	Study population 407 per 1000	161 per 1000 (88 to 277)	OR 0.28 (0.14 to 0.56)	189 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^a	
Death Follow-up: 6 months	Study population 8 per 1000	7 per 1000 (1 to 49)	OR 0.93 (0.13 to 6.71)	263 (3 RCTs)	⊕⊕⊕⊕ VERY LOW ^a	

Improvement ≥ 1 Rutherford category	Study population	OR 1.81 (1.02 to 3.21)	193 (2 RCTs)	$\oplus\oplus\oplus\oplus$ VERY LOW ^a
Follow-up: 6 months	427 per 1000 574 per 1000 (432 to 705)			

***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 certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by three levels because of significant risk of performance and attrition bias, the small numbers of studies and participants, and other biases due to lack of accounting for the type of stent being treated and need for bailout stenting.

BACKGROUND

Description of the condition

Peripheral arterial disease (PAD) of the lower extremities is closely associated with atherosclerosis, a progressive and chronic disease process that leads to hardened vessels and decreased blood flow (Stary 1994). Although many people with PAD of the lower extremities are asymptomatic, others present with a variety of symptoms, including pain with walking (intermittent claudication), pain at rest, and tissue loss in the affected limbs (McDermott 2001). PAD is a highly prevalent condition that increases with age and occurs in more than 10% of individuals above the age of 60 (Criqui 2015).

Numerous treatment modalities have been used for the management of PAD of the lower extremities. Medical therapies aim to arrest the progression of atherosclerotic disease and improve clinical outcomes by modifying patient risk factors (Ali 2012). Open surgical and endovascular interventions are used in conjunction with medical therapies to improve blood delivery to ischemic tissues by bypassing or otherwise opening arterial blockages with wires, catheters, and other specialized devices (Conte 2015).

Of the growing number of interventions available for treating patients with lower extremity PAD, deployment of stents across a stenotic or occluded arterial segment has become a routine practice in certain circumstances, such as with long lesions and those that do not respond well to balloon angioplasty alone (OHTAC 2010). Stenting provides the mechanical support required to maintain the patency of arterial lesions, but its effectiveness is limited by the occurrence of neointimal proliferation, known as "intimal hyperplasia," and by overgrowth of the inner lining of the artery within the stent. This process, known as "in-stent restenosis," may limit blood flow through the stent and may sometimes result in recurrence of ischemic symptoms (Alfonso 2014).

Description of the intervention

Numerous endovascular interventions have been described for the treatment of in-stent restenosis, including repeat uncoated balloon angioplasty, also known as "plain old balloon angioplasty (POBA)" alone, cutting balloon angioplasty, angioplasty with drug-eluting balloons (DEBs), repeat stenting, and atherectomy (Singh 2014).

For all of these interventions, a wire is used first to cross the stenotic or occlusive lesion within the stent before treatment can be administered. Use of DEBs requires pre-dilation of the stenotic lesion with a plain balloon. A second balloon is then used to coat the inside of the stent with a cytotoxic chemical in the hope of reducing neointimal proliferation.

How the intervention might work

Uncoated balloon angioplasty has been used widely and successfully for the treatment of lower extremity PAD and in-stent restenosis, but its use is limited by recurrence of the neointimal hyperplastic process. DEBs address this limitation by applying a chemical to the stent that exerts an antiproliferative effect and arrests the restenotic process (Waksman 2009).

The most commonly used DEB cytotoxic agent is the taxane paclitaxel, a chemotherapeutic medication that exerts its cytotoxic effect by stabilizing microtubules (Marupudi 2007). Paclitaxel is a

safe and effective DEB agent for treatment of PAD and has been used successfully to decrease the incidence of binary restenosis in femoropopliteal vessels (Canaud 2014).

Why it is important to do this review

Numerous prospective studies have compared DEB versus uncoated balloon angioplasty for treatment of in-stent restenosis. DEBs have shown promising results in the treatment of coronary in-stent restenosis (Indermuehle 2013). However, the certainty of evidence for their use in femoropopliteal vessels remains unclear. Furthermore, DEB technologies are more expensive and are less widely available than uncoated balloon angioplasty. Our review seeks to assess the efficacy of this intervention and to determine whether it is associated with improved clinical outcomes.

OBJECTIVES

To assess the safety and efficacy of DEBs compared with uncoated balloon angioplasty in people with in-stent restenosis of the femoropopliteal arteries as assessed by criteria such as amputation-free survival, vessel patency, target lesion revascularization, binary restenosis rate, and death. We define "in-stent restenosis" as 50% or greater narrowing of a previously stented vessel by duplex ultrasound or angiography.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that compared drug-eluting balloons (DEBs) versus uncoated balloon angioplasty for in-stent restenosis of the femoropopliteal arteries. We define "in-stent restenosis" as 50% or greater narrowing of a previously stented vessel by duplex ultrasound or angiography.

Types of participants

We included people undergoing drug-eluting or uncoated balloon angioplasty for treatment of in-stent restenosis of the femoropopliteal arteries.

Types of interventions

We sought to compare DEBs versus uncoated balloon angioplasty for treatment of in-stent restenosis of femoropopliteal arteries. Analysis excluded hybrid studies in which DEBs are utilized simultaneously with open surgery, as well as studies that include atherectomy procedures, cutting balloon angioplasty, vascular brachytherapy, and repeat stenting with plain or drug-eluting stents for management of in-stent restenosis.

Types of outcome measures

Primary outcomes

- Amputation-free survival, defined as the probability of being alive without loss of the affected lower extremity
- Vessel patency, both primary and secondary, measured by late lumen loss, target lesion revascularization (TLR), and rate of binary restenosis, defined as 50% or greater narrowing of the vessel by duplex ultrasound or angiography
- Death

Secondary outcomes

- Change in Rutherford category of PAD
- Change in the Society for Vascular Surgery Wound, Ischemia, and Foot Infection (WIFI) stage (Mills 2014)
- Change in ankle-brachial index (ABI)
- Change in quality of life (QoL) scores, measured by validated instruments such as Short Form 36 (SF-36)
- Change in functional walking ability, measured by change in walking distance (on a treadmill or by other walking test) or use of a walking impairment questionnaire

Search methods for identification of studies

We applied no language, publication year, or publication status restrictions.

Electronic searches

The Cochrane Vascular Information Specialist searched the following databases for relevant trials.

- Cochrane Vascular Specialised Register (February 2, 2017).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1), in the Cochrane Library, via the Cochrane Register of Studies Online.

See [Appendix 1](#) for details of the search strategy that were used to search CENTRAL.

The Information Specialist also searched the following trials registries for details of ongoing and unpublished studies (February 2, 2017).

- ClinicalTrials.gov (clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- International Standard Randomized Controlled Trials Number (ISRCTN) Register (isrctn.com/).

The Information Specialist subsequently conducted top-up searches of the following databases.

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched from January 1, 2017, to November 28, 2017).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Register of Studies Online (CRSO; 2017, Issue 10).
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, and Ovid MEDLINE®) (searched from January 1, 2017, to November 28, 2017).
- Embase Ovid (searched from January 1, 2017, to November 28, 2017).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Ebsco (searched from January 1, 2017, to November 28, 2017).
- Allied and Complementary Medicine Database (AMED) Ovid (searched from January 1, 2017, to November 28, 2017).

The Information Specialist modeled search strategies for the listed databases on the search strategy designed for CENTRAL. When

appropriate, the search strategies were combined with adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials (as described in Chapter 6, of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). We have provided search strategies for the major databases in [Appendix 3](#).

The Information Specialist also performed top-up searches of the following trials registries on November 28, 2017.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We further examined the bibliographies of studies identified in our search to identify other relevant articles.

Data collection and analysis

Selection of studies

Two review authors (AK, WA) independently selected trials for inclusion in this review from studies identified by the search. A third review author (AD) assessed these trials, determined their suitability, and adjudicated disagreements between the first two review authors. We have outlined in the [Criteria for considering studies for this review](#) section the inclusion criteria used to determine suitability.

Data extraction and management

Two review authors (AK, WA) extracted relevant data from the included studies. We collected participant demographics (age, gender, PAD comorbidities, Rutherford PAD category, and baseline ABI), interventions (types and duration of DEBs and uncoated balloon angioplasty), and outcomes (as specified in the [Criteria for considering studies for this review](#) section). A third review author (AD) cross-checked data.

Statistical analysis complied with the standard methods of Cochrane Vascular. We used the computer software package Review Manager 5.3 (RevMan) to perform all statistical analyses and to generate figures ([Review Manager 2014](#)).

Assessment of risk of bias in included studies

Two review authors (AK, WA) carried out a thorough risk of bias assessment of all included studies using the Cochrane tool for assessing risk of bias (Higgins 2011). This tool assesses bias in six different domains, with each domain receiving a score of high, low, or unclear, depending on each review author's judgement. A third review author (AD) adjudicated disagreements. We contacted study authors when we needed clarification to better assess risk of bias.

Measures of treatment effect

We used the mean difference (MD) to calculate and report continuous outcome measures, such as change in QoL scores. If included studies used different scales, we calculated the standardized mean difference (SMD) instead. We also calculated the associated 95% confidence interval (CI) between the two treatment groups. We calculated and reported dichotomous (binary) outcome measures, such as target lesion revascularization, using the hazard ratio (HR) or the risk ratio (RR) with associated 95% CI, depending

on reported data. We carried out analyses at different time points, as reported by the trials. We based our calculations on an intention-to-treat approach.

