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Angiographic and clinical efficacy of Paclitaxel-Coated versus Uncoated-Balloon angioplasty for femoro-popliteal revascularization.

A meta-analysis of randomized trials

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1. List of abbreviations

PTA Percutaneous transluminal angioplasty

ABI Ankle Brachial Index

SFA Superficial femoral artery

TASC Inter-Society Consensus for the Management of PAD

UCB Uncoated Convetional Balloon

PAD Peripheral artery disease

PCB Paclitaxel Coated Balloon

FPA Femoro-popliteal artery

TASC Trans -Atlantic Intersociety Consensus

LLL Late lumen loss

TLR Target lesion revascularization

TVR Target vessel revascularization

PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses

OR Pooled Calculated Odds Ratio

WMD weighted mean difference

MD Mean difference

CI Confidence intervals

NNT Number needed to treat

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2. Introduction

2.1 Preface

Peripheral arterial disease (PAD) is one manifestation of systemic atherosclerosis. The prevalence of PAD increases with the age of the population It is important to remember the significant association of coincident coronary artery disease and cerebrovascular disease in these patients, because it represents the major cause of morbidity and mortality in the PAD population.[1]

Remarkable technological advances in the past decade, along with patient preference, have shifted revascularization strategies from traditional open surgical approaches toward lower-morbidity percutaneous endovascular treatments. Catheter-based revascularization of the lower extremities was pioneered by Charles Dotter[2] and advanced among others by Andreas Grüntzig, who employed then newly developed inflatable balloon catheters that could dilate vascular stenosis.[3]

Endovascular therapy offers several distinct advantages over open surgical revascularization for selected lesions. It is performed with local anesthesia, which enables the treatment of patients who are at high risk for general anesthesia.

The morbidity and mortality from catheter-based therapy is extremely low especially compared with open surgical revascularization. After successful percutaneous revascularization, patients are ambulatory on the day of treatment, and unlike after vascular surgery, they can often return to normal activity within 24 to 48 hours of an uncomplicated procedure.

Endovascular therapies generally do not preclude or alter subsequent surgery and may be repeated if necessary. Multiple specialties, including interventional cardiology, have contributed to the advancement of the field of peripheral vascular intervention of the past several decades.[4]

2.2 Treatment option for PAD

Medical therapy, percutaneous intervention, and surgery have been compared in several trials in symptomatic patients with femoral-popliteal disease.

A meta-analysis that compared PTA (percutaneous transluminal angioplasty) with exercise therapy in patients with intermittent claudication reported similar quality-of-life outcomes at 3and 6 months but also found that functional capacity and (ankle brachial index, ABI) improved more with endovascular therapy than with exercise.[5]

Cost-effectiveness and quality-of-life outcomes favour the performance of percutaneous therapy whenever feasible as a more effective treatment than exercise alone. A matched-cohort study of 526 patients with intermittent claudication found significant advantages for a revascularization strategy (surgery or PTA) compared to medical therapy.[6]

Revascularization was more effective than medical therapy for improvement in physical function, bodily pain, and walking distance. Patients with the greatest improvement in their ABI results had the best clinical improvement, which indicates that the degree of revascularization was related to a successful outcome. [6]

If the 5-year patency rate is estimated to be more than 30%, the authors concluded that percutaneous therapies would be superior to surgery.[7]

Clinical success in patients with (superficial femoral artery, SFA) lesions depends on a durable, long-lasting procedure. The availability of stents, more than any other advance, has pushed the growth of catheter based procedures by improving the safety, durability, and predictability of percutaneous revascularization. Multiple clinical trials in small numbers of patients had previously failed to show any advantage for stents compared with PTA. For that reason the Trans-Atlantic Inter-Society Consensus for the Management of PAD (TASC II) suggests percutaneous revascularization in the following situations[8] (**Figure 1**).

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Figure 1. Modified TASC Classification of Femoro-Popliteal Lesions

A. Endovascular treatment of choice:

Single <3-cm stenosis (unilateral/bilateral)

B. Endovascular more often used:

Single 3- to 5-cm stenosis

Heavily calcified stenoses ≤3 cm

Multiple lesions each ≤3 cm (stenoses or occlusions)

Single or multiple lesions, in the absence of continuous tibial runoff, to improve inflow for infrageniculate bypass

C. Endovascular if possible:

Single stenosis or occlusion 5 to 10 cm

Multiple stenoses or occlusion, each 3 to 5 cm

D. Surgery preferred, endovascular considered on case-by-case basis:

Complete occlusion of CFA or SFA or popliteal and proximal crural arteries

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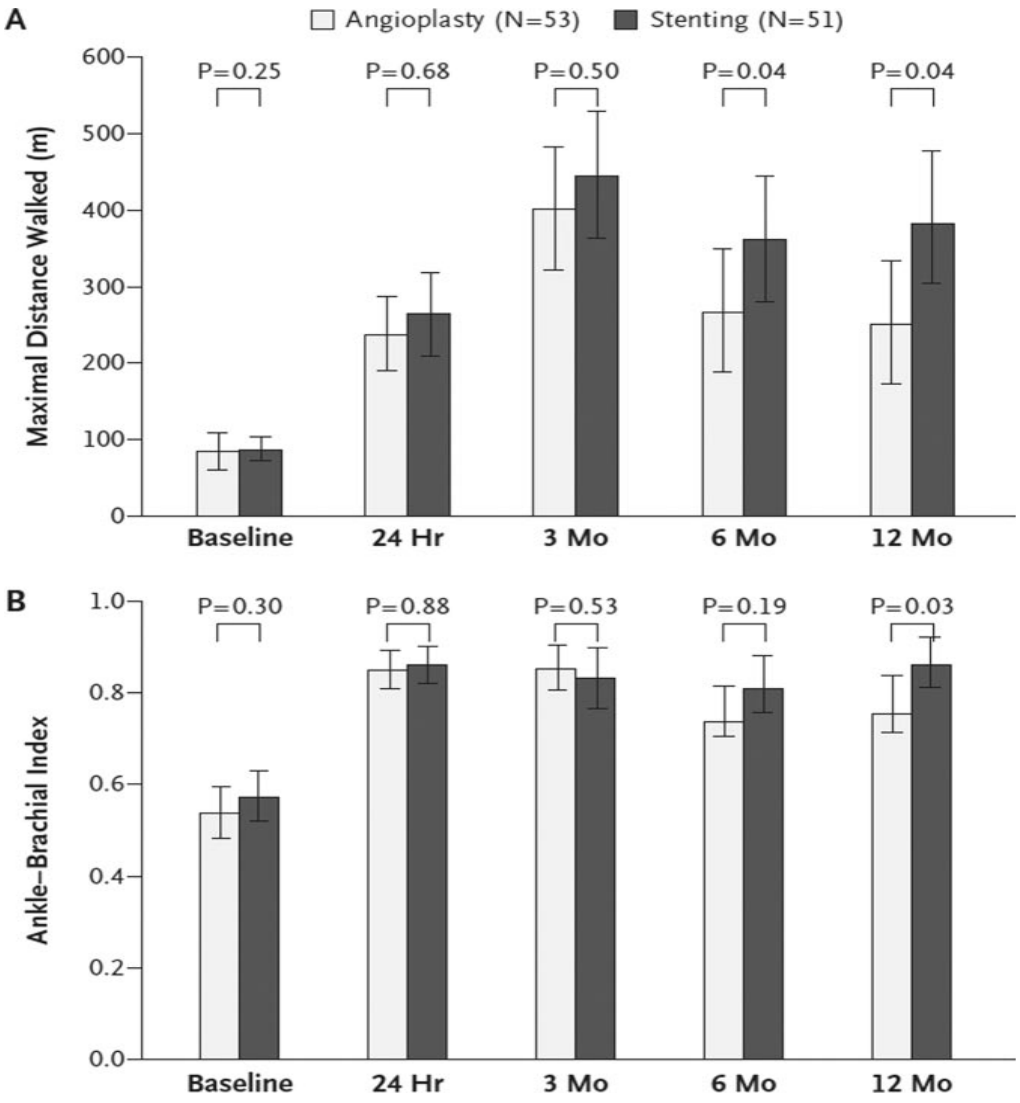
A meta-analysis did, however, demonstrate better patency at 3 years for stents than for PTA in the most severely affected patients, those with occlusions and CLI.[9]

2.3 Role of the Stenting

A recent randomized controlled trial demonstrated a better outcome for primary SFA stent placement than a strategy of provisional stent placement for superficial femoral artery lesions. [10] The authors demonstrated not only was restenosis significantly lower in the stent group at 6 and 12 months, but there was also better functional improvement higher (ABI) and walking distance in the primary stent group (**Figure 2A - 2B**).



