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META-ANALYSIS
Interventional cardiology

Endovascular revascularization strategies for aortoiliac and femoropopliteal artery disease: a meta-analysis

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Abstract

Aims Optimal endovascular management of intermittent claudication (IC) remains disputed. This systematic review and meta-analysis compares efficacy and safety outcomes for balloon angioplasty (BA), bare-metal stents (BMS), drug-coated balloons (DCB), drug-eluting stents (DES), covered stents, and atherectomy.

Methods and results Electronic databases were searched for randomized, controlled trials (RCT) from inception through November 2021. Efficacy outcomes were primary patency, target-lesion revascularization (TLR), and quality-of-life (QoL). Safety endpoints were all-cause mortality and major amputation. Outcomes were evaluated at short-term (<1 year), mid-term (1–2 years), and long-term (≥2 years) follow-up. The study was registered on PROSPERO (CRD42021292639). Fifty-one RCTs enrolling 8430 patients/lesions were included. In femoropopliteal disease of low-to-intermediate complexity, DCBs were associated with higher likelihood of primary patency [short-term: odds ratio (OR) 3.21, 95% confidence interval (CI) 2.44–4.24; long-term: OR 2.47, 95% CI 1.93–3.16], lower TLR (short-term: OR 0.33, 95% CI 0.22–0.49; long-term: OR 0.42, 95% CI 0.29–0.60) and similar all-cause mortality risk, compared with BA. Primary stenting using BMS was associated with improved short-to-mid-term patency and TLR, but similar long-term efficacy compared with provisional stenting. Mid-term patency (OR 1.64, 95% CI 0.89–3.03) and TLR (OR 0.50, 95% CI 0.22–1.11) estimates were comparable for DES vs. BMS. Atherectomy, used independently or adjunctively, was not associated with efficacy benefits compared with drug-coated and uncoated angioplasty, or stenting approaches. Paucity and heterogeneity of data precluded pooled analysis for aortoiliac disease and QoL endpoints.

Conclusion Certain devices may provide benefits in femoropopliteal disease, but comparative data in aortoiliac arteries is lacking. Gaps in evidence quantity and quality impede identification of the optimal endovascular approach to IC.

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Structured Graphical Abstract

Key Question

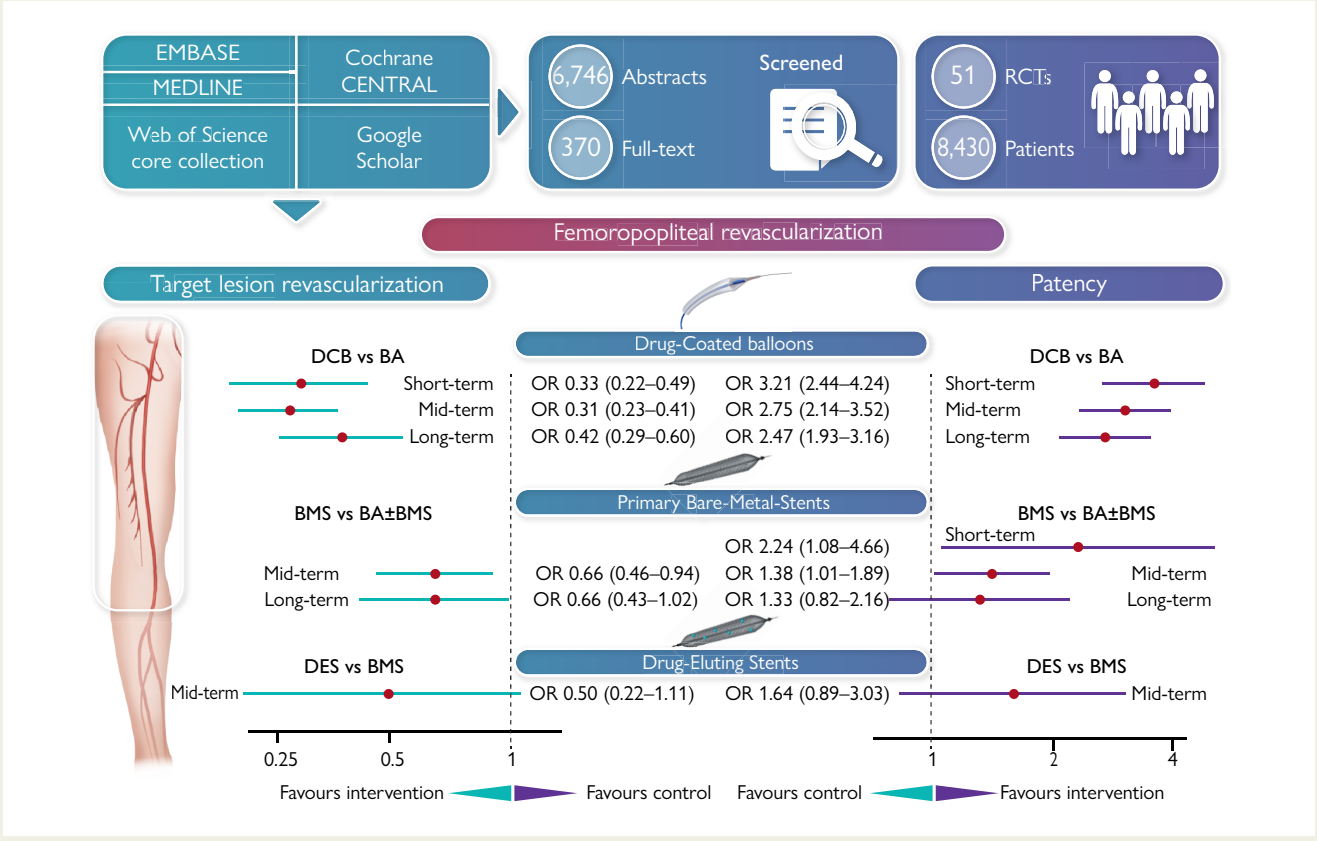
Is there a difference in efficacy and safety outcomes between endovascular revascularization strategies for treatment of femoropopliteal artery disease in patients with intermittent claudication?