Unit of analysis issues

The unit of analysis was the treated limb for anatomical outcomes such as late lumen loss or binary restenosis. Conversely, the unit of analysis was the patient for outcomes such as quality of life or death.

Dealing with missing data

We contacted study authors to inquire about missing or incomplete data. In the event that a significant quantity of data was missing from an included study and attempts to contact study authors were unsuccessful, we assessed the risk of bias associated with including the study in the meta-analysis and performed a sensitivity analysis.

Assessment of heterogeneity

We assessed interstudy heterogeneity by using a forest plot (Schünemann 2011). We calculated χ^2 and I^2 values to measure the amount of heterogeneity (Higgins 2003). I^2 values less than 50% indicated low heterogeneity, I^2 values between 50% and 75% indicated moderate heterogeneity, and I^2 values greater than 75% indicated significant heterogeneity (Deeks 2011).

Assessment of reporting biases

We planned to construct a funnel plot to assess publication bias when 10 or more studies were available for a particular outcome (Sterne 2011).

Data synthesis

To calculate the pooled treatment effect data, we used random-effects or fixed-effect models, depending on the degree of interstudy heterogeneity. If the calculated degree of interstudy heterogeneity was significant (defined as I^2 greater than 75%), we used the random-effects model. Otherwise, we used the fixed-effect model. We calculated 95% CIs for continuous and dichotomous outcome variables, as detailed above. We created a forest plot for each treatment effect as per Cochrane Vascular guidelines.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses by type of DEB, type and dose of pharmacological agent used in the DEB, and clinical severity of PAD, as defined by the change in Rutherford category or the Wiffl stage. We also planned to perform subgroup analyses for people with diabetes and for the types of antiplatelet agents prescribed for participants in the included trials.

Sensitivity analysis

We planned to exclude studies at high risk of bias from the pooled analysis and to repeat the analysis to assess their impact. We planned to perform a sensitivity analysis by sequentially excluding studies at high risk of bias.

"Summary of findings"

We prepared a "Summary of findings" table using the GRADEpro Guideline Development Tool to present the main findings of the review for the time point at which the most relevant data were available from the included studies (www.grade-pro.org; Atkins 2004). The population consisted of people with PAD, and we compared DEBs versus uncoated balloon angioplasty for treatment of in-stent restenosis of femoropopliteal arteries. We included in our "Summary of findings" table the main outcomes listed under [Types of outcome measures](#) that we considered essential for decision-making. We evaluated the certainty of the evidence using the GRADE approach (Schünemann 2011b). We assigned one of four levels of quality: high, moderate, low, or very low, based on overall risk of bias, directness of evidence, inconsistency of results, precision of estimates, and risk of publication bias, as previously described (Higgins 2011).

RESULTS

Description of studies

Results of the search

Please see [Figure 1](#) for search results.

Figure 1. Study flow diagram.

Included studies

This review includes three randomized controlled trials that compared DEB versus uncoated balloon angioplasty for treatment of symptomatic in-stent restenosis of the femoropopliteal arteries ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). The [Characteristics of included studies](#) tables present the details of those studies.

The three included studies were conducted in Germany - [FAIR](#); [ISAR-PEBIS](#) - and in Austria - [PACUBA](#). All studies included patients with in-stent restenosis in the femoropopliteal arteries and used paclitaxel-coated balloons, although at different dosages (Medtronic IN.PACT Admiral 3.5 mcg/mm² in [FAIR](#) and [ISAR-PEBIS](#) vs Eurocor Freeway 3 mcg/mm² in [PACUBA](#)). We also identified two ongoing trials ([Copa Cabana](#); [TRC-14004848](#)). Details of the ongoing trials are presented in the [Characteristics of ongoing studies](#) tables.

We contacted the authors of all included and ongoing studies to request study data.

Excluded studies

We excluded seven studies from our review ([Bosiers 2015](#); [ConSeQuent](#); [DEBATE-ISR](#); [EXCITE ISR](#); [NCT00481780](#); [NCT02832024](#); [RELIN](#)), and we listed reasons for exclusion in the [Characteristics of excluded studies](#) tables. We excluded studies because they compared stenting in [Bosiers 2015](#) and [RELIN](#), laser atherectomy in [EXCITE ISR](#), or cutting balloon angioplasty in [NCT00481780](#) versus uncoated balloon angioplasty for in-stent restenosis. The [ConSeQuent](#) trial compared DEB versus uncoated balloon angioplasty for native vessel restenosis rather than in-stent restenosis. The [DEBATE-ISR](#) study compared a prospective cohort of patients receiving DEB therapy for in-stent restenosis against

a historical cohort of diabetic patients. Finally, the [NCT02832024](#) study compared stent deployment versus atherectomy versus uncoated balloon angioplasty alone for in-stent restenosis.

3. All three included studies were at a high risk of performance and attrition bias because of significant differences in bailout stenting rates and lack of clarity on the types of stents treated for in-stent restenosis.

Risk of bias in included studies

Please refer to the "Risk of bias" tables in the [Characteristics of included studies](#) tables and summary results in [Figure 2](#) and [Figure](#)

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
FAIR							
ISAR-PEBIS							
PACUBA							

Allocation

The included studies were at low risk of selection bias in random sequence generation or allocation concealment. The [FAIR](#) trial used a block randomization study design with a block size of 10 and an allocation ratio of 1:1, and concealed the allocation sequence from investigators by using sequentially numbered and opaque sealed envelopes. The [ISAR-PEBIS](#) study used computer sequence generation to randomize participants after making the decision to proceed with an intervention. These researchers similarly accomplished the allocation of treatment by using sealed and opaque envelopes. The [PACUBA](#) trial investigators used a 1:1 randomization protocol with computer-generated sequences and concealed allocation via use of sealed envelopes.

Blinding

All three included studies were at high risk of performance bias because the operators were not blinded ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). Conversely, however, the outcomes assessors in two

trials were blinded to the treatment arm ([ISAR-PEBIS](#); [PACUBA](#)), placing them at low risk for detection bias. It is unclear whether the outcomes assessors in the [FAIR](#) trial were blinded to the treatment arm.

Incomplete outcome data

All three included studies were at high risk of attrition bias due to loss to follow-up ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). In the [FAIR](#) trial, approximately one-third of participants were lost to follow-up at 12 months. Similarly, in the [ISAR-PEBIS](#) trial, approximately 25% of DEB participants and 21% of uncoated balloon angioplasty participants did not undergo angiography as per the trial's primary endpoint requirement. In the [PACUBA](#) trial, eight participants in the DEB group (23%) and six in the uncoated balloon angioplasty group (15%) were lost to follow-up.

Selective reporting

All three included studies were at low risk for reporting bias ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). Trial authors reported all outcomes that were specified in the study protocols.

Other potential sources of bias

Two major sources of bias in all included trials were specifying the types of stents treated for in-stent restenosis and addressing the differences in bailout stenting requirements between treatment arms ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)).

Study authors did not specify whether stents that were treated were bare-metal, covered, or drug-eluting, nor did they stratify the results by length of the stent or duration of time since stent implantation.

The other major source of bias is the disparity in the incidence of bailout stenting between treatment arms in all three included studies. In the [FAIR](#) study, four uncoated balloon angioplasty participants received bailout stenting compared with one participant in the DEB arm. Conversely, in the [ISAR-PEBIS](#) study, 26% of DEB participants received bailout stenting compared with 6% of uncoated balloon angioplasty participants ($P = 0.02$). In the [PACUBA](#) study, four DEB participants received bailout stenting compared with one uncoated balloon angioplasty participant. Authors of the included studies did not stratify reported results by bailout stent implantation status.

Furthermore, study populations in the [PACUBA](#) trial were not similar, as the uncoated balloon angioplasty group reported more advanced lesions (Tosaka II and TASC B and C) than were noted in the DEB group (67% Tosaka class II lesions in the uncoated balloon angioplasty group vs 46% in the DEB group, 36% TASC B and 26% TASC C lesions in the uncoated balloon angioplasty group vs 23% and 14% in the uncoated balloon angioplasty group, respectively).

Effects of interventions

See: [Summary of findings for the main comparison Drug-eluting balloon angioplasty at 6 months compared to uncoated balloon angioplasty at 6 months for in-stent restenosis of the femoropopliteal arteries](#)

Primary outcomes

Amputation-free survival

None of the included studies reported amputation-free survival ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)).

Amputation

The three included studies reported no major or minor lower extremity amputations at one, six, 12, or 24 months of follow-up ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). We judged the certainty of evidence to be very low, however, as none of the included trials were powered to detect differences in clinical endpoints such as amputation, and all of the included trials were at significant risk of performance and attrition bias.

Vessel patency

Primary vessel patency

One study reported primary vessel patency ([PACUBA](#)). Study authors defined primary vessel patency as a $< 50\%$ reduction in diameter stenosis by colored duplex ultrasound and reported no statistically significant differences between DEB and uncoated balloon angioplasty treatment arms. Study authors reported that primary vessel patency was 97.1% (95% confidence interval (CI) 0.91 to 1.00), 58.8% (95% CI 0.44 to 0.78), and 40.7% (95% CI 0.25 to 0.64) in the DEB group, and 97.1% (95% CI 0.91 to 1.00), 31.3% (95% CI 0.18 to 0.52), and 13.4% (95% CI 0.05 to 0.36) in the uncoated balloon angioplasty group at one, six, and 12 months, respectively. Study authors did not report the number of participants included in the calculations, however, so it is not possible to determine whether these percentages were calculated using an intention-to-treat analysis, nor could we perform a pooled analysis of trial results.