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An interesting observation was that stent fractures, which have been associated with restenosis in SFA lesions, were only reported in 2% of the stents used in this trial (Dynalink/Absolute, Abbott Vascular). There are differences regarding stent fracture among SFA stents that are presumably related to their composition and architecture. A recently published series found fracture rates of 28% for the SMART stent (Cordis), 19% for the Wallstent (Boston Scientific), and 2% for the Dynalink/Absolute stent (Abbott Vascular). The issue of stent fracture is a complex one, with attendant restenosis being greater in the fracture territory and the length of lesion/presence of multiple overlapping stents also being an apparent contributing factor.[11, 12]

A second randomized controlled trial compared balloon angioplasty versus implantation of a single nitinol stent in 244 with patients with shorter SFA lesions (mean lesion length, 45±28 mm). At 12 months, there was no significant difference in terms of angiographic and clinical restenosis between the treatment groups (31.7% versus 38.6%, respectively; p=0.38). The authors concluded that in short lesions stent placement not improves the primary patency at 1 year follow-up. [13]

Although the role of the stent appears controversial in different randomised trials, it seems that a better outcome is more evident in long lesions of the SFA.

In the RESILIENT (Randomized Study Comparing the Edwards Self-ExpandIng Lifestent versus Angioplasty Alone In Lesions INvolving The SFA and/or Proximal Popliteal Artery) trial a total of 206 patients from 24 centers in the United States and Europe with obstructive lesions of the superficial femoral artery and proximal

popliteal artery and intermittent claudication were randomized to implantation of nitinol stents or percutaneous transluminal angioplasty. The mean total lesion length was 71 mm for the stent group and 64 mm for the angioplasty group. Acute lesion success (<30% residual stenosis) was superior for the stent group compared with the angioplasty group (95.8% versus 83.9%; $p<0.01$). Twenty-nine (40.3%) patients in the angioplasty group underwent bailout stenting because of a suboptimal angiographic result or flow-limiting dissection. Bailout stenting was treated as a target lesion revascularization and loss of primary patency in the final analysis. At 12 months, freedom from target lesion revascularization was 87.3% for the stent group compared with 45.1% for the angioplasty group ($p<0.0001$). Duplex ultrasound-derived primary patency at 12 months was better for the stent group (81.3% versus 36.7%; $p<0.0001$, **Figure 3**).

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Figure 3: Results of the Stent vs PTA at 6 and 12 month follow-up.

	Stent (n=134)	PTA (n=72)	Percent Difference	*P**
6-month freedom from MACE†	93.1	92.8	0.3	0.95
12-month freedom from MACE	85.8	86.6	−0.8	0.88
6-month effectiveness measures				
Freedom from TLR	98.5	52.6	45.9	<0.0001
Freedom from TLR/TVR	94.6	52.6	42.0	<0.0001
Primary patency	94.2	47.4	46.8	<0.0001
Secondary patency	100	98.3	1.7	0.31
Clinical success	81.4	30.9	50.5	<0.0001
12-month effectiveness measures				
Freedom from TLR	87.3	45.1	42.2	<0.0001
Freedom from TLR/TVR	83.5	45.1	38.4	<0.0001
Primary patency	81.3	36.7	44.6	<0.0001
Secondary patency	100	98.3	1.7	0.31
Clinical success	72.3	32.3	40.0	<0.0001

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Through 12 months, fractures occurred in 3.1% of stents implanted.

No stent fractures resulted in loss of patency or target lesion revascularization.

In this multicenter trial, primary implantation of a self-expanding nitinol stent for long lesions in the superficial femoral artery and proximal popliteal artery was associated with better acute angiographic results and improved patency compared with balloon angioplasty alone.[14]

2.4 The era of local Drug Delivery in PAD

Although the implantation of nitinol stent seems to reduce TLR and target vessel revascularization (TVR) of long lesions of the SFA at mid-term follow-up, the long term patency still remains a serious problem. Initial attempts to transfer the benefit of local drug delivery to the femoral-popliteal arteries have not been successful.

A randomized controlled trial of sirolimus-eluting nitinol stents compared with bare-metal nitinol stents in de novo femoral arteries with an average lesion length of 8.5 cm was performed in patients in European centers. After 18 months of follow-up, there appeared to be no advantage regards the restenosis rate of the drug-eluting stent (20.7%) over the bare metal nitinol stent (17.9%). In the initial phase of the trial, failure of the drug-coated stent was attributed to stent fractures, seen in 18% of cases, but in the second phase of the trial, stent fractures were only seen in 8% of cases and were not associated with restenosis.[15, 16]

Several studies in cell culture and in swine have demonstrated sustained inhibition of the proliferation of vascular smooth-muscle cells after the exposure of cells or tissues

to paclitaxel, a highly lipophilic antineoplastic drug, for just a few seconds to a few minutes. This underlines the rationale for drug-coated balloon treatment.

A recent clinical trial suggested significant inhibition of re-restenosis after treatment of restenosis in coronary bare metal stents by paclitaxel-coated balloon angioplasty.[17] Initial experience with paclitaxel eluting balloon in the peripheral artery disease seems to be promising. The THUNDER trial (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) a prospective, randomized, multicenter trial for the superficial femoral artery lesions demonstrated that the primary end point of mean late lumen loss was significantly lower in the group treated with paclitaxel-coated balloons than in the control group (0.4±1.2 mm vs. 1.7±1.8 mm, $p<0.001$). The angiographic restenosis rate was significantly lower among patients treated with paclitaxel-coated balloons than among patients in the control group (17% vs. 44%, $p=0.01$). Target-lesion revascularization was performed in 20 of 54 patients in the control group (37%), as compared with and 2 of 48 patients in the group treated with paclitaxel-coated balloons (4%, $p<0.001$). The rate of target-lesion revascularization at 12 months remained low in the group treated with paclitaxel-coated balloons.[18]

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3. Aim of the study

Percutaneous transluminal balloon angioplasty represents a well-known revascularization strategy for atherosclerotic peripheral artery disease.[19]

In this superficial femoral artery bed, uncoated balloon (UCB) angioplasty has been associated with poor outcomes both at acute (vessel ruptures or recoil, flow-limiting dissections, suboptimal results) and mid-term follow-up (rapid restenotic occlusion of the target vessel).[19, 20]

Recently, percutaneous balloon catheters, coated with the anti-proliferative drug paclitaxel, have been developed, with the purpose of defeat restenosis of peripheral vessels. After preliminary experience on animal models,[17, 21]paclitaxel-coated balloon (PCB) showed encouraging angiographic results as compared to UCB angioplasty, in patients suffering for femoro-popliteal artery (FPA) atherosclerotic disease.[18, 22]