Key Finding

In femoropopliteal disease, drug-coated balloons were associated with improved efficacy compared to balloon angioplasty. Primary bare metal stenting (BMS) was associated with temporary efficacy benefits over provisional BMS. There was no difference in efficacy between drug-eluting stents and BMS.

Take Home Message

Specific endovascular techniques may provide benefits in femoropopliteal disease. Yet, substantial evidence gaps and deficiencies in underlying study quality limit the identification of the optimal endovascular approach.



Major findings from a random-effects meta-analysis investigating the efficacy and safety of endovascular revascularization strategies in the treatment of intermittent claudication at short- (<1 year), mid- (1–2 years), and long-term (≥2 years) follow-up. The forest plots display pooled odds ratios with associated 95% confidence intervals for the outcomes target-lesion revascularization (left) and primary patency (right) comparing drug-coated vs. uncoated balloon angioplasty, primary vs. provisional bare-metal stenting and drug-eluting vs. bare-metal stenting in femoropopliteal artery disease. BA, balloon angioplasty; BMS, bare-metal stents; CI, confidence interval; DCB, drug-coated balloons; DES, drug-eluting stents; OR, odds ratio; RCT, randomized controlled trial.

Keywords Intermittent claudication • Endovascular revascularization • Drug-coated balloon • Drug-eluting stent • Atherectomy • angioplasty

Introduction

Intermittent claudication (IC) constitutes the most common symptomatic manifestation of lower extremity arterial disease (LEAD), frequently resulting in functional disability refractory to conservative measures.[1]

Endovascular revascularization aims to provide sustained symptomatic relief at minimum risk, yet early-generation device-based techniques are limited by suboptimal long-term outcomes. Novel technologies such as drug-eluting devices, covered stents, and debulking approaches were rapidly adopted to increase the durability of therapeutic success. Nowadays, almost half of endovascular procedures for femoropopliteal lesions include

drug-coated balloons (DCB) or stents.[2] However, the optimal and anatomically assignable approach for endovascular management of patients with IC remains disputed. This absence of consensus reflects the myriad of technologies available, the paucity of high-quality comparative trials, and the heterogeneity in disease pattern and severity among study participants. Previous meta-analyses have pooled data spanning the entire spectrum of LEAD severity, not differentiating between IC and chronic limb-threatening ischaemia (CLTI), while focusing exclusively on specific device groups, anatomical segments, or follow-up time points, thereby limiting their ability to underpin clinical decision-making in patients with IC.[3–5]

We, therefore, conducted a systematic review and meta-analysis comparing short-, mid-, and long-term efficacy and safety outcomes of endovascular revascularization strategies in patients with IC stratified by aortoiliac and femoropopliteal atherosclerotic disease.

Methods

The conduct of this systematic review and meta-analysis is based on recently published guidelines[6] and the Cochrane Handbook for Systematic Reviews of Interventions.[7] Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[8] The study was registered on the International prospective register of systematic reviews PROSPERO (CRD42021292639). The present analysis was commissioned by the European Society for Vascular Surgery for the purpose of international guideline development.

Search strategy and study selection

From inception through November 2021, the electronic databases EMBASE, MEDLINE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar were systematically searched for pertinent studies published in English. References of included articles were manually searched to identify additional eligible studies. The search strategy consisted of three main themes, defined by key terms and corresponding Medical Subject Headings: (i) LEAD and alternative disease acronyms, (ii) endovascular revascularization techniques, and (iii) efficacy and safety endpoints. The complete search strategy is available in the Supplementary material online, Appendix S1. Following deletion of duplicate records,[9] abstract screening was performed independently by teams of paired, blinded reviewers using the software tool Rayyan Systems (Cambridge, MA, USA). Studies were considered eligible for inclusion if (i) they were randomized trials with active controls; (ii) they compared efficacy or safety endpoints between two or more of the following device-based interventions: balloon angioplasty (BA), DCB, drug-eluting stents (DES), bare-metal stents (BMS), covered stents or atherectomy; (iii) they reported exact proportions of participants with aortoiliac and femoropopliteal disease; (iv) they primarily investigated *de novo* atherosclerotic lesions; and (v) the proportion of study participants with IC exceeded 70%, or estimates for IC patients were provided separately. Trials examining isolated infrapopliteal artery disease were excluded, since IC presently does not constitute an appropriate clinical indication for endovascular revascularization of crural lesions, which should generally be reserved for treatment of tissue loss in CLTI.[10,11]