Secondary vessel patency

Late lumen loss

None of the included studies reported late lumen loss ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)).

Target lesion revascularization

One study reported TLR at six and 24 months of follow-up ([ISAR-PEBIS](#)). At six months, participants treated with DEB had lower odds of requiring TLR compared with participants who underwent uncoated balloon angioplasty ([Analysis 2.1](#); odds ratio (OR) 0.05, 95% CI 0.00 to 0.92; 70 participants; 1 study; very low-certainty evidence). Similarly, at 24 months, participants treated with DEB had lower odds of requiring TLR compared with participants who underwent uncoated balloon angioplasty ([Analysis 4.1](#); OR 0.24, 95% CI 0.08 to 0.70; 70 participants; 1 study).

Freedom from target lesion revascularization

Two studies reported freedom from TLR at six and 12 months ([FAIR](#); [PACUBA](#)). In the [FAIR](#) trial, freedom from TLR at six months was reported as $96.4\% \pm 3\%$ standard error (SE) for DEB, and as $81\% \pm 5\%$ SE for uncoated balloon angioplasty ($P = 0.0117$). At 12 months, freedom from TLR was reported as $90.8\% \pm 6\%$ SE for DEB and $52.6\% \pm 10\%$ SE for uncoated balloon angioplasty ($P < 0.0001$). The [PACUBA](#) trial reported freedom from TLR as 88.2% (95% CI 0.78 to 0.99) at six months for DEB and 83.8% (95% CI 0.72 to 0.97) for uncoated balloon angioplasty. At 12 months, study authors reported freedom from TLR as 49% (95% CI 0.32 to 0.75) for DEB and 22.1% (95% CI 0.10 to 0.47) for uncoated balloon angioplasty. Study authors did not report the number of participants included in the calculations, however, so it is not possible to determine whether these percentages were calculated using an intention-to-treat analysis, nor could we perform a pooled analysis of trial results.

Binary restenosis rate

Two studies reported binary restenosis at six months ([FAIR](#); [ISAR-PEBIS](#)), and one study reported binary restenosis at 12 months ([FAIR](#)). The [FAIR](#) trial authors defined binary restenosis as a peak systolic velocity ratio ≥ 2.4 by duplex ultrasound, and the [ISAR-PEBIS](#) trial authors did not list their criteria for binary restenosis. At six months, participants treated with DEB had significantly lower odds of binary restenosis compared with those treated

with uncoated balloon angioplasty ([Analysis 2.2](#); OR 0.28, 95% CI 0.14 to 0.56; 189 participants; 2 studies; very low-certainty evidence). Similarly, at 12 months, participants treated with DEB had significantly lower odds of binary restenosis compared with those treated with uncoated balloon angioplasty (OR 0.34, 95% CI 0.15 to 0.76; 119 participants; 1 study).

Death

All three included studies reported death at six months ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)), two studies reported death at 12 months ([FAIR](#); [PACUBA](#)), and one study reported death at 24 months ([ISAR-PEBIS](#)). The [PACUBA](#) study did not report any deaths during the course of the study for participants treated with DEB or uncoated balloon angioplasty. At six months, DEB showed no mortality advantage over uncoated balloon angioplasty ([Analysis 2.3](#); OR 0.93, 95% CI 0.13 to 6.71; 263 participants; 3 studies; very low-certainty evidence). Similarly, DEB offered no mortality advantage over uncoated balloon angioplasty at 12 months ([Analysis 3.2](#); OR 0.60, 95% CI 0.10 to 3.73; 193 participants; 2 studies) nor at 24 months ([Analysis 4.2](#); OR 7.21, 95% CI 0.36 to 144.95; 70 participants; 1 study).

Secondary outcomes

Change in Rutherford category of PAD

None of the included studies reported the change in category of PAD ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). However, the [PACUBA](#) trial reported the number of participants who had improvement ≥ 1 Rutherford category at one, six, and 12 months, and the [FAIR](#) trial reported the number of participants who experienced improvement ≥ 1 Rutherford category at six months. At one month, DEB showed no advantage over uncoated balloon angioplasty for participants experiencing improvement ≥ 1 Rutherford category ([Analysis 1.1](#); OR 2.33, 95% CI 0.55 to 9.83; 74 participants; 1 study). However, participants treated with DEB had significantly greater odds of experiencing improvement ≥ 1 Rutherford category at six months ([Analysis 2.4](#); OR 1.81, 95% CI 1.02 to 3.21; 193 participants; 2 studies; very low-certainty evidence) and at 12 months ([Analysis 3.3](#); OR 2.08, 95% CI 1.13 to 3.83; 193 participants; 2 studies).

Change in the Society for Vascular Surgery Wound, Ischemia, and Foot Infection (WIFI) stage

None of the included studies reported change in WIFI stage ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)).

Change in ankle-brachial index (ABI)

None of the included studies reported change in ABI ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). Two studies reported ABI at baseline ([FAIR](#); [PACUBA](#)), and one study reported ABI at one month ([PACUBA](#)). Both the [FAIR](#) and [PACUBA](#) studies reported ABI at six and 12 months. The mean ABI at baseline was 0.63 ± 0.27 for DEB participants and 0.64 ± 0.25 for uncoated balloon angioplasty participants in the [FAIR](#) trial, and 0.65 ± 0.16 for DEB participants and 0.65 ± 0.16 for uncoated balloon angioplasty participants in the [PACUBA](#) trial. At one month, the mean ABI was 0.88 ± 0.14 for DEB participants and 0.9 ± 0.13 for uncoated balloon angioplasty participants in the [PACUBA](#) trial. At six months, the mean ABI was 0.9 ± 0.25 for DEB participants and 0.86 ± 0.3 for uncoated balloon angioplasty participants in the [FAIR](#) trial, and 0.79 ± 0.13 for DEB participants and 0.78 ± 0.18 in the [PACUBA](#) trial. At 12 months, the mean ABI was 0.86 ± 0.3 for DEB participants and 0.9 ± 0.17 for uncoated

balloon angioplasty participants in the [FAIR](#) trial, and 0.79 ± 0.2 for DEB participants and 0.84 ± 0.3 for uncoated balloon angioplasty participants in the [PACUBA](#) trial. The authors of both the [FAIR](#) and [PACUBA](#) studies did not report the number of participants included in the calculations, however, so it is not possible to determine whether these percentages were calculated using an intention-to-treat analysis, nor could we perform a pooled analysis of trial results.

Change in quality of life (QoL) scores

None of the included studies reported change in QoL scores ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)).

Change in functional walking ability

None of the included studies reported change in functional walking ability ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)).

Subgroup analysis

It is not possible to carry out a subgroup analysis, as data were not available from more than two trials for any of the reported outcomes.

Sensitivity analysis

It is not possible to carry out a sensitivity analysis because of the small number of included studies and the discrepancy in time points at which included studies reported outcomes. Furthermore, none of the included studies were powered to detect clinical endpoints, and several of our pre-specified outcomes were not reported.

DISCUSSION

Summary of main results

Drug-eluting balloon (DEB) angioplasty was associated with lower odds of requiring target lesion revascularization (TLR) for up to 24 months and lower rates of binary restenosis for up to 12 months when compared with uncoated balloon angioplasty for treatment of symptomatic in-stent restenosis. The drug-eluting balloon was also associated with greater odds of improvement in the Rutherford category of peripheral arterial disease (PAD) for up to 12 months when compared with uncoated balloon angioplasty. We noted no clear difference in amputation or mortality between DEB and uncoated balloon angioplasty at up to 24 months of follow-up. Because of lack of reporting, evidence was insufficient to suggest an advantage for DEB in primary vessel patency; amputation-free survival; late lumen loss; change in Society for Vascular Surgery Wound, Ischemia, and Foot Infection (WIFI) stage; ankle-brachial index (ABI); quality of life (QoL) scores; or functional walking ability when compared with uncoated balloon angioplasty for treatment of in-stent restenosis. Data from the three included trials were also insufficient for performance of subgroup or sensitivity analyses.

Overall completeness and applicability of evidence

All studies reported on symptomatic in-stent restenosis. All included studies reported a number of anatomical and clinical outcomes that are relevant to practitioners who treat in-stent restenosis. Unfortunately, all included studies had significant limitations (listed in [Risk of bias in included studies](#)). All three trials were at high risk of bias due to significant losses of participants to follow-up, lack of blinding, and lack of stratification by type of

stent implanted and requirement for bailout stenting. Use of TLR as an outcome measure is also potentially problematic, as it is a highly subjective measure that makes it difficult to standardize who will be offered a reintervention. Similarly, change in Rutherford category is a highly subjective measure, and it does not seem that any of the included trials used objective measures, such as treadmill testing, to enable determination of Rutherford category. Most of the participants in the trial did not have evidence of critical limb ischemia, as defined by a Rutherford category ≥ 4 , which is the main indication for many physicians in treating peripheral arterial disease. Furthermore, it is not possible to perform any subgroup analyses nor to exclude any trials from a sensitivity analysis. Finally, the included studies did not assess many of the pre-planned outcomes identified in our study protocol, and some of the outcomes data, such as the ABI, were not amenable to pooled analysis because of the format in which they were reported. Given that we identified at least two ongoing studies (listed in [Ongoing studies](#)), we are hopeful that it will become possible someday to carry out a more rigorous examination of the role of DEB in treating in-stent restenosis.