Although late lumen loss (LLL) and target lesion revascularization (TLR) were significantly reduced, the small number of patients tempered the relevance of these results. Moreover, recent studies did not confirm the clinical advantage associated with PCB use.[23, 24]

As a result, the benefit of PCB for FPA percutaneous revascularization still remains controversial. Against this background, we performed a study-level meta-analysis of randomized trials investigating angiographic and clinical outcomes associated with PCB versus UCB angioplasty for FPA disease**.**

4. Methods

4.1 Search strategy and selection criteria

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific sessions abstracts and relevant websites, without language, publication date or publication status restrictions. Reference lists of the eligible studies and previous reviews were checked to identify further evaluable articles. The last search was run in December 2011. Search terms included the keywords and the corresponding Medical Subject Headings (MeSH) for: “superficial femoral artery”, “popliteal artery”, “angioplasty”, “drug-eluting balloon”, “paclitaxel-eluting balloon” and “randomized trial”. Inclusion criteria were: (1) randomized design; (2) intention to treat analysis; (3) ≥6-month follow-up. Exclusion criteria were: (1) other vessel treated than FPA, (2) comparison other than PCB versus UCB, (3) irretrievable or duplicated data.

4.2 Data collection and assessment of risk of bias

Two investigators independently assessed reports for eligibility at title and/or at abstract level, with divergences resolved by a third investigator. Studies that met inclusion criteria were selected for further analysis. The risk of bias was evaluated by the same two reviewer authors, in accordance with The Cochrane Collaboration method[25] based on the following methodological items: adequacy of random sequence generation and allocation concealment, blinding (at participant, personnel or outcome assessors level), incomplete outcome data depiction, freedom from

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selective outcome report and adequate description of sample size calculation. No quality score was adjudicated , as previous report failed to prove their value.[26]

4.3 Outcome variables

The primary outcome of this meta-analysis is 6-month LLL at angiographic surveillance. Secondary outcomes are: angiographic restenosis, and TLR and mortality at the longest available follow-up. All endpoints were evaluated as per protocol definitions (Table 1).

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Table 1. Endpoints definitions of included trials.

Trial	***THUNDER*[5]**	***FemPac*[6]**	***LEVANT I*[7]**	***PACIFIER*[8]**
LLL	Difference between the minimum lumen diameters after dilation and at the 6-month follow-up	Difference between the minimal luminal diameter after the procedure and at 6 months by quantitative angiography	n/r	n/r
Angiographic Restenosis	Stenosis of ≥50% of the diameter of the reference-vessel segment	Stenosis ≥50% in the treated lesion	n/a*	Binary restenosis
TLR	Any repeat revascularization of the target lesion	Any repeat revascularization of the target lesion	Any repeat revascularization of the target lesion	Any repeat revascularization of the target lesion
Death	n/r	n/r	n/r	Death of any cause

LLL: Late lumen loss; TLR: Target lesion revascularization. n/r: not reported; n/a: not available.

Trial acronyms: THUNDER: Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries trial; FemPac: Femoral Paclitaxel trial; LEVANT I: Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropoliteal Restenosis; PACIFIER: Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis. *Cumulative TLR/>50% diameter stenosis data at 6-month follow-up available.

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4.4 Statistical analysis

Statistical analysis was performed with RevMan software (*Review Manager [RevMan]. Version 5.1, The Cochrane Collaboration, Copenaghen*), and Stata 11.0 statistical software (*STATA Corp, College Station, Texas, USA*). The κ statistic was used to assess agreement between reviewers for study selection. Odds ratio (OR), weighted mean difference (WMD) and 95% confidence intervals [95% CI] were used as summary statistics. Treatment effect could not be assessed in trials in which no event was reported within groups. For trials in which only 1 of the treatment groups had no events of interest, the treatment effect estimate and its standard error were approximated from 2 x 2 contingency tables, after adding 0.5 to each cell.[27]

The random effects (DerSimonian and Laird model) were used to calculate pooled OR for categorical and WMD for continuous variables. In case of statistical significance, the number needed to treat (NNT) with relative CI was provided, if appropriate. The Breslow–Day chi-squared test ($p<0.1$) and the I^2 statistic were calculated to test the statistical evidence of heterogeneity across the studies. As a guide, I^2 values < 25% indicated low, 25–50% moderate, and >50% high heterogeneity.[25]

Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, as well as Egger's and Begg´s test,[28] as formal statistical tests for publication bias, to overcome any subjective evaluation. Random effects model was used to take into account the mean of a distribution of effects across studies and it provides wider confidence intervals for the regression coefficients than fixed effect

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analysis, if residual heterogeneity exists. The weight used for each trial was the inverse of the sum of the within trial variance and the residual between trial variance, in order to correspond to a random effects analysis. In order to estimate the additive (between-study) component of variance, tau-2, the restricted maximum likelihood method, was used to take into account the occurrence of residual heterogeneity. A random effect meta-regression analysis was conducted to estimate the extent to which including three covariates - the nature of the study with respect to publication status (full-length article/meeting presentation), sample size (≥100 patients versus <100 patients) and blinding (single/double) - might have influenced the treatment effect. Finally, an influence analysis, in which meta-analysis estimates are computed omitting one study at time, was performed.

The study was carried out in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[29]

5 Results

5.1Eligible studies

We screened the title and/or the abstract of 95 potentially eligible publications (**Figure 4**). Of these, 87 citations were excluded since they were not relevant to this study or duplicated. Thus, 8 studies were assessed for eligibility and 4 studies were eliminated since inclusion criteria were not met. Finally, 4 trials (two full-length manuscripts,[18, 22] two meeting presentations,[23, 24] n= 433 patients) were included in

the meta-analysis. The inter-observer agreement for study selection was good, with a κ value of 0.87. Main characteristics of included studies were reported in **Table 1**.