Data collection and quality assessment

Full-text review, data extraction, and risk of bias assessment were undertaken by two independent investigators. Inter-reviewer discrepancies were resolved by consensus or adjudicated by a third reviewer if disagreement persisted. For studies comprising <70% of patients with IC, authors were contacted for IC subgroup data. Results from studies defining bailout stenting as patency loss were only extracted if alternative analyses were presented. For the Zilver-PTX trial,[12–14] we only extracted data obtained from the second randomization (provisional DES vs. provisional BMS), as data from the first randomization (DES vs. percutaneous transluminal angioplasty ± DES/BMS) were reported on a per-protocol basis. Risk of bias assessment was performed at the study level using the revised Cochrane Risk-of-Bias 2 tool.[15]

Outcomes and endpoint definitions

Primary outcomes of interest were primary patency and target-lesion revascularization (TLR). Primary patency was defined as freedom from restenosis as assessed by duplex ultrasound, digital subtraction, or computed tomography angiography, in the absence of prior TLR. Target-lesion revascularization was defined as requirement for repeat endovascular or surgical intervention at the original lesion site or within the same vessel segment. The secondary efficacy outcome was quality-of-life (QoL), as assessed by standardized and validated, questionnaire-based methods (e.g. Walking Impairment Questionnaire, EuroQoL-5D). Safety endpoints were all-cause mortality and major amputation. Outcomes were evaluated at short-term (<1 year), mid-term (≥1 year, < 2 years), and long-term (≥2 years) follow-up.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were chosen as principal summary statistics and derived from crude event numbers. Rate calculation was precluded by infrequent reporting of trial duration per treatment arm and attrition to follow-up. If three or more estimates were available, ORs were pooled using the DerSimonian and Laird random-effects model. For studies with zero events in one treatment arm, the 0.5 continuity correction was applied.[7] Statistical heterogeneity was determined using Higgins I^2 statistics, with I^2 statistics of <25%, 25%–50%, and >50% as thresholds for low, moderate, and high heterogeneity, respectively. Considering the limited power of Q-statistics, we used *P*-values <0.10 as thresholds to define the presence of significant heterogeneity. Publication bias was evaluated visually using funnel plots and statistically using the Egger test, if 10 or more studies were available.

For the primary analysis, calculated odds were based on treatment arm sample sizes available at each follow-up duration, considering loss to follow-up (available case analysis).[16,17] Sample sizes for data presented solely as proportions from Kaplan–Meier analysis were estimated using standard errors or 95% CIs (see Supplementary material online, Appendix S2). To evaluate the impact of missing participant data on pooled effect estimates, we conducted both stratified analyses by percentage loss to follow-up and imputation-based sensitivity analyses across a range of assumptions, including (i) 'none had the event' scenario, (ii) worst-case scenario, and (iii) best-case scenario.[16,17] Further sensitivity analyses were performed for primary patency by excluding studies allowing enrolment and analysis of multiple lesions/limbs per patient and studies not employing independent core laboratories for imaging assessment, if eight or more studies were included in meta-analysis. Pre-specified random-effects meta-regression and subgroup analyses were conducted to explore potential sources of heterogeneity (lesion length, proportion of IC, and risk of bias), if eight or more studies were incorporated in meta-analysis. Analyses were performed using STATA 16.1 (Statacorp, College Station, TX, USA, 2017). *P*-values <0.05 (two-tailed) were considered significant.

Results

The study selection process is depicted in *Figure 1*. Following screening of 6746 abstracts, 51 RCTs enrolling 8430 patients/lesions were included. Thirty-four studies were incorporated into meta-analysis with the remainder synthesized narratively. Study characteristics are summarized in *Table 1*, while endpoints and inclusion criteria are displayed in Supplementary material online, *Table S1*. The majority of trials focused on femoropopliteal disease (47 RCTs, $n = 7602$), received industry sponsoring (65%), and adopted open-label designs (53%). Median follow-up duration was 24 months (IQR 12–36 months), and the median proportion of IC was 92% (IQR 82.0%–96.4%). Cardiovascular risk factors were common; 37.5% (IQR 31.3%–47.3%) had diabetes mellitus, 10.1% (IQR 7.9%–16.6%) had chronic kidney disease, and 53.6% (IQR 40.6%–76.3%) were