Quality of the evidence

This review was based on three studies that recruited a relatively small number of participants and were powered primarily to detect anatomical rather than clinical outcomes. However, all analyses in this review are based on data from a single trial or from two trials. As such, caution should be taken in over-interpreting clinical findings, such as the incidence of amputation or change in ABI. Studies used two DEBs with different paclitaxel doses, and two of the three studies were sponsored by a DEB manufacturer (Medtronic). Unfortunately, the included studies did not report most of the outcomes that we identified as important in this review. Finally, all three studies were at high risk of performance, attrition, and other biases, and this negatively impacts the overall quality of the evidence.

See [Summary of findings for the main comparison](#).

Potential biases in the review process

We carried out this review according to the principles outlined in the Cochrane guidelines. We encountered difficulty obtaining data from the [FAIR](#) and [ISAR-PEBIS](#) authors, as well as from authors of the ongoing studies ([Copa Cabana](#); [TRC-14004848](#)). Because of the limited number of studies included in this review, we were unable to carry out any subgroup or sensitivity analyses.

Agreements and disagreements with other studies or reviews

We identified two systematic reviews that examined the role of DEB for in-stent restenosis ([Cassese 2017](#); [Wu 2017](#)). [Cassese 2017](#), the first review, similarly reported superior outcomes with DEB compared with uncoated balloon angioplasty in TLR and binary restenosis, and showed significant improvement in Rutherford

category. The Cassese review differs from our review on several points, however. First, the [Cassese 2017](#) review authors chose to include a non-randomized study that we excluded ([DEBATE-ISR](#)), along with unpublished data from the [Copa Cabana](#) trial, which we have not been able to verify. Furthermore, [Cassese 2017](#) authors did not include [ISAR-PEBIS](#) in the analysis. Second, review authors for [Cassese 2017](#) did not specify the time points at which the analysis was carried out, electing instead to report outcomes for the included studies at an unspecified time point. As such, it is not possible to assess whether their reported improvement in TLR, for example, occurred at six or 12 months, because the studies that they included in their analysis reported outcomes at different time points.

The second systematic review also reported superior outcomes with DEB compared with uncoated balloon angioplasty in TLR and binary restenosis, as well as clinical improvement ([Wu 2017](#)), which, in our study, we identified as a positive change in Rutherford category. However, [Wu 2017](#) also included [DEBATE-ISR](#) in the analysis (which we excluded because it is non-randomized) and did not include data from the [ISAR-PEBIS](#) trial.

AUTHORS' CONCLUSIONS

Implications for practice

All three included trials were powered to detect anatomical rather than clinically relevant endpoints ([FAIR](#); [ISAR-PEBIS](#); [PACUBA](#)). Our analysis showed an advantage for DEB over uncoated balloon angioplasty for treatment of in-stent restenosis for up to two years in some domains. However, the certainty of the evidence is generally very low because of the small number of included studies and the risk of bias in those studies. As such, evidence is insufficient at present to show the superiority of DEB over uncoated balloon angioplasty for treatment of in-stent restenosis. This has important implications for practice, given the increased costs associated with the use of DEBs, which are generally more expensive than uncoated balloon angioplasty catheters.

Implications for research

To properly evaluate the role of DEBs in treating patients with in-stent restenosis, appropriately powered, independently funded clinical trials are needed to generate rigorous and reliable data that can be used in a future iteration of this review and that answer questions that are clinically relevant to patients. Questions that can be answered in future trials involve the characteristics of stents that would benefit most from DEB angioplasty for in-stent restenosis and the effective dose of paclitaxel that would prevent further restenosis.

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Kayssi 2017

Kayssi A, Al-Jundi W, Papia G, Kucey DS, Forbes T, Rajan DK, et al. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for the treatment of in-stent restenosis of the femoropopliteal arteries. *Cochrane Database of Systematic Reviews* 2017, Issue 1. [DOI: [10.1002/14651858.CD012510](https://doi.org/10.1002/14651858.CD012510)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

FAIR

Methods	<p>Study design: prospective, multicenter trial</p> <p>Method of randomization: block randomization (1:1 uncoated balloon angioplasty or DEB)</p> <p>Blinding: non-blinded</p> <p>Exclusions post randomization: none</p> <p>Losses to follow-up: 6 months: DEB 16.1%, uncoated balloon angioplasty 17.5%; 12 months: DEB 29%, uncoated balloon angioplasty 29.8%</p> <p>Study enrollment period: January 2010 to November 2012</p> <p>Cross-over: none</p>
Participants	<p>Country: Germany</p> <p>Setting: 5 vascular centers</p> <p>Number of participants: 119</p> <p>Age (mean): DEB 69 ± 8 years, uncoated balloon angioplasty 67 ± 9 years</p> <p>Gender: DEB 53.2% male, uncoated balloon angioplasty 70.2% male</p> <p>Rutherford class: 1: DEB 43.5%, uncoated balloon angioplasty 147.4%; 2: DEB 51.6%, uncoated balloon angioplasty 42.1%; 4: DEB 1.6%, uncoated balloon angioplasty 10.5%; 5: DEB 3.2%, uncoated balloon angioplasty 0%</p>

FAIR (Continued)

Inclusion criteria: superficial femoral artery in-stent restenosis of up to 20 cm in length; diameter stenosis at least 70% by duplex ultrasound (DUS); popliteal artery and 1 of infrapopliteal vessels patent for sustained distal runoff; chronic limb ischemia (Rutherford 2 to 4)

Exclusion criteria: untreated ipsilateral iliac artery stenosis, ongoing dialysis treatment, treatment with oral anticoagulants other than antiplatelet agents

Interventions	<p>Uncoated balloon angioplasty: 57 participants</p> <p>Uncoated balloon angioplasty device: Admiral Xtreme (Medtronic)</p> <p>DEB: 62 participants</p> <p>DEB device: IN.PACT Admiral (Medtronic)</p> <p>Drug used: paclitaxel 3.5 mcg/mm²</p> <p>Vessel treated: superficial femoral artery</p> <p>Anticoagulation/antiplatelets: preoperatively: pre-medication with aspirin 100 mg/d and clopidogrel 75 mg/d for at least 10 days. Participants not on this regimen were given a bolus of 500 mg aspirin intravenously and clopidogrel 600 mg orally before or immediately after the intervention. Postoperative-ly: participants received aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for at least 6 months</p>	
Outcomes	<p>Primary: incidence of binary recurrent in-stent restenosis at 6 months as assessed by ultrasound (peak systolic velocity ratio ≥ 2.4)</p> <p>Secondary:</p> <ul style="list-style-type: none">• Procedural endpoints: primary angiographic success (successful access and deployment of the device with ≤ 50% diameter residual stenosis without bailout procedures), cumulative incidence of binary recurrent restenosis at 12 months, Kaplan-Meier estimate of freedom from target lesion revascularization based on recurrent restenosis ≥ 50% reocclusion and clinical signs through 6- and 12-month follow-up (not including procedural bailout)• Hemodynamic endpoints: ankle brachial index at 6 and 12 months and immediate and sustained hemodynamic success (ankle brachial index improvement ≥ 0.15 from baseline to discharge and to 6 and 12 months without the need for target lesion revascularization)• Clinical endpoints: sustained clinical improvement by ≥ 1 Rutherford category relative and absolute claudication distance at 6 and 12 months; major adverse vascular events, defined as all-cause death, myocardial infarction, major amputation, major bleeding, and thrombosis or surgical intervention related to the target limb	
Notes	<p>Follow-up: 6 and 12 months</p> <p>Sponsor: Medtronic</p> <p>Strengths/limitations:</p> <ul style="list-style-type: none">• Strengths: used widely available devices, simple and generalizable study design• Limitations: significant 12-month loss to follow-up (29% and 29.8% in the uncoated balloon angioplasty and DEB arms, respectively), not powered to detect clinical outcomes, industry sponsored	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization was used in the study with a block size of 10 and an allocation ratio of 1:1

FAIR (Continued)

Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed from investigators by sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was non-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical status was evaluated before the procedure and again at 6 and 12 months, but whether the outcome assessment was blinded remains unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximately one-third of trial participants were lost to follow-up at 12 months
Selective reporting (reporting bias)	Low risk	All outcomes specified in the study protocol were reported
Other bias	High risk	Study authors did not specify the types of stents that were treated in this study. It is possible that particular types of stents (e.g. covered vs bare-metal) might respond differently to treatment. Furthermore, more uncoated balloon angioplasty participants received bailout stenting compared with DEB participants (4 vs 1 participant)

ISAR-PEBIS

Methods	<p>Study design: prospective, randomized, active-controlled trial</p> <p>Method of randomization: 1:1 uncoated balloon angioplasty or DEB</p> <p>Blinding: single (outcomes assessor)</p> <p>Exclusions post randomization: none</p> <p>Losses to follow-up: 6 months: DEB 3%, uncoated balloon angioplasty 3%; 24 months: DEB 22%, uncoated balloon angioplasty 15%</p> <p>Study enrollment period: April 2010 to December 2013</p> <p>Cross-over: none</p>
Participants	<p>Country: Germany</p> <p>Setting: 2 vascular centers</p> <p>Number of participants: 70</p> <p>Age (mean): DEB 70 ± 10 years, uncoated balloon angioplasty 68 ± 10 years</p> <p>Gender: DEB 67% male, uncoated balloon angioplasty 70% male</p> <p>Rutherford class: 2: DEB 3%, uncoated balloon angioplasty 0%; 3: DEB 94%, uncoated balloon angioplasty 97%; 4: DEB and uncoated balloon angioplasty 0%; 5: DEB 3%, uncoated balloon angioplasty 3%</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Symptomatic ≥ 70% in-stent restenosis of the superficial femoral artery (Rutherford stage 2 to 6)