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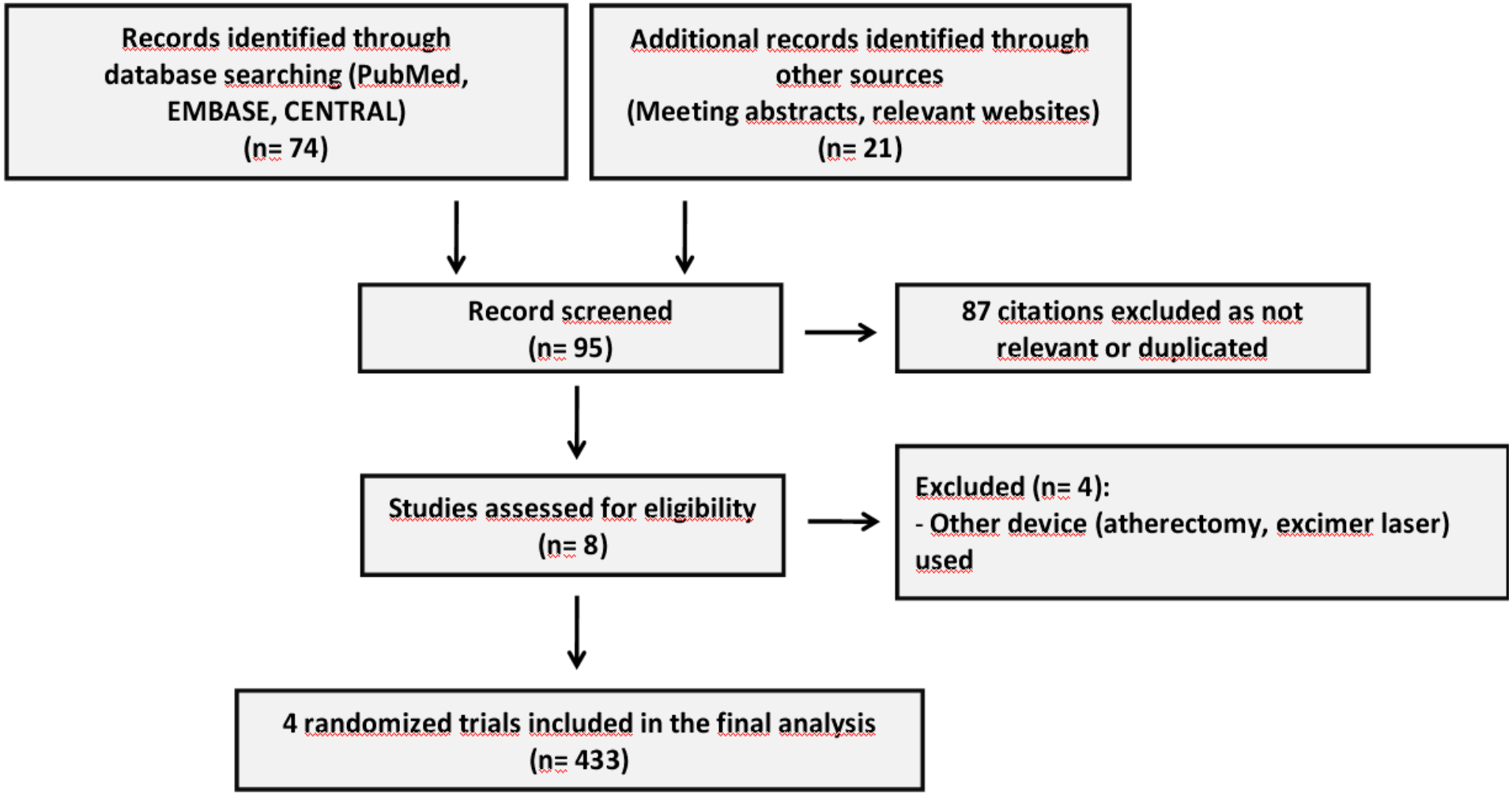
Records identified through database searching (PubMed, EMBASE, CENTRAL) (n= 74)
Additional records identified through other sources (Meeting abstracts, relevant websites) (n= 21)
Record screened (n= 95)
87 citations excluded as not relevant or duplicated
Studies assessed for eligibility (n= 8)
Excluded (n= 4):
- Other device (atherectomy, excimer laser) used
4 randomized trials included in the final analysis (n= 433)

Figure 4

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Table 1. Main features of included trials.#

Trial	***THUNDER*[5]**	***FemPac*[6]**	***LEVANT I*[7]**	***PACIFIER*[8]**
Year/ Multi-centre	2004-2005/Yes	2004-2006/Yes	2009/Yes	2010-2011/Yes
Patients (n)	154	87	101	91
Mean age (years)*	68/69	67/70	67/70	71/71
Restenotic lesion (%)*	29/37	36/33	11/12	31/17
Diabetes mellitus (%)*	46/50	40/55	45/50	43/28
Provisional stenting (%)*	4/22[§]	9/14	n/a[†]	21/34
Relevant inclusion/exclusion criteria	Age 18-95 years; Rutherford stages 1-5; ≥1 lesion (de novo or restenosis); ≥70% of vessel diameter; ≥2 cm in length/Poor inflow; no patent crural artery; acute symptom onset; ≤1 year life expectancy	Age 18-90 years; Rutherford stages 1-5; occlusion or stenosis ≥70% of vessel diameter; successful guidewire passage/Acute symptom onset; leg-threatening ischemia; distal outflow <1 vessel; life expectancy <2 years	Age ≥18 years; Rutherford stages 2-5; 1 lesion (de novo or restenosis); >70% of vessel diameter; ≥4 to ≤15 cm in length; ≥4 to ≤6 mm reference vessel diameter; successful guidewire passage; inflow free from significant lesion (>50% stenosis)/#nadequate outflow; severe calcification; previous surgery of target lesion; acute/sub-acute thrombosis	Adult patients, Rutherford stages 2-5; occlusion or stenosis >70% of vessel diameter; ≥3 to ≤30 cm in length/Acute thrombus or aneurysm in the index limb/ vessel; failure in guidewire passage; poor inflow; distal outflow <1 vessel

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Primary/secondary endpoints	6-month LLL/Technical success; 6-month angiographic restenosis rate; Rutherford stage change; ABI; patency rate; TLR incidence	6-month LLL/6-month restenosis rate; TLR; Rutherford stage change; ABI; amputation; thrombotic complications; clinical adverse events	6-month LLL/ 30-day device-related adverse events; 6-month primary patency, TLR, TVR	6-month LLL/6-month binary restenosis rate; TLR; Rutherford stage change; event free survival
Post-procedure antiplatelet therapy	Aspirin (100 mg/die) indefinitely; Clopidogrel (75 mg/die) for 4 weeks.[¶]	Aspirin (100 mg/die) indefinitely; Clopidogrel (75 mg/die) indefinitely.	Clopidogrel (75 mg/die) for 1 month (if no stent is implanted) or 3 months (if a stent is implanted)	n/r
Angiographic follow-up /time (months)	Yes/6[#]	Yes/6, 18, 24	Yes/6	Yes/6
Registration number	NCT00156624	NCT00472472	NCT00930813	NCT01083030

LLL: Late lumen loss; ABI: Ankle-brachial index; TLR: Target lesion revascularization; TVR: Target vessel revascularization; NCT: National clinical trial. n/r: not reported.

Trial acronyms: THUNDER: Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries trial; FemPac: Femoral Paclitaxel trial; LEVANT I: Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropoliteal Restenosis; PACIFIER: Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis.
[*]Paclitaxel-coated versus Uncoated-balloon angioplasty for all comparisons. [§]p= 0.0009; [†]Randomization to Paclitaxel-coated versus Uncoated-balloon angioplasty (1:1 ratio) was performed after a protocol mandated predilation and provisional stenting. [¶]Patients not already taking aspirin and clopidogrel were administered loading doses of 300 mg of each drug 12 hours before the procedure. [#]Additional follow-up at 1 and 2 years was planned after the 6-month follow-up indicated differences between treatment groups.

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Briefly, patients with symptomatic FPA disease (Rutherford Class 1-[18] or 2-5[22-24]) and ≥70% stenosis or occlusion evidence have been randomized to PCB or UCB angioplasty. Balloon-catheters used were coated with paclitaxel (dose 3[18, 22, 24] $\mu g/mm^2$ or 2[23] $\mu g/mm^2$ of balloon surface) or uncoated. Drug was directly delivered from balloon surface in to the vessel wall without a carrier[22] or with a vehicle (urea,[24] contrast medium[18], **Figure 5**); in one trial the compound used remained unknown.[23] Key devices characteristics are detailed (**Table 2 – Supplementary Data**).