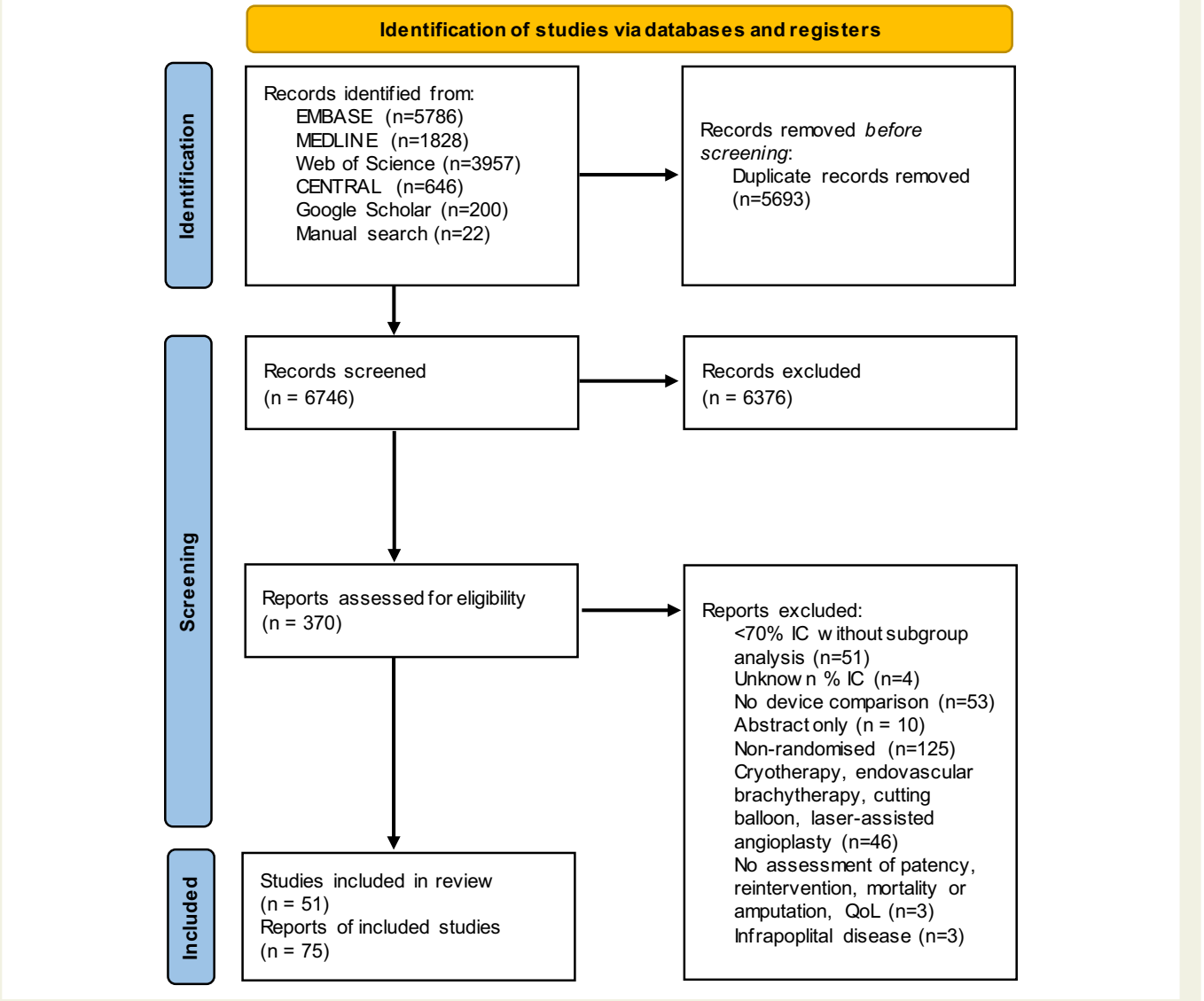


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart describing study selection.[8]

past or active smokers. Treated lesions were of intermediate length (median 72.2 mm, IQR 59.3–98.9 mm) with occlusive disease present in 30.7% (IQR 20.5%–47.0%). Most trials (82%) displayed moderate-to-high risk of bias (see Supplementary material online, *Table S2*).

Low event numbers for major amputation at short- (9 events in 2785 patients), mid- (21 events in 4745 patients), and long-term (26 events in 2637 patients) precluded pooled analysis for this rare endpoint. Similarly, quantitative analysis for QoL outcomes was not feasible due to generalized underreporting and major inter-study variability regarding questionnaire types, versions, and reported parameters. Quality-of-life measures were provided by 8 studies (15.6%) at short-term, 17 (33.3%) at mid-term, and 12 (23.5%) at long-term follow-up, with no trial demonstrating statistically significant differences in QoL measures for any device comparison, regardless of questionnaire type, anatomic segment, or follow-up time point considered.

Aortoiliac disease

Four RCTs comprising 1182 patients were available for analysis in aortoiliac disease (see Supplementary material online, *Table S3*).[18–25] Two trials compared primary BMS implantation to BA with provisional BMS in 396 patients with short iliac lesions. In the STAG trial for treatment of iliac occlusions (length 54.1 ± 15.8 mm), patency rates did not differ through a 2-year follow-up. The study was halted early due to increased major complications for provisional vs. primary stenting (20% vs. 5%, $P = 0.01$), driven by distal embolization.[22] The Dutch Iliac Stent Trial provided data on patency, reintervention, mortality, and amputation rates up to 72 months post-intervention with no differences in outcomes at all follow-up times.[18,20,21]

Primary stenting strategies were compared by two RCTs. The ICE trial allocated 660 patients to primary self-expanding BMS or balloon-expandable BMS implantation for common or external iliac artery lesions (length 37.5 ± 30.0 mm). Mid-term patency (OR 2.69, 95% CI 1.31–5.52) and TLR risk (OR 0.41, 95% CI 0.17–0.97) favoured