ISAR-PEBIS (Continued)

- Written, informed consent by participant or her/his legally authorized representative for participation in the study

Exclusion criteria:

- Acute ischemia and/or acute thrombosis of the superficial femoral artery
- Untreated ipsilateral iliac artery stenosis > 70%
- Not at least 1 vessel runoff
- Popliteal involvement with stenosis > 70%
- Severe renal insufficiency (glomerular filtration rate < 30 mL/min/m²)
- Malignancies or other comorbid conditions (e.g. severe liver, renal, and pancreatic disease) with life expectancy less than 12 months, or that may result in protocol non-compliance
- Pregnancy (present, suspected, or planned) or positive pregnancy test
- Previous enrollment in this trial
- Inability of the patient to fully cooperate with the study protocol

Interventions	<p>Uncoated balloon angioplasty: 34</p> <p>Uncoated balloon angioplasty device: Pacific Xtreme (Medtronic)</p> <p>DEB: 36</p> <p>DEB device: In.Pact Admiral (Medtronic)</p> <p>Drug used: paclitaxel 3.5 mcg/mm²</p> <p>Vessel treated: superficial femoral artery</p> <p>Anticoagulation/antiplatelets: loading dose of clopidogrel (600 mg) was administered to all clopidogrel-naïve participants before angiography. Immediately after the decision was made to perform the intervention, participants were given 500 mg aspirin intravenously and 5000 U heparin intra-arterially. After the intervention, all participants received aspirin 100 mg per day indefinitely and clopidogrel 75 mg per day for at least 6 months</p> <p>Pre-dilation before DEB: yes, pre-dilation was performed in both study groups with a standard balloon catheter inflated for 2 minutes with a vessel:balloon diameter ratio of 1:1</p>
Outcomes	<p>Primary: percentage diameter stenosis, as measured by repeat angiography at 6 to 8 months</p> <p>Secondary:</p> <ul style="list-style-type: none"> • All-cause mortality • Major adverse peripheral events (MAPEs) defined as acute thrombosis of SFA or ipsilateral amputation or revascularization • Time to onset of any of MAPE • Binary restenosis rate • Percentage diameter stenosis in duplex ultrasound
Notes	<p>Follow-up: 6 and 24 months</p> <p>Sponsor: investigator-initiated trial</p> <p>Strengths/limitations:</p>

ISAR-PEBIS (Continued)

- **Strengths:** used widely available devices, simple and generalizable study design
- **Limitations:** significant loss to follow-up for primary outcome (25% of DEB and 21% of uncoated balloon angioplasty participants), not powered to detect clinical outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer sequence was generated after the decision was made to proceed with an intervention
Allocation concealment (selection bias)	Low risk	Allocation to treatments was accomplished by using sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study operators were non-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	A significant number of participants (25% of DEB and 21% of uncoated balloon angioplasty participants) did not undergo primary endpoint testing (angiography)
Selective reporting (reporting bias)	Low risk	All outcomes specified in the study protocol were reported
Other bias	High risk	Study authors did not specify the types of stents that were treated in this study. It is possible that particular types of stents (e.g. covered vs bare-metal) might respond differently to treatment. Furthermore, more uncoated balloon angioplasty participants received bailout stenting compared with DEB participants (26% vs 6% of participants; $P = 0.02$)

PACUBA

Methods	Study design: prospective, dual-center trial Method of randomization: 1:1 randomization via computer-generated sequences Blinding: single-blinded Exclusions post randomization: 1 participant in the uncoated balloon angioplasty group because of lack of technical success due to vessel calcification Losses to follow-up: 1 month: DEB 3%, uncoated balloon angioplasty 3%; 6 months: DEB 3%, uncoated balloon angioplasty 8%; 12 months: DEB 23%, uncoated balloon angioplasty 15% Study enrollment period: November 2010 to December 2012 Cross-over: none
Participants	Country: Austria Setting: 2 academic vascular centers

PACUBA (Continued)

Number of participants: 74

Age (mean): DEB 68 ± 9 years, uncoated balloon angioplasty 68 ± 0.4 years

Gender: DEB 57% male, uncoated balloon angioplasty 59% male

Rutherford class: 2: DEB 9%, uncoated balloon angioplasty 21%; 3: DEB 91%, uncoated balloon angioplasty 79%

Results show more Tosaka class I lesions in the DEB group (23%) compared with the uncoated balloon angioplasty group (5%), and more Tosaka class II lesions in the uncoated balloon angioplasty group (67%) compared with the DEB group (46%). Similarly, study authors reported more TASC A lesions in the DEB group (23%) compared with the uncoated balloon angioplasty group (5%), and more TASC B and C lesions in the uncoated balloon angioplasty group (36% and 26%, respectively) compared with the uncoated balloon angioplasty group (23% and 14%, respectively)

Inclusion criteria:

- Age > 50 years
- Patient legally authorized to provide written informed consent
- Patient willing and likely to comply with the follow-up schedule
- Patient symptomatic Rutherford-Becker 2 to 5 (Fontaine II to IV)
- In-stent restenosis in the superficial femoral artery and the P1 segment of the popliteal artery
- Tibial runoff of at least 1 artery, which, however, may be stenotic but amenable to PTA

Exclusion criteria:

- Unable to give informed consent
- Enrolled in another study with any investigational drug or device
- Major surgical procedures (not including minor amputations) within 30 days before this study or planned within 30 days of entry into this study
- Pregnancy
- Any known allergy, hypersensitivity or intolerance to radiological contrast media, ASA, clopidogrel or ticlopidine, or paclitaxel
- Life expectancy less than 1 year

Interventions

Uncoated balloon angioplasty: 39 participants

Uncoated balloon angioplasty device: unspecified

DEB: 35 participants

DEB device: FREEWAY 0.035 DEB (Eurocor)

Drug used: paclitaxel 3 mcg/mm²

Vessels treated: superficial femoral artery and P1 segment of the popliteal artery

Anticoagulation/antiplatelets: aspirin and clopidogrel given at least 1 day before the intervention. Otherwise a loading dose of clopidogrel 300 mg was given during the intervention. All participants received aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for 3 months post intervention

Pre-dilation before DEB: yes

Outcomes

Primary:

PACUBA (Continued)

- Primary patency at 6-month follow-up, defined as < 50% diameter stenosis as demonstrated by duplex ultrasound and CT angiogram in the absence of clinically driven target lesion revascularization during follow-up

- Clinically driven target lesion revascularization defined as reintervention of the target lesion due to presence of a symptomatic > 50% diameter stenosis

Secondary: severe adverse events

Notes

Follow-up: clinical evaluation at 1, 6, and 12 months follow-up after the index procedure. Duplex ultrasound performed at 24 hours, 6 months, and 12 months, and CT angiogram at 12 months after the index procedure

Sponsor: investigator-initiated trial

Strengths/limitations:

- **Strengths:** not industry sponsored

- **Limitations:** main limitation is that no participants with critical limb ischemia (Rutherford class 4 or greater) were included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial was randomized 1:1 via computer-generated sequences
Allocation concealment (selection bias)	Low risk	Allocation to treatments was accomplished by using sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study design was single-blinded (outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Core laboratory adjudication was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Eight participants in the DEB group (23%) and 6 in the uncoated balloon angioplasty group (15%) were lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes specified in the study protocol were reported
Other bias	High risk	Study authors did not specify the types of stents that were treated in this study. It is possible that particular types of stents (e.g. covered vs bare-metal) might respond differently to treatment. Furthermore, more DEB participants received bailout stenting compared with uncoated balloon angioplasty participants (4 vs 1 participants). No statistical analysis was performed to compare the study population's baseline characteristics, but the difference in the number of TASC and TASC lesions between DEB and uncoated balloon angioplasty groups suggests that DEB lesions were less severe

ASA: aspirin.

CT: computed tomography.

DEB: drug-eluting balloon.

DUS: duplex ultrasound.

MAPE: major adverse peripheral event.

PTA: percutaneous transluminal angioplasty.

SFA: superficial femoral artery.

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

Study	Reason for exclusion
Bosiers 2015	Randomized controlled trial of covered stent deployment vs balloon angioplasty alone for femoropopliteal artery in-stent restenosis. No use of drug-eluting balloon technologies in the interventional arm
ConSeQuent	Randomized controlled trial of DEB vs uncoated balloon angioplasty for native femoropopliteal artery restenosis rather than in-stent restenosis
DEBATE-ISR	Non-randomized study of DEB in a prospective cohort of patients presenting with femoropopliteal artery in-stent restenosis vs an historical cohort of patients who received uncoated balloon angioplasty for in-stent restenosis
EXCITE ISR	Randomized controlled trial of laser and balloon angioplasty vs balloon angioplasty alone for femoropopliteal artery in-stent restenosis. No use of drug-eluting balloon technologies in the interventional arm
NCT00481780	Randomized controlled trial of cutting balloon angioplasty vs balloon angioplasty alone for femoropopliteal artery in-stent restenosis. No use of drug-eluting balloon technologies in the interventional arm
NCT02832024	Randomized controlled trial of stent deployment vs atherectomy vs balloon angioplasty alone for femoropopliteal artery in-stent restenosis. No use of drug-eluting balloon technologies in the interventional arm
RELINE	Randomized controlled trial of covered stent deployment vs balloon angioplasty alone for femoropopliteal artery in-stent restenosis. No use of drug-eluting balloon technologies in the interventional arm

DEB: drug-eluting balloon.