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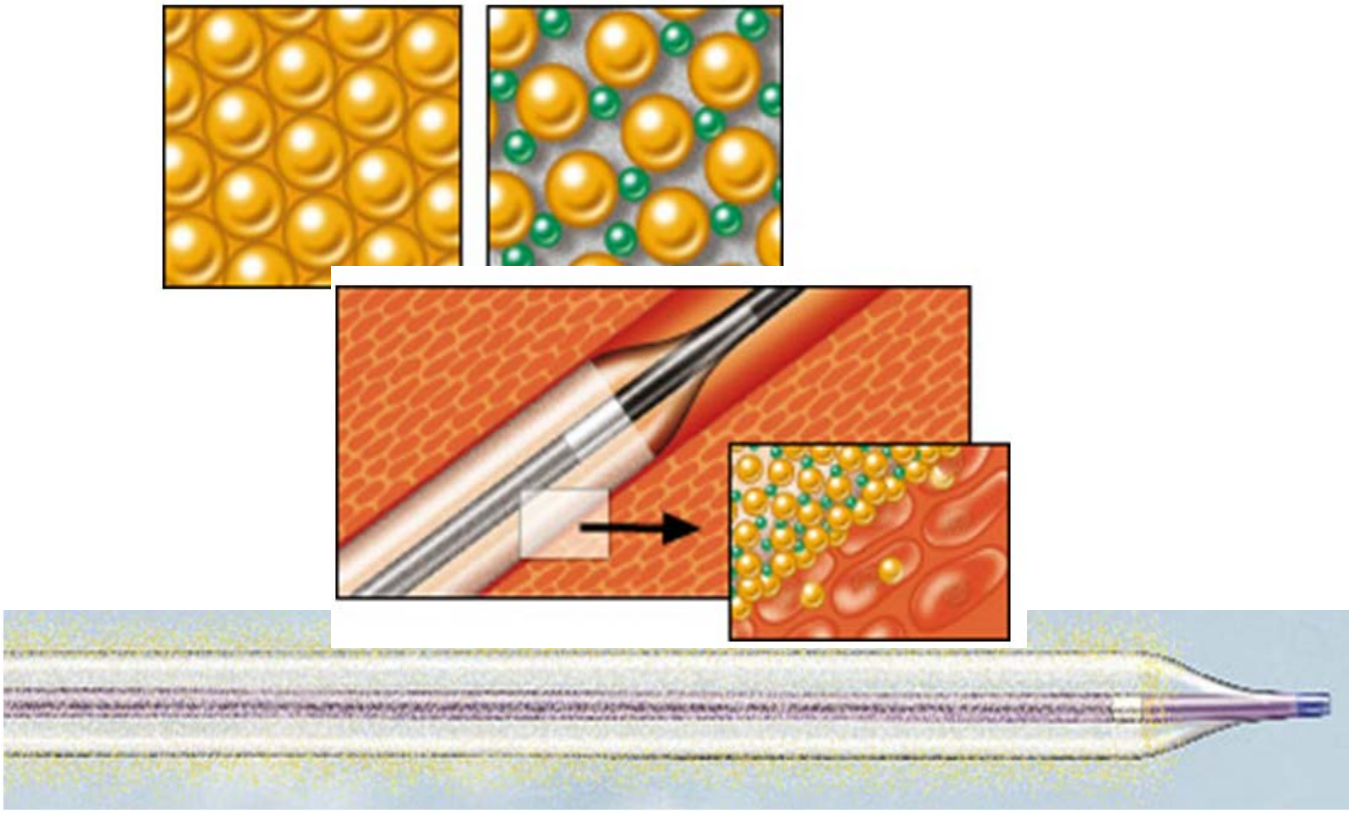

Figure 5.

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Table 2 – Supplementary Data. Main features of devices used.

Trial	***THUNDER*[5]**	***FemPac*[6]**	***LEVANT I*[7]**	***PACIFIER*[8]**
Drug dose/Balloon surface	3 μg/mm^2	3 μg/mm^2	2 μg/mm^2	3 μg/mm^2
Drug/Balloon loading component	Ethyl acetate/Acetone	Ethyl acetate/Acetone	Unknown*	Urea¶
Elution excipient	Iopromide	None	Unknown*	Urea¶
Excipient hydrophilicity	+	-	n/a	+++
Manufacturer	Bavaria Medizin Technologie/Bayer AG	Bavaria Medizin Technologie/Bayer AG	Lutonix Inc.	Medtronic-Invatec Inc.

Trial acronyms: THUNDER: Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries trial; FemPac: Femoral Paclitaxel trial; LEVANT I: Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropoliteal Restenosis; PACIFIER: Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis. *Drug carrier is a molecular entity on the Food and Drug Administration IV-approved list. (Informations at ttp://www.lutonix.com/product/technology/moxy. Last access performed on January 2012). ¶Dosage 0.5 μg/mm^2; n/a: not assessable.

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One study[18] comprised a third treatment arm (n= 52, paclitaxel addition to angiographic contrast medium) that was discarded. Thus, 381 patients (186 randomized to PCB and 195 randomized to UCB) were available for final analysis. Patients with previous angioplasty (with or without stent) were included. The main exclusions criteria were in/outflow disease and acute symptoms onset or FPA thrombosis. Provisional bare-nitinol stenting was allowed in case of suboptimal result after dilation. In one trial[23] all cases underwent per protocol predilation with an undersized UCB with or without stenting. The randomisation to PCB or UCB occurred at this time point.

All patients received active or control treatment on top of medical therapy. Postoperative antiplatelet management was available in all trials but one.[24] Clinical features well-matched typical PAD population and treatment groups were well paired among studies. For PCB versus UCB angioplasty arms, mean age ranged from 67 to 71 and from 69 to 71 years, whilst mean lesion length from 4.0 to 8.1 mm and from 4.2 to 8.0 mm. Median follow-up was 10.3 months. In all studies, LLL (mm) at 6-month angiographic follow-up was the primary endpoint.

The risk of bias among studies was reported in **Table 2**.

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Table 2. Risk of bias assessment.

Trial	*THUNDER*[5]	*FemPac*[6]	*LEVANT I*[7]	*PACIFIER*[8]
Random sequence generation	Yes	Yes	Yes	Yes
Allocation concealment	Yes	No	No	No
Blinding of participants and personnel*	Yes	Yes	Yes[#]	Yes
Blinding of outcome assessment[§]	Yes	Yes	Yes	Yes
Incomplete outcome data	Yes	Yes	Yes	Yes
Selective outcome reporting	Yes	Yes	Yes	Yes
Sample size calculation	Yes	Yes	No	No

[*]According to slight differences in the appearance of the balloons (mainly the surface coating), blinding of investigators was not possible in all studies. [#] Partecipants only. [§]All trials indicated independent outcome assessors at least for primary endpoint adjudication.

Trial acronyms: THUNDER: Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries trial; FemPac: Femoral Paclitaxel trial; LEVANT I: Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropoliteal Restenosis; PACIFIER: Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis.

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5.2 Clinical endpoints

Angiographic surveillance at 6-month follow-up, was available in 307 patients (80.5%) and documented superiority of PCB against UCB in terms of LLL (range -0.05, 0.50 versus 0.61, 1.7 mm; WMD= -0.75 [-1.06, -0.45], p<0.00001).

Low heterogeneity was encountered (I^2=24%, p for heterogeneity - phet = 0.27; **Figure 6 - Panel A**). Data concerning angiographic restenosis, was available in 233 participants (58.5%, 3 trials[18, 22, 24]), confirmed higher efficacy of PCB versus UCB (18.7% versus 45.5%; OR= 0.26 [0.14–0.48], p= <0.0001) with a NNT=4 [2.6-6.6]. No heterogeneity was found (I^2=0%, phet=1.00; **Figure 7 - Panel A**).

Data concerning overall TLR was available for a total of 360 patients (94.4%) and occurred in 90 patients (25%). A significant TLR reduction for PCB versus UCB was found (12.2% versus 27.7%; OR [95% CI]= 0.23 [0.13–0.40], p= <0.00001) with a NNT=4 [2.9-5.9].