Table 1 Summary of study and participant characteristics

Study characteristics	
Study centre, *n* (%)	
Single centre	6 (12)
Multicentre	45 (88)
Study regions, *n* (%)[a]	
Asia	6 (12)
Europe	37 (73)
America	10 (19)
Australia	2 (4)
Blinding status, *n* (%)	
Open-label	27 (53)
Single-blind	16 (31)
Unknown	8 (16)
Study size, *n* (%)	
≤100	14 (27)
100–200	22 (42)
≥200	15 (28)
Maximum follow-up duration, *n* (%)	
Short-term (<1y)	0 (0)
Mid-term (1–2y)	20 (39)
Long-term (≥2y)	31 (61)
Study sponsor, *n* (%)	
Industry sponsored	33 (65)
Non-industry sponsored	9 (18)
Unknown	9 (18)
Loss to follow-up, median % (IQR)	19.5 (10.3–28.7)
Intervention:control ratio	1:0.82
Participant characteristics	
Target-lesion anatomy, *n* (%)	
Aortoiliac	4 (8)
Femoropopliteal	47 (92)
Proportion of IC, median % (IQR)	92 (82.0–96.4)
Age in years, median (IQR)	68 (66–70)
Male sex, median % (IQR)	68 (63.5–72)
Diabetes mellitus, median % (IQR)	37.5 (31.3–47.3)
Smoking history, median % (IQR)	53.6 (40.6–76.3)
Chronic kidney disease, median %(IQR)	10.1 (7.9–16.6)
Coronary artery disease, median % (IQR)	40.8 (31.8–49.5)
Lesion length in mm, median (IQR)	72.2 (59.3–98.9)
Total occlusions, median % (IQR)	30.7 (20.5–47.0)
Intervention characteristics	
Drug-coated balloon, *n* (%)[a]	23 (45)
Bare-metal stent, *n* (%)[a]	18 (35)
Drug-eluting stent, *n* (%)[a]	5 (10)
Atherectomy, *n* (%)[a]	7 (14)
Covered stent, *n* (%)[a]	4 (8)
Provisional stenting, median % (IQR)	14.1 (5.3–21.0)
Control characteristics	
Balloon angioplasty, *n* (%)[a]	42 (82)
Bare-metal stent, *n* (%)[a]	10 (20)
Drug-coated balloon, *n* (%)[a]	4 (8)
Provisional stenting, median % (IQR)	21.0 (11.5–32.0)
Outcome assessment	
Primary patency, *n* (%)[a]	
Short-term	23 (45)
Mid-term	35 (69)
Long-term	25 (49)
Target-lesion revascularization, *n* (%)[a]	
Short-term	19 (37)
Mid-term	35 (69)
Long-term	22 (43)
Major amputations, *n* (%)[a]	
Short-term	16 (31)
Mid-term	26 (51)
Long-term	18 (35)
All-cause mortality, *n* (%)[a]	
Short-term	17 (33)
Mid-term	32(63)
Long-term	23 (45)
Quality of Life, *n* (%)[a]	
Short-term	8 (16)
Mid-term	17 (33)
Long-term	12 (23)

IQR, interquartile range.
[a]Summary is not additive (will not add up to total number).

self-expanding stents with safety endpoints remaining equivocal.[23] In the COBEST trial, covered stenting resulted in advantageous mid-term patency compared with BMS (OR 3.15, 95% CI 1.29–7.66). Patency benefits for covered stenting were sustained on 5-year post-hoc analysis, while no differences in mortality and amputation were observed.[25] The COBEST trial demonstrated high risk of bias.

Femoropopliteal disease

Forty-seven RCTs comprising 7602 patients/lesions were available in femoropopliteal disease (see Supplementary material online, *Table S4*). Quantitative analysis was performed for DCB ± BMS vs. BA ± BMS; BMS vs. BA ± BMS; and DES vs. BMS. Pooled estimates, statistical heterogeneity and publication bias for each device comparison, outcome, and follow-up duration are summarized in *Table 2*. Funnel plots for visual assessment of publication bias are presented in Supplementary material online, *Figures S1-S3*.

Drug-coated vs. plain balloon angioplasty

Twenty-one RCTs evaluated DCB angioplasty for femoropopliteal lesions.[26–59] While 18 trials compared DCB to BA with provisional BMS placement, three RCTs explored DCB vs. BA during primary stenting approaches.[29,30,50,55] Lesions were of intermediate length (74.0 mm, IQR 65.4–89.0 mm) with low proportions of occlusive disease (28.9%, IQR 21.2%–44.5%). Most studies (71%) demonstrated moderate-to-high risk of bias. Short-, mid-, and long-term patency data for DCB vs. BA were available from 14 ($n = 2221$, 1419 events), 14 ($n = 2939$, 1765 events), and 10 ($n = 1594$, 731 events) RCTs, respectively. Likelihood estimates for patency favoured DCB over BA at short-term (OR 3.21, 95% CI 2.44–4.24; I^2 29%, *P* for heterogeneity [p_{het}] = 0.15), mid-term (OR 2.75, 95% CI 2.14–3.52; I^2 40.6%, $p_{het} = 0.06$), and long-term (OR 2.47, 95% CI 1.93–3.16; I^2 2.6%, $p_{het} = 0.42$) follow-up (*Figure 2*). Short-, mid-, and long-term TLR data were provided by 13 ($n = 2155$, 22 events), 19 ($n = 3682$, 488 events), and 10 ($n = 1578$, 355 events) RCTs, respectively. Drug-coated balloons angioplasty was associated with lower TLR risk at short-term (OR 0.33, 95% CI 0.22–0.49; I^2 26.7%, $p_{het} = 0.18$), mid-term (OR 0.31, 95% CI 0.23–0.41; I^2 39.5%, $p_{het} = 0.04$), and long-term (OR 0.42, 95% CI 0.29–0.60; I^2 41.7%, $p_{het} = 0.08$) follow-*P* (*Figure 3*). All-cause mortality was reported by 13 ($n = 1979$, 32 events), 18 ($n = 3580$, 91 events), and 12 ($n = 1894$, 155 events) RCTs at short-, mid-, and long-term, respectively. Risk estimates for all-cause mortality were similar between DCB and BA at short-term (OR 1.03, 95% CI 0.50–2.13; I^2 0%, $p_{het} = 0.90$), mid-term (OR 0.90, 95% CI 0.57–1.42; I^2 0%, $p_{het} = 0.91$), and long-term (OR 0.96, 95% CI 0.67–1.39; I^2 0%, $p_{het} = 0.62$) follow-up (*Figure 4*).