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

[Copa Cabana](#)

Trial name or title	Cotavance™ paclitaxel-coated balloon versus uncoated balloon angioplasty for treatment of in-stent restenosis in SFA and popliteal arteries
Methods	Study design: randomized controlled trial
Participants	<p>Country: Germany</p> <p>Setting: 6 academic centers in Germany</p> <p>Number of participants: 112</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • In-stent restenosis or reocclusion at the target lesion due to an interventional treatment > 3 months before enrollment

Copa Cabana (Continued)

- Evidence of $\geq 70\%$ stenosis or occlusion in the SFA and/or popliteal that is 3 to 27 cm long and is confirmed by angiography
- Reference vessel diameter of 3 to 7 mm (reference vessel diameter = normal vessel diameter 1 cm proximal of the index lesion)
- Patients (men and women) with PAD disease category 2 to 5 according to Rutherford classification
- Patient eligible for an operative vascular intervention in case of complications during the procedure
- Female patients of childbearing potential with negative pregnancy test 7 days before the time of intervention
- Fully informed and signed consent obtained from each patient
- Patient willing and able to continue study participation after study procedure to ensure completion of all procedures and observations required by the protocol
- Patient with evidence of at least 1 runoff vessel who does not also require treatment for significant ($\geq 50\%$ stenosis or occlusion) stenosis during the index procedure to the ankle/foot of the limb to be treated. Treatment of infrapopliteal lesions must be staged at least 30 days before or after the index procedure
- If restenosis occurs in both arms within 30 days or later (re-restenosis) - treatment with 2 drug-eluting balloons at the same location (double dose)

Exclusion criteria:

- More than 2 lesions in the target vessel requiring treatment (if the distance between 2 lesions is less than 2 cm, the lesions should be counted as 1 lesion). The second lesion should also be treated with coated or uncoated balloons (according to randomization)
- Guidewire cannot cross lesion and/or an intentional subintimal approach in the stented lesion is required
- Stent fracture grade 2 to 4
- Inflow lesion (proximal to the study lesion) with flow limitation not successfully treated before treatment of the study lesion
- Acute thrombosis of the study lesion requiring lysis or thrombectomy before treatment of the study lesion
- Acutely occurring symptoms with a lysis or an operation as a therapeutic option within the last 6 weeks within the study limb
- Potential loss of leg due to critical or acute ischemia
- No patent distal runoff vessel
- Aneurysm in the blood vessel intended for intervention in this study
- Blood platelet count $< 100,000/\text{mm}^3$ or $> 700,000/\text{mm}^3$, leukocyte count $< 3000/\text{mm}^3$
- Contraindication to anticoagulation or any antiplatelet agent (e.g. aspirin, heparin, clopidogrel, ticlopidine, abciximab), or to paclitaxel
- Known intolerance or contraindication (e.g. severe hepatic (with ALAT and/or ASAT > 3 times the normal reference range) or renal (creatinine > 1.1 mg/dL in women and > 1.5 mg/dL in men) to contrast agents, which cannot be adequately pre-treated (e.g. with adequate hydration)
- Severe illnesses such as cancer, liver or renal disease, myocardial insufficiency leading to protocol deviation, and/or reduced life expectancy of less than 2 years
- Manifesting hyperthyreosis

Copa Cabana (Continued)

- Latent hyperthyreosis without adequate therapy (e.g. previous blocking with Natriumperchlorat (Irenat))
- Significant gastrointestinal hemorrhage within 6 months before study participation
- History of hemorrhagic diathesis or coagulopathy or rejection of blood transfusion
- Medical reason against double antiplatelet therapy in anticoagulated patient (e.g. receiving Coumadin)
- Any severe medical condition that might interfere with interpretation of the data or might result in unacceptable risk for the patient's participation in the study, according to the judgment of the clinical investigator
- Female patient who is pregnant or lactating
- Patient younger than 18 years of age
- Participation in another clinical study up to 30 days before study entry
- Previous participation in the same trial (only 1 leg can be treated within the study)

Interventions	<p>Uncoated balloon angioplasty device: unspecified</p> <p>DEB device: Cotavance DEB (Medrad)</p> <p>Vessels treated: femoropopliteal arteries</p>
Outcomes	<p>Primary: late lumen loss at 6 months</p> <p>Secondary:</p> <ul style="list-style-type: none"> • Procedural success • Target lesion revascularization • Target vessel revascularization • Binary restenosis rate • Rutherford category • Ankle-brachial index • Late lumen loss at 24 months • Minimum lumen diameter • Hospitalization • Safety, defined as 30-day freedom from procedure-related death, unplanned amputation, and target lesion revascularization • Restenosis pattern • Target lesion revascularization, clinical success, and angiographic outcome
Starting date	2012
Contact information	Dr. Gunnar Tepe (gunnar.tepe@ro-med.de)
Notes	Sponsor: self-funded study

TRC-14004848

Trial name or title	Drug-eluting balloon versus standard balloon angioplasty for the treatment of in-stent restenosis in the femoral-popliteal artery: a randomized, controlled prospective study
Methods	Study design: randomized controlled trial
Participants	<p>Country: China</p> <p>Setting: Beijing PLA General Hospital</p> <p>Number of participants: 120</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Males and females ≥ 18 years < 80 years old • History of bare-metal stenting angioplasty in the femoral-popliteal artery for treatment of atherosclerosis obliterans • Intermittent claudication or critical limb ischemia 7 days after stenting angioplasty, referred to as Rutherford classification (category 2, 3, and 4) • $\geq 50\%$ restenosis in the minimal luminal diameter within the stent-covered vessel, plus 10-mm segments proximally and distally, vs the mean diameter stent measured by computed tomographic angiography (CTA) • Single vessel runoff or better with at least 1 of 3 vessels (anterior tibial artery, posterior tibial artery, and peroneal artery) patent to the lower third of the calf • Treatment and follow-up should be voluntary and informed consent form would be signed by the patient or a legal guardian <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Paclitaxel allergy or iodine allergy • < 18 or ≥ 80 years of age • Current medical condition with life expectancy less than 3 months • Symptomatic myocardial infarction within 3 months or uncontrollable heart failure • Severe respiratory failure ($PO_2 < 60$ mmHg or $PCO_2 > 50$ mmHg) • Renal failure with creatine level higher than 200 mmol/L • Severe liver dysfunction with alanine aminotransferase level over 3 times
Interventions	<p>Uncoated balloon angioplasty device: unspecified</p> <p>DEB device: unspecified</p> <p>Vessels treated: femoropopliteal arteries</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> • Luminal restenosis rate within the stent-covered vessel, plus 10-mm segments proximally and distally by Doppler ultrasound • Peak systolic velocity ratio relative to adjacent segment <p>Secondary:</p> <ul style="list-style-type: none"> • Ankle brachial index

TRC-14004848 (Continued)

- Intimal thickness of lesion segment by Doppler ultrasound
- Pulse wave velocity

Starting date	Pending as of February 2017
Contact information	Dr. Shen Chenyang (scy@pkuph.edu.cn), Department of Vascular Surgery, Peking University People's Hospital, 11 Xizhimen South Street, Xicheng District, Beijing, China, 100044
Notes	Sponsor: self-funded study

ALAT: alanine aminotransferase.
ASAT: aspartate aminotransferase.
CTA: computed tomography angiography.
DEB: drug-eluting balloon.
PAD: peripheral arterial disease.
PCO₂: partial pressure of carbon dioxide.
PO₂: partial pressure of oxygen.
SFA: superficial femoral artery.

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement $\geq$ 1 Rutherford category	1	74	Odds Ratio (M-H, Fixed, 95% CI)	2.33 [0.55, 9.83]

Analysis 1.1. Comparison 1 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 1 month, Outcome 1 Improvement $\geq$ 1 Rutherford category.

Comparison 2. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Target lesion revascularization	1	70	Odds Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.92]
2 Binary restenosis	2	189	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.56]
3 Death	3	263	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.13, 6.71]
4 Improvement ≥ 1 Rutherford category	2	193	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.02, 3.21]

Analysis 2.1. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 6 months, Outcome 1 Target lesion revascularization.

Analysis 2.2. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 6 months, Outcome 2 Binary restenosis.

Analysis 2.3. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 6 months, Outcome 3 Death.

Analysis 2.4. Comparison 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 6 months, Outcome 4 Improvement ≥ 1 Rutherford category.

Comparison 3. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Binary restenosis	1	119	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.76]
2 Death	2	193	Odds Ratio (M-H, Fixed, 95% CI)	0.6 [0.10, 3.73]
3 Improvement ≥ 1 Rutherford category	2	193	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [1.13, 3.83]

Analysis 3.1. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 12 months, Outcome 1 Binary restenosis.

Analysis 3.2. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 12 months, Outcome 2 Death.

Analysis 3.3. Comparison 3 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 12 months, Outcome 3 Improvement ≥ 1 Rutherford category.

Comparison 4. Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 24 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Target lesion revascularization	1	70	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.08, 0.70]
2 Death	1	70	Odds Ratio (M-H, Fixed, 95% CI)	7.21 [0.36, 144.95]

Analysis 4.1. Comparison 4 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 24 months, Outcome 1 Target lesion revascularization.

Analysis 4.2. Comparison 4 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at 24 months, Outcome 2 Death.