There was low heterogeneity (I^2=6%, phet=0.36). **Figure 7 Panel B**

Death occurrence was available in 368 participants (96.5%). Overall mortality was 4.8% (n =108) with no difference for PCB versus UCB (2.1% versus 3.2%; OR= 0.77 [0.20–2.93], p= 0.70). No heterogeneity was found (I^2=0%, phet= 0.43; **Figure 7 - Panel C**)

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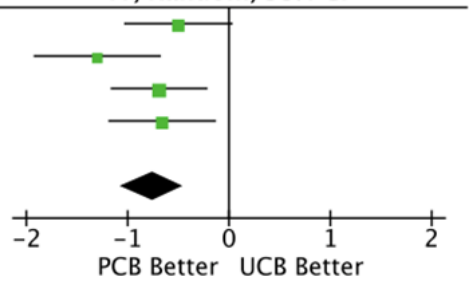
Study or Subgroup	PCB Mean	PCB SD	PCB Total	UCB Mean	UCB SD	UCB Total	Weight	Mean Difference IV, Random, 95% CI	Year
FemPac	0.5	1.1	31	1	1.1	34	25.2%	−0.50 [−1.04, 0.04]	2008
THUNDER	0.4	1.2	41	1.7	1.8	48	19.6%	−1.30 [−1.93, −0.67]	2008
LEVANT I	0.4	1.1	39	1.09	1	35	29.7%	−0.69 [−1.17, −0.21]	2010
PACIFIER	−0.05	1.1	40	0.61	1.3	39	25.5%	−0.66 [−1.19, −0.13]	2011
Total (95% CI)			**151**			**156**	**100.0%**	**−0.75 [−1.06, −0.45]**	

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.95$, df = 3 (P = 0.27); $I^2 = 24\%$

Test for overall effect: Z = 4.78 (P < 0.00001)



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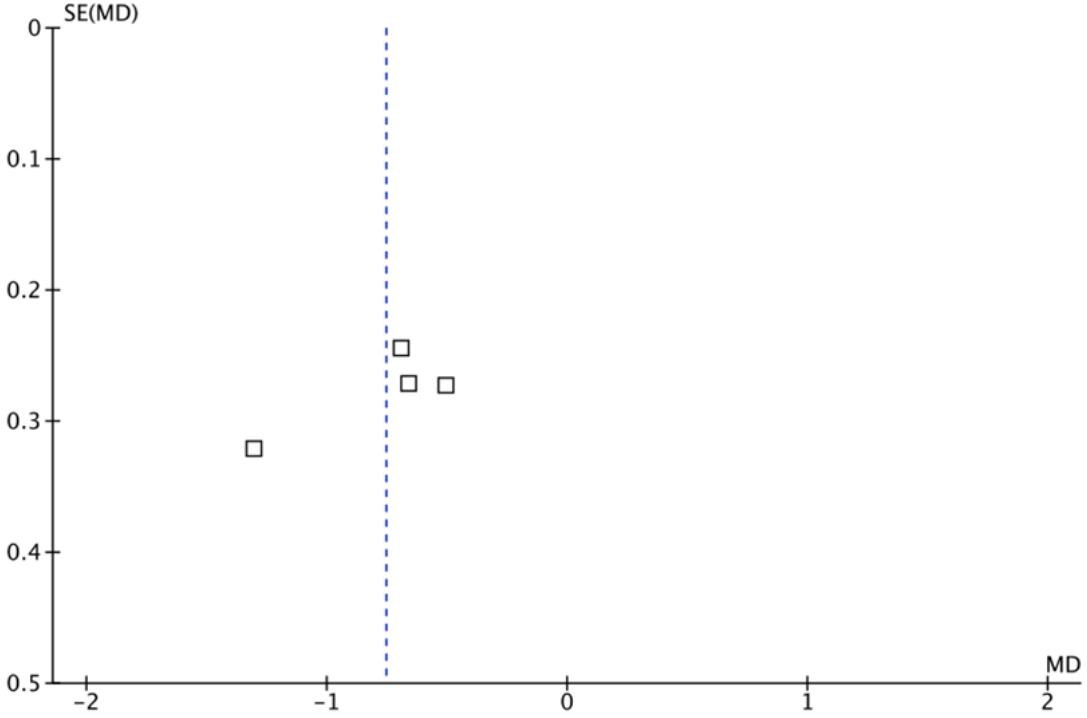

Figure 6

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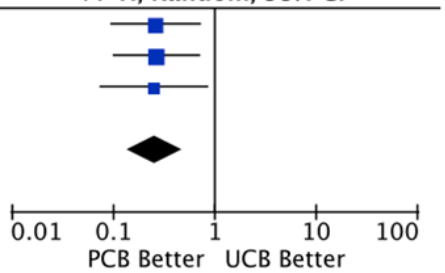
A.

Study or Subgroup	PCB Events	PCB Total	UCB Events	UCB Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
FemPac	10	31	22	34	36.1%	0.26 [0.09, 0.73]	2008
THUNDER	7	41	21	48	38.8%	0.26 [0.10, 0.71]	2008
PACIFIER	4	40	12	39	25.1%	0.25 [0.07, 0.86]	2011
Total (95% CI)		**112**		**121**	**100.0%**	**0.26 [0.14, 0.48]**	
Total events	21		55				

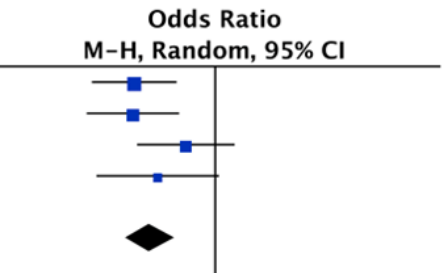
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 2 (P = 1.00); $I^2 = 0\%$
Test for overall effect: Z = 4.27 (P < 0.0001)



B.

Study or Subgroup	PCB Events	PCB Total	UCB Events	UCB Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
THUNDER	7	48	28	54	32.1%	0.16 [0.06, 0.42]	2008
FemPac	6	45	21	42	27.3%	0.15 [0.05, 0.44]	2008
LEVANT I	6	47	10	45	24.7%	0.51 [0.17, 1.55]	2010
PACIFIER	3	40	9	39	16.0%	0.27 [0.07, 1.09]	2011
Total (95% CI)		**180**		**180**	**100.0%**	**0.23 [0.13, 0.40]**	
Total events	22		68				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.19$, df = 3 (P = 0.36); $I^2 = 6\%$
Test for overall effect: Z = 5.09 (P < 0.00001)



C.

Study or Subgroup	PCB Events	PCB Total	UCB Events	UCB Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
FemPac	6	45	3	42	46.6%	2.00 [0.47, 8.57]	2008
THUNDER	2	48	1	54	19.4%	2.30 [0.20, 26.25]	2008
LEVANT I	1	48	3	49	21.5%	0.33 [0.03, 3.25]	2010
PACIFIER	0	41	2	41	12.6%	0.19 [0.01, 4.09]	2011
Total (95% CI)		**182**		**186**	**100.0%**	**1.04 [0.34, 3.18]**	
Total events	9		9				

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 3.37$, df = 3 (P = 0.34); $I^2 = 11\%$
Test for overall effect: Z = 0.06 (P = 0.95)

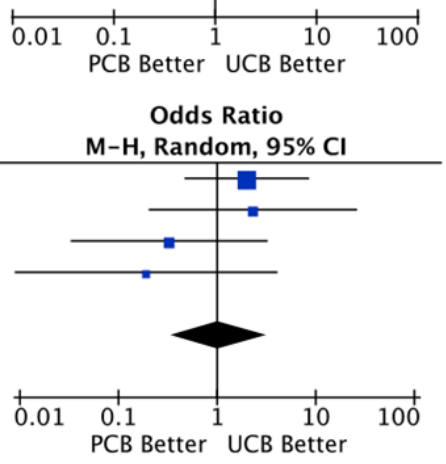


Figure 7

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Figures legend

Figure 4: PRISMA statement for trial selection process. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Figure 5: local delivery of paclitaxel into the arterial wall to inhibit restenosis during angioplasty of the leg.