Primary vs. provisional bare-metal stenting

Ten RCTs ($n = 1631$) compared primary BMS to BA with provisional BMS in femoropopliteal disease.[60–72] Insufficient data precluded meta-analysis of short-term TLR and mortality. Overall lesion complexity was low (length 42.3 mm, IQR 27.5–70.7 mm; 31.1% occlusions, IQR 21.9%–35.6%), while risk of bias was moderate-to-high for most trials (80%). Short-, mid-, and long-term patency data were available from four ($n = 499$, 351 events), nine ($n = 1507$, 733 events), and five ($n = 710$, 330 events) RCTs, respectively. Primary BMS was associated with favourable patency at short-term (OR 2.24, 95% CI 1.08–4.66; I^2 46.2%, $p_{het} = 0.13$) and mid-term (OR 1.38, 95% CI 1.01–1.89; I^2 35.6%, $p_{het} = 0.13$), while no differences were observed at long-term (OR 1.33, 95% CI 0.82–2.16; I^2 43.3%, $p_{het} = 0.13$) follow-up (*Figure 5*). Data on mid- and long-term TLR were reported by five ($n = 950$, 156 events) and three ($n = 556$, 128 events) trials, respectively. Lower TLR risk was observed with primary BMS at mid-term (OR 0.66, 95% CI 0.46–0.94; I^2 0%, $p_{het} = 0.85$), but this benefit was not sustained at long-term (OR 0.66, 95% CI 0.43–1.02; I^2 0%, $p_{het} = 0.71$) follow-up (*Figure 6*). Data on mid- and long-term all-cause mortality were pooled from five and three RCTs including 950 (26 events) and 679 patients (58 events), respectively. No difference in mortality risk was observed at mid-term (OR 2.15, 95% CI 0.91–5.09; I^2 0%, $p_{het} = 0.95$) and long-term (OR 0.95, 95% CI 0.55–1.66; I^2 0%, $p_{het} = 0.73$) (see Supplementary material online, *Figure S4*). Two RCTs comparing stainless steel BMS implantation to BA alone (without bailout stenting) were not included in quantitative synthesis.[73,74] Both trials demonstrated equivalent mid- and long-term patency rates in 104 patients with short femoropopliteal lesions.

Drug-eluting stents

Three RCTs totalling 471 patients examined DES vs. BMS implantation for femoropopliteal lesions, enabling meta-analysis of mid-term efficacy outcomes only.[12–14,75,76] All trials displayed moderate-to-high risk of bias. Lesion complexity was considerable (length 122.3 mm, IQR 72.5–143.5 mm; 42% total occlusions, IQR 36.8%–52.7%). No significant difference in likelihood of mid-term patency (OR 1.64, 95% CI 0.89–3.03; I^2 33.9%, $p_{het} = 0.22$) or TLR (OR 0.50, 95% CI 0.22–1.11; I^2 17.7%, $p_{het} = 0.30$) was observed (*Figure 7*). Long-term results for DES vs. BMS were provided by the Zilver-PTX and BATTLE trials.[14,75] In the Zilver-PTX trial, 120 patients with moderate-length femoropopliteal lesions (64.8 ± 39.7 mm) underwent secondary randomization to provisional DES or BMS implantation after suboptimal BA, observing no significant differences in 5-year patency (OR 2.28, 95% CI 0.95–5.45) and TLR (OR 0.42, 95% CI 0.15–1.18).[14] In the BATTLE trial, likelihood of primary patency (OR 1.25, 95% CI 0.57–2.72) and TLR (OR 0.78, 95% CI 0.30–2.05) also remained similar in DES and BMS arms through 24 months. Trends towards decreased all-cause mortality were identified for DES-treated patients (OR 0.13, 95% CI 0.02–1.07), while no major amputations were performed.[75]

Two RCTs compared DES and DCB use in femoropopliteal arteries. Enrolling 150 patients with challenging femoropopliteal lesions (length 152.6 ± 88.4 mm), long-term primary patency (OR 1.73, 95% CI 0.81–3.71), and TLR (OR 1.45, 95% CI 0.66–3.20) risk were comparable between DES and DCB arms in the REAL-PTX trial.[77] One-year restenosis risk was also equivocal for DES vs. DCB on subgroup analysis of 69 IC patients within the DRASTICO trial.[78]