APPENDICES

Appendix 1. CENTRAL search strategy, February 2, 2017

Search run on Thu Feb 2 2017

#1	MESH DESCRIPTOR Arteriosclerosis	868
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(Continued)

#2	MESH DESCRIPTOR Arteriosclerosis Obliterans	71
#3	MESH DESCRIPTOR Atherosclerosis	619
#4	MESH DESCRIPTOR Arterial Occlusive Diseases	724
#5	MESH DESCRIPTOR Intermittent Claudication	712
#6	MESH DESCRIPTOR Ischemia	789
#7	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2201
#8	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1107
#9	MESH DESCRIPTOR Iliac Artery	144
#10	MESH DESCRIPTOR Popliteal Artery	278
#11	MESH DESCRIPTOR Femoral Artery	810
#12	MESH DESCRIPTOR Tibial Arteries	33
#13	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	9119
#14	((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	7966
#15	(peripheral near3 dis*):TI,AB,KY	3371
#16	(claudic* or IC):TI,AB,KY	3063
#17	(isch* or CLI):TI,AB,KY	23713
#18	arteriopathic:TI,AB,KY	7
#19	dysvascular*:TI,AB,KY	10
#20	leg:TI,AB,KY	11505
#21	(lower limb):TI,AB,KY	2710
#22	(lower extrem*):TI,AB,KY	3406
#23	(above knee):TI,AB,KY	125
#24	(below knee):TI,AB,KY	248
#25	(femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or infrainguinal or tibial):TI,AB,KY	13629
#26	restenosis:TI,AB,KY	2489
#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	66811

(Continued)

#28	MESH DESCRIPTOR Angioplasty EXPLODE ALL TREES	4144
#29	MESH DESCRIPTOR Endovascular Procedures	203
#30	(angioplas* or percutan* or PTA):TI,AB,KY	13449
#31	valvuloplasty:TI,AB,KY	133
#32	(recanali* or revascular*):TI,AB,KY	7386
#33	dilat*:TI,AB,KY	7493
#34	(balloon or baloon):TI,AB,KY	6925
#35	endovascular:TI,AB,KY	1510
#36	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	26979
#37	MESH DESCRIPTOR Paclitaxel	1519
#38	(coated or uncoated):TI,AB,KY	3677
#39	(drug and (elut* or releas*)):TI,AB,KY	20097
#40	DEB:TI,AB,KY	97
#41	POBA:TI,AB,KY	44
#42	paclitax*:TI,AB,KY	4384
#43	sirolimus:TI,AB,KY	2036
#44	zotarolimus:TI,AB,KY	316
#45	rapalog:TI,AB,KY	1
#46	(IN.PACT or MOXY or Paseo or Lutonix or Paccoca or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE):TI,AB,KY	85
#47	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46	28056
#48	#27 AND #36 AND #47	1524
#49	* NOT SR-PVD:CC	979221
#50	#48 AND #49	1417

Appendix 2. Trial registries searches, February 2, 2017

ClinicalTrials.gov

95 studies found for: restenosis AND peripheral arterial AND randomized

World Health Organization International Clinical Trials Registry Platform

57 records for 56 trials found for: angioplasty and restenosis

ISRCTN Register

24 results angioplasty and restenosis

Appendix 3. Database searches, November 28, 2017

Source	Search strategy	Hits retrieved
CENTRAL	#1 MESH DESCRIPTOR Arteriosclerosis 872 #2 MESH DESCRIPTOR Arteriosclerosis Obliterans 73 #3 MESH DESCRIPTOR Atherosclerosis 684 #4 MESH DESCRIPTOR Arterial Occlusive Diseases 746 #5 MESH DESCRIPTOR Intermittent Claudication 738 #6 MESH DESCRIPTOR Ischemia 823 #7 MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES 2288 #8 MESH DESCRIPTOR Iliac Artery 154 #9 MESH DESCRIPTOR Femoral Artery 873 #10 MESH DESCRIPTOR Tibial Arteries 35 #11 (atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY 10322 #12 ((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or re-occlus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 9288 #13 (peripheral near3 dis*):TI,AB,KY 3862 #14 (claudic* or IC):TI,AB,KY 3571 #15 (isch* or CLI):TI,AB,KY 27272 #16 arteriopathic:TI,AB,KY 7 #17 dysvascular*:TI,AB,KY 12 #18 leg:TI,AB,KY 12842 #19 (lower limb):TI,AB,KY 3335 #20 (lower extrem*):TI,AB,KY 3915 #21 (above knee):TI,AB,KY 133 #22 (below knee):TI,AB,KY 263 #23 (femor* or iliac or popliteal or fempop* or crural or poplite* or in-frapopliteal or inguinal or femdist* or infringuinal or tibial):TI,AB,KY 15799 #24 restenosis:TI,AB,KY 2771 #25 MESH DESCRIPTOR Popliteal Artery 294 #26 MESH DESCRIPTOR leg 2742	336

(Continued)

#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 76401

#28 MESH DESCRIPTOR Angioplasty EXPLODE ALL TREES 4239

#29 MESH DESCRIPTOR Endovascular Procedures 261

#30 (angioplas* or percutan* or PTA):TI,AB,KY 15653

#31 valvuloplasty:TI,AB,KY 168

#32 ((recanali* or revascular*)):TI,AB,KY 8613

#33 dilat*:TI,AB,KY 8348

#34 (balloon or baloon):TI,AB,KY 7629

#35 endovascular:TI,AB,KY 2099

#36 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 31256

#37 MESH DESCRIPTOR Paclitaxel 1667

#38 (coated or uncoated):TI,AB,KY 4046

#39 ((drug and (elut* or releas*)):TI,AB,KY 22395

#40 DEB:TI,AB,KY 141

#41 POBA:TI,AB,KY 60

#42 paclitax*:TI,AB,KY 5425

#43 sirolimus:TI,AB,KY 2291

#44 zotarolimus:TI,AB,KY 382

#45 rapalog:TI,AB,KY 2

#46 ((IN.PACT or MOXY or Paseo or Lutonix or Paccoca or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE)):TI,AB,KY 101

#47 #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 31639

#48 #27 AND #36 AND #47 1864

#49 * NOT SR-PVD:CC 1088498

#50 #48 AND #49 1753

#51 01/01/2017 TO 28/11/2017:CD 109501

#52 #50 AND #51 336

Clinicaltrials.gov	randomized peripheral arterial restenosis First posted from 01/01/2017 to 11/28/2017 Last update posted from 01/01/2017 to 11/28/2017	1
ICTRP Search Portal	angioplasty and restenosis 01/01/2017 to 28/11/2017	1
MEDLINE	1 Arteriosclerosis/ 60027 2 Arteriosclerosis Obliterans/ 4192 3 Atherosclerosis/ 32486	238

(Continued)

- 4 Arterial Occlusive Diseases/ 28247
- 5 Intermittent Claudication/ 8184
- 6 Ischemia/ 50319
- 7 exp Peripheral Vascular Diseases/ 53026
- 8 exp Leg/bs [Blood Supply] 26583
- 9 Iliac Artery/ 14224
- 10 Popliteal Artery/ 9465
- 11 Femoral Artery/ 28635
- 12 Tibial Arteries/ 1574
- 13 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 151212
- 14 (peripheral adj3 dis*).ti,ab. 39838
- 15 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 179677
- 16 (claudic* or IC).ti,ab. 64521
- 17 (isch* or CLI).ti,ab. 364590
- 18 arteriopathic.ti,ab. 181
- 19 dysvascular*.ti,ab. 222
- 20 leg.ti,ab. 85167
- 21 lower limb.ti,ab. 29009
- 22 lower extrem*.ti,ab. 49907
- 23 above knee.ti,ab. 1924
- 24 below knee.ti,ab. 2912
- 25 (femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or infrainquinal or tibial).ti,ab. 243299
- 26 restenosis.ti,ab. 21527
- 27 or/1-26 1146562
- 28 exp Angioplasty/ 62714
- 29 Endovascular Procedures/ 13305
- 30 (angioplas* or percutan* or PTA).ti,ab. 166701
- 31 valvuloplasty.ti,ab. 4554
- 32 (recanali* or revascular*).ti,ab. 67105
- 33 dilat*.ti,ab. 140996
- 34 (balloon or baloon).ti,ab. 61847
- 35 endovascular.ti,ab. 42459
- 36 or/28-35 426689

(Continued)

- 37 Paclitaxel/ 25241
- 38 (coated or uncoated).ti,ab. 100498
- 39 (drug and (elut* or releas*)).ti,ab. 89291
- 40 DEB.ti,ab. 1321
- 41 POBA.ti,ab. 202
- 42 paclitax*.ti,ab. 26659
- 43 sirolimus.ti,ab. 7247
- 44 zotarolimus.ti,ab. 619
- 45 rapalog.ti,ab. 84
- 46 (INPACT or MOXY or Paseo or Lutonix or Paccoca or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE).ti,ab. 1092
- 47 or/37-46 223743
- 48 27 and 36 and 47 5834
- 49 randomized controlled trial.pt. 505458
- 50 controlled clinical trial.pt. 100426
- 51 randomized.ab. 442421
- 52 placebo.ab. 205527
- 53 drug therapy.fs. 2147127
- 54 randomly.ab. 305346
- 55 trial.ab. 466105
- 56 groups.ab. 1885958
- 57 or/49-56 4449754
- 58 exp animals/ not humans.sh. 4743200
- 59 57 not 58 3848554
- 60 48 and 59 2607
- 61 2017*.ed. 953719
- 62 60 and 61 238

Embase

- 1 Arteriosclerosis/ 14492
- 2 Arteriosclerosis Obliterans/ 11174
- 3 Atherosclerosis/ 111897
- 4 Arterial Occlusive Diseases/ 5724
- 5 Intermittent Claudication/ 5974
- 6 Ischemia/ 58464
- 7 exp Peripheral Vascular Diseases/ 1250931