Figure 6: Mean difference (MD) of late lumen loss (**Panel A.**) at follow-up associated with paclitaxel-coated balloon (PCB) versus uncoated balloon (UCB). The squares and the horizontal lines indicate the MD and the 95% CIs for each trial included; the size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis, with the centre indicating the point estimate and the left and the right ends the 95% CI. **Panel B.** Funnel plot of all studies included in the meta-analysis. The standard error (SE) of the ln mean difference (MD) was plotted against the MD of late lumen loss.

Figure 7: Odds ratio (OR) of angiographic restenosis (**Panel A.**), target lesion revascularization (**Panel B.**) and mortality (**Panel C.**) with paclitaxel-coated balloon (PCB) versus uncoated balloon (UCB)**.**

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5.3 Small study effects, sensitivity and influence analyses

Figure 6 (**Panel B**) shows the funnel plot distribution for primary end-point: the standard error (SE) of the ln mean difference (MD) was plotted against the MD of 6-month LLL. Since visual estimation can be misleading, we performed both Egger's (p= 0.29) and Begg´s (p= 0.60) tests validating the absence of bias due to small study effects. Moreover, no significant influence of prespecified covariates on the treatment effect was observed, including the publication status (p=0.31), sample size (p=0.21) and blinding (p=0.31). Influence analysis demonstrated that no single study significantly altered the summary ORs for primary endpoint, since one at a time study omission did not result in a movement of the point estimate outside the 95% CI.

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6. Discussion

This is a meta-analysis of randomized trials assessing outcomes of PCB versus UCB angioplasty in patients undergoing revascularization for FPA disease.

The main findings are: 1) PCB significantly reduces LLL and restenosis at 6-month angiographic follow-up when compared with UCB angioplasty; 2) revascularization with PCB is associated with lower TLR risk; 3) the use of PCB versus UCB has no impact on mortality hazard.

6.1 Experimental and clinical background

Scheller et al. initially started the concept of using a balloon catheter to deliver paclitaxel for arterial disease in animal models.[17] Subsequent clinical trials validated PCB as a treatment option for coronary bare-metal stent restenosis, supporting the effectiveness up to 24-month follow-up.[30]

The role of PCB was investigated in the peripheral field with the aim to replicate the results achieved in coronary disease: animal data,[21] as well as early clinical trials,[18, 22] confirmed that local paclitaxel release efficaciously suppresses neointimal growth after femoro-popliteal angioplasty.

6.2 Angiographic and clinical efficacy of PCB

Late lumen loss and the rate of angiographic restenosis are common end points in clinical trials investigating new approaches to the reduction of restenosis.

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Measurements of neointima inhibition are validated endpoints that can accurately predict TLR occurrence in coronary artery disease.[31]

However, these angiographic end points may not necessarily reflect clinical benefit[32].

In the first randomised trials (Thunder[18], Fem-Pac[22]) the use of PCB was not only associated with a reduction in the LLL but also with reduced target-lesion revascularization (TLR) at the 6-and 24-month follow-up. Nevertheless, the limited population enrolled in any trial and the lack of clinical benefit in the two recent trials,[23, 24] call into question the clinical impact of PCB in this arterial district .

In the present meta-analysis we could confirm the evidence of a lower LLL associated with the use of PCB at 6 months follow-up.

This angiographic finding is accompanied by the parallel absolute risk reduction of both angiographic restenosis (26.7% [15.2%, 38.1%]) and TLR (25.5% [17.0%, 34.1%]). Therefore, although angiographic findings may be regarded as consistent with what already know, the evidence of a significant TLR risk reduction associated with PCB use, confirm the clinical impact of treatment with PCB.

In terms of safety concerns of Paclitaxel, this meta-analysis demonstrates that mortality is not increased with the use of PCB versus UCB angioplasty in femoro-popliteal disease.

6.3 “Class-effect” of PCB?

The selected randomised studies adopted different balloon catheters with a different drug dose on balloons surface: 2 μg/mm in the LEVANT trial

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and 3 μg/mm in the Thunder, FemPac and PACIFIER trials.

Although the dose of Paclitaxel is far to influence the overall efficacy,[33] some importance of excipients for drug delivery should be discussed. The animal studies demonstrated the higher the bioavailability of paclitaxel at the target site, the more the drug is absorbed from the vessels wall[33] so that the excipient can play a pivotal role with respect to drug transfer in the arterial wall.

In the current study, we did not investigate the impact on outcomes of different excipients: nevertheless, although the "class-effect" of PCB cannot be excluded, it is of interest that the platform using a highly hydrophilic excipient (urea) resulted in more LLL reduction.

Thus, it would be timely to compare different PCB platforms in simple (short, de novo) as well as challenging lesion subsets (long occlusion, in-stent restenosis[34]).

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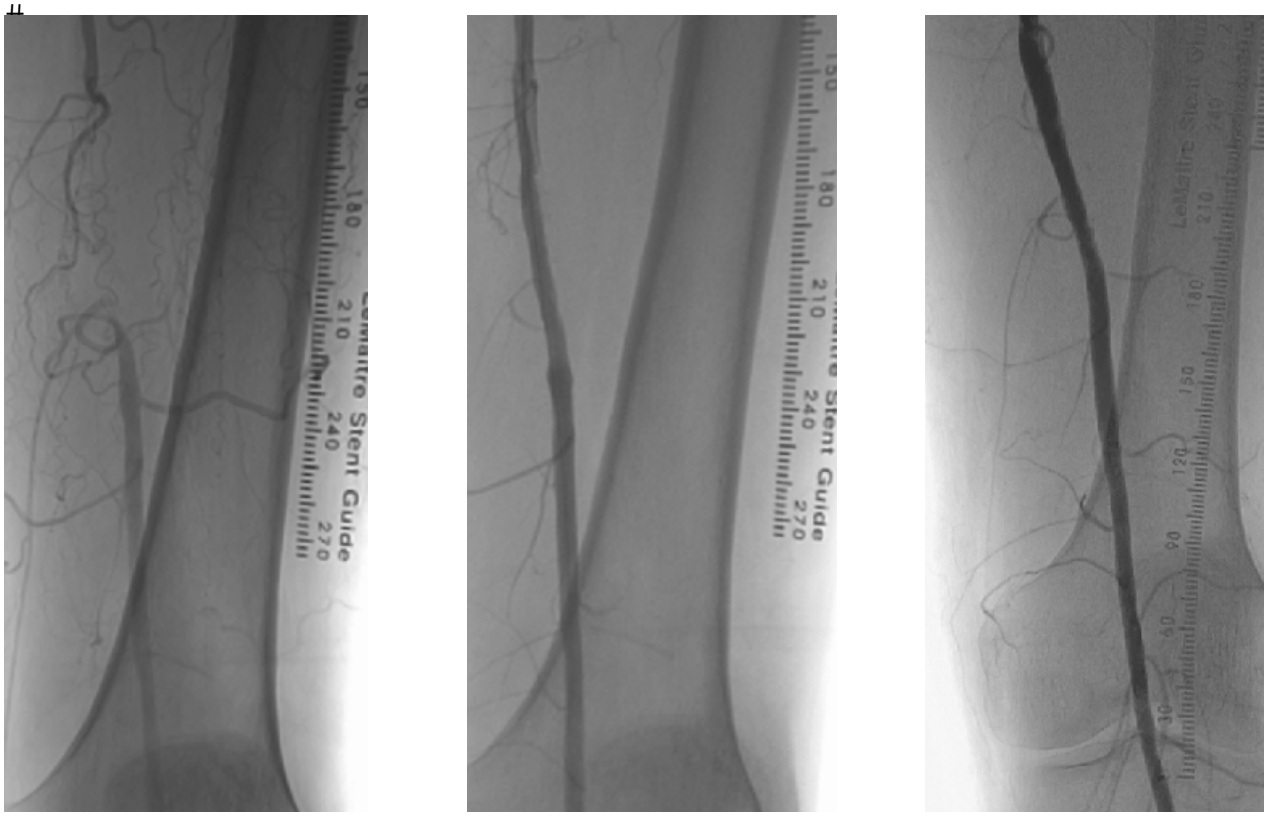

Figure 8.