Atherectomy

Seven RCTs including 514 patients examined atherectomy use for femoropopliteal disease (length 88.1 mm, IQR 68.9–106.3 mm; 24.5% occlusions, IQR 12.5%–48.6%).[50,79–85] Risk of bias was considered intermediate-to-high for all studies. Two early trials allocated 103 patients with IC to directional atherectomy or BA, finding trends towards lower 1-year (OR 0.24, 95% CI 0.05–1.12)[82] and 2-year (OR 0.38, 95% CI 0.13–1.12)[83,84] patency with atherectomy use. Adjunctive BA with upfront atherectomy was evaluated by two RCTs. Shammas et al. assigned 58 patients to atherectomy plus BA or BA alone, finding no differences in mid-term TLR (OR 0.30, 95% CI 0.05–1.88).[81] Distal macroembolization (within embolic protection devices) occurred more frequently with atherectomy (64.7% vs. 0%, $P < 0.001$). In the COMPLIANCE 360 study, atherectomy with adjunctive BA produced no additional benefits in freedom from mid-term restenosis or TLR.[80] The ISAR-STATH trial allocated 155 patients to three treatment arms: atherectomy with provisional BMS, plain or DCB angioplasty with adjunctive BMS, respectively.[50] Compared with DCB with BMS, likelihood of primary patency at 6 months was significantly lower (OR 0.25, 95% CI 0.09–0.71) and TLR risk at 24 months significantly higher (OR 5.49, 95% CI 2.04–14.75) with atherectomy use. Long-term TLR

Table 2 Summary of pooled effect estimates for quantitative analyses in the femoropopliteal segment

Outcome	Number of studies	Total participants	Events intervention	Events control	OR	Lower CI	Upper CI	I^2	*P* for heterogeneity	*P* for publication bias
DCB ± BMS vs. BA ± BMS										
Short-term patency	14	2221	877	542	3.21	2.44	4.24	29	0.15	0.004
Mid-term patency	14	2939	1245	520	2.75	2.14	3.52	40.6	0.06	0.45
Long-term patency	10	1594	509	222	2.47	1.93	3.16	2.6	0.42	0.20
Short-term TLR	13	2155	64	158	0.33	0.22	0.49	26.7	0.18	0.56
Mid-term TLR	19	3682	176	312	0.31	0.23	0.41	39.5	0.04	0.003
Long-term TLR	10	1578	153	202	0.42	0.29	0.60	41.7	0.08	0.20
Short-term mortality	13	1979	16	16	1.03	0.50	2.13	0	0.90	0.13
Mid-term mortality	18	3580	50	41	0.90	0.57	1.42	0	0.92	0.05
Long-term mortality	12	1894	89	66	0.96	0.67	1.39	0	0.62	0.94
BMS vs. BA ± BMS										
Short-term patency	4	499	211	140	2.24	1.08	4.66	46.2	0.13	NA
Mid-term patency	9	1507	405	328	1.38	1.01	1.89	35.6	0.13	NA
Long-term patency	5	710	166	164	1.33	0.82	2.16	43.3	0.13	NA
Mid-term TLR	5	950	69	87	0.66	0.46	0.94	0	0.85	NA
Long-term TLR	3	556	60	68	0.66	0.43	1.02	0	0.71	NA
Mid-term mortality	5	950	19	7	2.15	0.91	5.09	0	0.95	NA
Long-term mortality	3	679	31	27	0.95	0.55	1.66	0	0.73	NA
DES vs. BMS										
Mid-term patency	3	471	182	166	1.64	0.89	3.03	33.9	0.22	NA
Mid-term TLR	3	471	13	24	0.50	0.22	1.11	17.7	0.30	NA

BA, balloon angioplasty; BMS, bare-metal stent; CI, confidence interval; DCB, drug-coated balloon; DES, drug-eluting stent; NA, not applicable; OR, odds ratio; TLR, target-lesion revascularization.

risk numerically favoured BA with BMS over atherectomy (OR 0.52, 95% CI 0.23–1.18) without statistical significance being reached. Safety endpoints remained comparable between treatment arms. Atherectomy prior to DCB was compared with DCB angioplasty alone by two trials, both identifying no significant differences in primary patency, reintervention and mortality at short-, mid-, and long-term follow-up.[79,85] No major amputations were registered in either trial.

Covered stents

Three RCTs applied covered stenting in femoropopliteal arteries (length 180 mm, IQR 125–181 mm; 58.8% occlusions, IQR 41.9%–65.6%).[86–89] Saxon et al. compared covered stenting to BA with provisional BMS in 197 intermediate-length femoropopliteal lesions (70 ± 40 mm), observing superior 1-year patency results (OR 2.77, 95% CI 1.42–5.40) in the intervention group.[86] Long-term outcomes of covered vs. uncovered stenting were explored by two RCTs, including 289 patients with complex femoropopliteal lesions. The VIBRANT trial reported equivalent patency (OR 0.92, 95% CI 0.26–3.34) and TLR risks (OR 1.02, 95% CI 0.52–2.02) at 3 years post-intervention.[87] Mortality was numerically higher in the experimental arm (OR 3.28, 95% CI 0.83–12.91), while no amputations were registered. In the VIASTAR trial, 1-year patency results were equivocal, but favoured covered stenting at 2 years (OR 2.49, 95% CI 1.06–5.88).[88,89] However, long-term TLR risk did not differ between groups (OR 0.76, 95% CI 0.31–1.84).