633

(Continued)

- 8 Iliac Artery/ 9653
- 9 Popliteal Artery/ 5112
- 10 Femoral Artery/ 20342
- 11 Tibial Arteries/ 2034
- 12 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 140600
- 13 (peripheral adj3 dis*).ti,ab. 42066
- 14 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 188142
- 15 (claudic* or IC).ti,ab. 51017
- 16 (isch* or CLI).ti,ab. 388806
- 17 arteriopathic.ti,ab. 82
- 18 dysvascular*.ti,ab. 168
- 19 leg.ti,ab. 78344
- 20 lower limb.ti,ab. 32148
- 21 lower extrem*.ti,ab. 48968
- 22 above knee.ti,ab. 1407
- 23 below knee.ti,ab. 2163
- 24 (femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or infrainquinal or tibial).ti,ab. 223048
- 25 restenosis.ti,ab. 26376
- 26 exp Angioplasty/ 67815
- 27 Endovascular Procedures/ 19628
- 28 (angioplas* or percutan* or PTA).ti,ab. 186707
- 29 valvuloplasty.ti,ab. 4263
- 30 (recanali* or revascular*).ti,ab. 80742
- 31 dilat*.ti,ab. 143183
- 32 (balloon or baloon).ti,ab. 69520
- 33 endovascular.ti,ab. 56266
- 34 or/26-33 471247
- 35 Paclitaxel/ 87997
- 36 (coated or uncoated).ti,ab. 87359
- 37 (drug and (elut* or releas*)).ti,ab. 107786
- 38 DEB.ti,ab. 2103
- 39 POBA.ti,ab. 502
- 40 paclitax*.ti,ab. 38355

(Continued)

41 sirolimus.ti,ab. 12272

42 zotarolimus.ti,ab. 1541

43 rapalog.ti,ab. 132

44 (INPACT or MOXY or Paseo or Lutonix or Paccoca or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE).ti,ab. 1671

45 or/35-44 283715

46 or/1-25 1781664

47 34 and 45 and 46 16133

48 randomized controlled trial/ 436425

49 controlled clinical trial/ 408134

50 random\$.ti,ab. 1129645

51 randomization/ 68144

52 intermethod comparison/ 223370

53 placebo.ti,ab. 214681

54 (compare or compared or comparison).ti. 326079

55 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1558492

56 (open adj label).ti,ab. 59910

57 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 153101

58 double blind procedure/ 119054

59 parallel group\$1.ti,ab. 18934

60 (crossover or cross over).ti,ab. 70012

61 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. 240625

62 (assigned or allocated).ti,ab. 281778

63 (controlled adj7 (study or design or trial)).ti,ab. 252369

64 (volunteer or volunteers).ti,ab. 167849

65 trial.ti. 205628

66 or/48-65 3366239

67 47 and 66 7694

68 2017*.dc. 1656576

69 67 and 68 633

AMED

1 Arteriosclerosis/ 78

2

2 Atherosclerosis/ 209

3 Intermittent Claudication/ 72

(Continued)

4 Ischemia/ 253

5 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)) .ti,ab. 451

6 (peripheral adj3 dis*) .ti,ab. 431

7 (atherosclero* or arteriosclero* or PVD or PAOD or PAD) .ti,ab. 783

8 (claudic* or IC) .ti,ab. 1020

9 (isch* or CLI) .ti,ab. 1615

10 arteriopathic .ti,ab. 1

11 dysvascular* .ti,ab. 56

12 leg .ti,ab. 4485

13 lower limb .ti,ab. 2285

14 lower extrem* .ti,ab. 3083

15 above knee .ti,ab. 142

16 below knee .ti,ab. 353

17 (femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or infrainguinal or tibial) .ti,ab. 4656

18 restenosis .ti,ab. 35

19 exp Angioplasty/ 16

20 (angioplas* or percutan* or PTA) .ti,ab. 765

21 valvuloplasty .ti,ab. 6

22 (recanali* or revascular*) .ti,ab. 133

23 dilat* .ti,ab. 215

24 (balloon or baloon) .ti,ab. 89

25 endovascular .ti,ab. 28

26 (coated or uncoated) .ti,ab. 117

27 (drug and (elut* or releas*)) .ti,ab. 115

28 DEB .ti,ab. 1

29 paclitax* .ti,ab. 79

30 (INPACT or MOXY or Paseo or Lutonix or Paccoca or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE) .ti,ab. 17

31 or/1-18 16723

32 or/19-25 1169

33 or/26-30 328

34 31 and 32 and 33 2

CINAHL

S55 S46 AND S53 AND S54 24

24

(Continued)

S54 EM 2017 177,835

S53 S47 OR S48 OR S49 OR S50 OR S51 OR S52 951,324

S52 TX randomly 41,642

S51 TX "treatment as usual" 709

S50 TX "double-blind*" 755,121

S49 TX "single-blind*" 8,665

S48 TX trial 236,355

S47 MH "Clinical Trials" 90,798

S46 S26 AND S34 AND S45 1,583

S45 S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 21,062

S44 TX IN.PACT or MOXY or Paseo or Lutonix or Paccoca or PANTERA or ELUTAX or DIOR or FREEWAY or SeQuent or GENIE 513

S43 TX rapalog 6

S42 TX zotarolimus 127

S41 TX sirolimus 2,040

S40 TX paclitax* 3,181

S39 TX POBA 13

S38 TX DEB 1,259

S37 TX (drug and (elut* or releas*)) 13,648

S36 TX coated or uncoated 2,367

S35 (MH "Paclitaxel") 2,289

S34 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 42,521

S33 TX endovascular 4,527

S32 TX balloon or baloon 6,457

S31 TX dilat* 9,790

S30 TX (recanali* or revascular*) 7,744

S29 TX valvuloplasty 297

S28 TX angioplas* or percutan* or PTA 22,778

S27 (MH "Angioplasty+") 8,833

S26 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 135,601

S25 TX restenosis 2,254

S24 TX femor* or iliac or popliteal or fempop* or crural or poplite* or in-frapopliteal or inguinal or femdist* or infringuinal or tibial 24,317

(Continued)

S23 TX below knee 1,598

S22 TX above knee 754

S21 TX lower extrem* 13,945

S20 TX lower limb 7,329

S19 TX leg 23,610

S18 TX dysvascular* 165

S17 TX arteriopathic 10

S16 TX isch* or CLI 37,878

S15 TX claudic* or IC 6,833

S14 TX (peripheral n3 dis*) 8,837

S13 TX ((arter* or vascular or vein* or veno* or peripher*) n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)) 12,203

S12 TX atherosclero* or arteriosclero* or PVD or PAOD or PAD 25,428

S11 (MH "Tibial Arteries") 134

S10 (MH "Femoral Artery") 1,180

S9 (MH "Popliteal Artery") 352

S8 (MH "Iliac Artery") 449

S7 (MH "Leg/BS") 441

S6 (MH "Peripheral Vascular Diseases") 2,952

S5 (MH "Ischemia") 3,239

S4 (MH "Intermittent Claudication") 831

S3 (MH "Arterial Occlusive Diseases") 1,581

S2 (MH "Atherosclerosis") 3,139

S1 (MH "Arteriosclerosis") 4,830

CONTRIBUTIONS OF AUTHORS

AK: protocol drafting, acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting, future review updates, guarantor of the review.

WAJ: protocol drafting, acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting.

GP: data interpretation, review drafting.

DK: data interpretation, review drafting.

TF: data interpretation, review drafting.

DR: data interpretation, review drafting.

RN: data interpretation, review drafting.

AD: data interpretation, review drafting, future review updates.

DECLARATIONS OF INTEREST

AK: none known.

WAJ: none known.

GP: received consultancy fees from WL Gore for acting as a reviewer of complications for a study involving an endovascular device and for support for speaking/lectures. He has received a grant from Gore for creation of a database for endovascular aneurysm repair research and from Abbott for development of a database for peripheral endovascular procedures. He has received honoraria from WL Gore and Medtronic for lectures and for speaking.

DK: none known.

TF: none known. Reports that his host institution, the University of Toronto Division of Vascular Surgery, receives academic support from several industry partners (Cook Medical, Medtronic, Liva Nova, CHS, Lemaitre, Gore) in the form of unrestricted educational grants.

DR: received consultancy fees for lectures around dialysis interventions and support for a live case course from CR Bard.

RN: has declared that he received payment for roles within the Scientific Advisory Boards of Graftworx and WL Gore; and from Fresenius for presenting an educational program for podiatric audiences and for legal defence malpractice work. He has no financial relationships related to the topic of this review.

AD: none known.

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol identified numerous anatomical and clinical outcomes that were not reported by any of the included trials. Because it was reported in two of the included studies, the review included outcomes such as ABI values, rather than change in ABI, and freedom from TLR, which we had not identified as an outcome of interest in the protocol. Unfortunately, it is not possible to perform any subgroup or sensitivity analyses as had been intended in the protocol because of the small number of included studies.

NOTES

Parts of the methods section of this review are based on a standard template established by Cochrane Vascular.

INDEX TERMS

Medical Subject Headings (MeSH)

*Femoral Artery; *Popliteal Artery; *Stents; Amputation; Angioplasty, Balloon [adverse effects] [*methods]; Ankle Brachial Index; Constriction, Pathologic [etiology] [mortality] [therapy]; Randomized Controlled Trials as Topic; Recurrence; Vascular Patency

MeSH check words

Humans