Recanalization of de novo superficial femoral artery occlusion (**left**) with paclitaxel-coated balloon. Acute (**middle**) and six-month (**right**) angiographic outcomes.

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6.4 Stenting in PCB trials

In all studies included in case of suboptimal result or complication after balloon dilation (i.e. flow limiting dissection), provisional stenting was permitted. Across trials this percentage ranged from 4 to 21% and from 14 to 34% in PCB versus UCB respectively. It is a common sense that stents provide additional safety benefit over angioplasty in sealing intimal lesions and residual dissections after balloons dilation. As a confirmation, similar to the case in coronary disease randomised trials comparing angioplasty versus stent implantation always produced a significant proportion of crossover among treatment arms.[14, 35] Unfortunately, for the present study, it was not possible to ascertain whether investigators stented the entire segments dilated or only the tracts with suboptimal results. Moreover, whether PCB versus UCB angioplasty might lead to a lower (stenting) rate or whether PCB is superior to UCB angioplasty plus stenting was not the purposes of our analysis.
As a matter of fact, UCB angioplasty still remains the control comparator in current randomized studies investigating different revascularization strategies for FPA disease.[14, 35] On the one hand, the clinical relevance of such performed studies is questioned, considering the weak comparator (PTA) on the other hand, this aspect reflects the scarce penetration of PCB into daily practice due to the lack of solid evidence.
Thus, is important to design large, randomized studies comparing more recent devices and techniques and to investigate whether some strategies should be

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combined (i.e. PCB and stenting) in order to improve outcomes in peripheral revascularization of de novo as well as restenotic lesions.

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6.5 Study limitations

The present report is a meta-analysis at study level, and as such we could not properly assess the role of confounding factors. This meta-analysis has no extended follow-up. Even though we did not investigate long-term benefits of PCB versus UCB, available data on limited numbers of patients suggest that PCB clinical superiority still exists at 24 months.[18, 22] Some trials were underpowered to detect significant differences in main outcomes: this aspect reinforced the necessity of the present study.

Finally, recent technological[35, 36] and pharmacological innovations[37] might have improved revascularization efficacy in peripheral district: at this regard, the efficacy of PCB as compared with new devices needs specifically designed studies.

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Conclusions

This study supports the angiographic and clinical superiority of PCB versus UCB angioplasty in femoro-popliteal disease with no difference in safety outcomes. Longer follow-up studies are needed to fully indicate the role of PCB in clinical practice.

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Abstract

Backgrounds: In femoro-popliteal (FPA) disease, paclitaxel-coated balloon (PCB) improved angiographic outcomes as compared with uncoated balloon (UCB) angioplasty. Nevertheless, clinical efficacy of PCB remained uncertain.

Methods: We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific session abstracts and relevant websites for trials of PCB versus UCB angioplasty. Keywords were: “superficial femoral artery”, “popliteal artery”, “angioplasty”, “drug-eluting balloon”, “paclitaxel-eluting balloon” and “randomized trial”. Inclusion criteria were: (1) randomized design; (2) intention to treat analysis; (3) ≥6-month follow-up. Exclusion criteria were: (1) other vessel treated than FPA, (2) other device used than PCB or UCB, (3) irretrievable or duplicated data. No restrictions (language, publication date or status) were applied. Primary endpoint was 6-month angiographic late lumen loss (LLL). Secondary endpoints were: angiographic restenosis, target lesion revascularization (TLR) and mortality, as per protocol defined.

Results: A total of 381 patients (4 trials) were included (PCB= 186 versus UCB= 195). Median follow-up was 10.3 months. Angioplasty with PCB was superior to UCB in terms of LLL (range -0.05, 0.50 versus 0.61, 1.7 mm; weighted mean difference - WMD [95% confidence interval]= -0.75 [-1.06, -0.45], p<0.00001), angiographic restenosis (18.7% versus 45.5%; odds ratio - OR= 0.26 [0.14–0.48], p= <0.0001) and TLR (12.2% versus 27.7%; OR [95% CI]= 0.23 [0.13–0.40], p=

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<0.00001). No mortality difference is found for PCB versus CB (2.1% versus 3.2%; OR= 0.77 [0.20–2.93], p= 0.70).

Conclusions: In femoro-popliteal disease, PCB leads to superior angiographic and clinical efficacy as compared with UCB. There was no difference regarding safety concern.

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Weiterbildung
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Berufliche Tätigkeiten

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2005-2006 Assistenzarzt beim Herrn Prof. Dr. L.Inglese; Spedale Policlinico San Donato Milanese

2006-2007 Oberarzt, zuständig für Herzkatheterlabor
“Casa di Cura Abano Terme”; Padova

Seit 2008: Oberarzt, interventionelle Kardiologe und Angiologie beim Herrn Prof. Dr. A.Schömig; Deutsches Herzzentrum ;Technische Universität München

Klinische Tätigkeiten im Bereich der interventionellen Kardiologie und Angiologie

- Anwendung aller diagnostischen und therapeutischen Techniken der interventionellen Kardiologie einschließlich mehr als 2500 koronare Angioplastien Stentimplantationen, Rotablationen, intravaskulärer Ultraschall (IVUS), invasive Flußdrahtmessung, Kohernztomographie (OCT).Vitiendiagnostik und Rechtsherzkatether. Perikardpunktion und Myokardbiopsien.

- Interventionelle Behandlung des akuten Myokardinfarkts mittels PTCA und Stentimplantation einschließlich unterstützender Maßnahmen (intraaortale Ballonpumpe IABP; passagerer Schrittmacher).

- Anwendung aller diagnostischen und therapeutischen Techniken der interventionellen Angiologie mit mehr als 1500 Interventionen.

- Angioplastien und Stentimplantation im Bereich der supra-aortalen Gefäßen (A.carotis, A. subclavia, A. vertebralis) mit Anwendung von Protektionessystemen.

- Interventionelle Behandlung im Bereich der Becken-Beingefäße: komplexe periphere Interventionen mit Atherektomie, Thrombusaspiration, Drug-eluting Ballon, Drug-eluting Stent und gecovertem Stent. Behandlungen der Unterschenkelgefäße bei kritischer Beinischämie.

- Behandlung der therapierefraktären Hypertonie mittels Hochfrequenzablation der A. renalis (katheterbasierte renale Sympathicusdenervation).

- Interventionelle Schrittmachersondenextraktion, ZVK und Portextraktionen.

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Forschung im Bereich der interventionellen Kardiologie und Angiologie

1.Konzeption und Durchführung randomisierter klinischen Studien:

-ISAR-STATH: randomisierter Vergleich von Atherektomie versus Drug-eluting Ballon und Stent versus Stent alleine im Bereich der A. fem. sup.

-ISAR-PEBIS: randomisierter Vergleich von Drug-eluting Ballon und konventionellem Ballon bei in-Stent Re-stenose der A. fem. sup.

-ISAR-GRADE: Vergleich verschiedener Energien bei der Hochfrequenzablation der A. ren.

2. Analyse von Plaquematerial verschiedener Gefäßlokalisationen (Immunhistologie, Genexpression)

3. Vergleich de novo Arteriosklerose mit Restenosen der A. fem. sup. (Genexpression, Immunhistologie)

4. Assoziation immunhistologische Parameter mit der Restenose der A. fem. sup.

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