Subgroup analysis and meta-regression

Outcome estimates generally remained consistent with main findings following subgroup analysis for DCB vs. BA (see Supplementary material online, *Table S5*). However, meta-regression identified loss to follow-up as a potential source of heterogeneity for short-term patency ($P = 0.009$) and long-term mortality ($P = 0.04$). Additionally, there was significant interaction between lesion length and risk of long-term TLR ($P = 0.02$). For BMS vs. BA ± BMS, risk of bias ($P = 0.03$), attrition to follow-up ($P = 0.04$), and lesion length ($P = 0.01$) significantly modified likelihood of mid-term patency (see Supplementary material online, *Table S6*).

Sensitivity analysis

Sensitivity analyses exploring the influence of missing participant data according to varying assumptions ('none had the event', worst case,

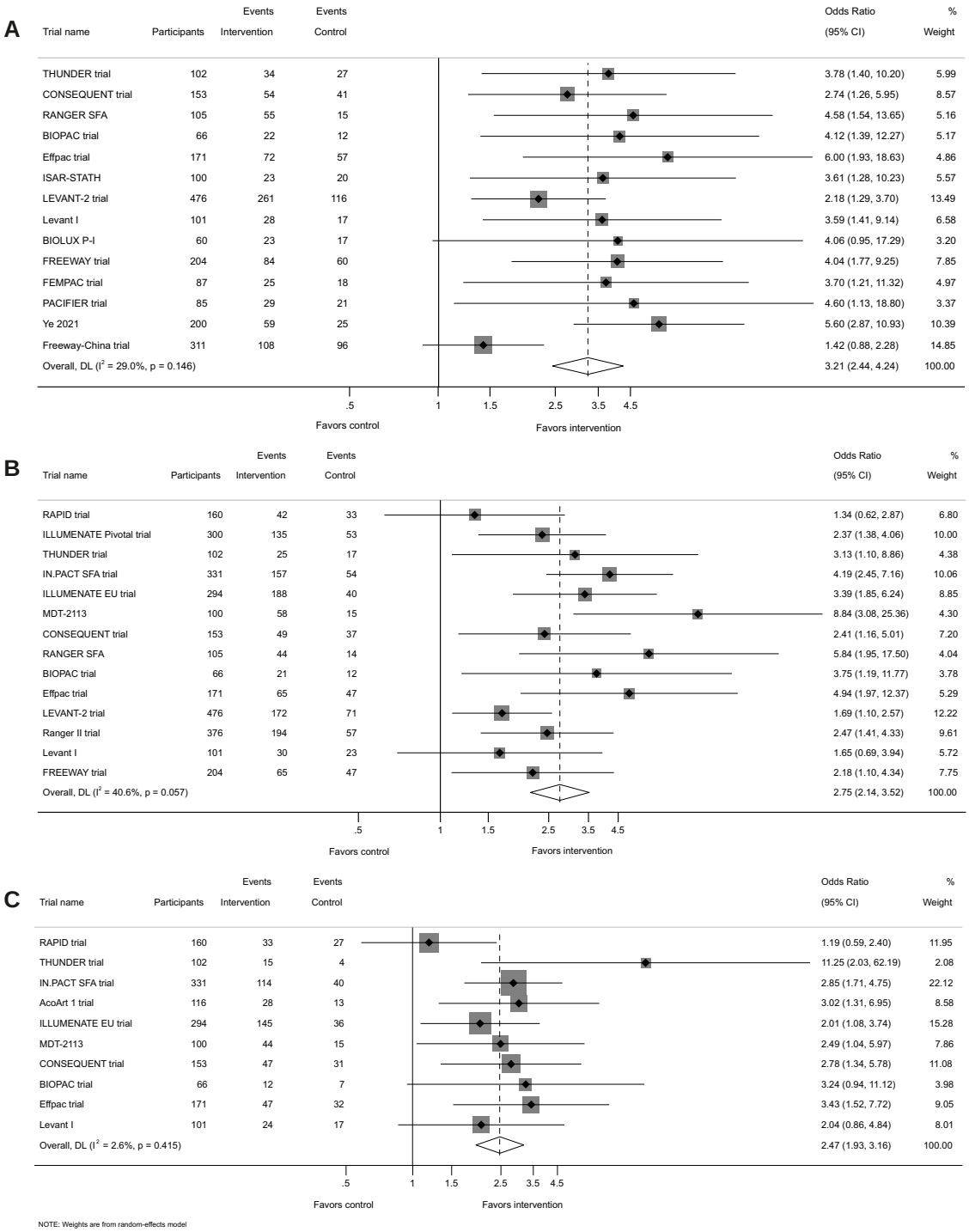


Figure 2 Effect estimates for primary patency comparing drug-coated balloon ± bare-metal stent vs. balloon angioplasty ± bare-metal stent in femoropoliteal lesions at (*A*) short-term follow-up; (*B*) mid-term follow-up; and (*C*) long-term follow-up. The summary estimates presented were calculated using random-effects models (D + L). The sizes of the data markers are proportional to the inverse of the variance of the odds ratio; the confidence intervals are represented by the bars.

and best case) in line with the intention-to-treat principle are shown in Supplementary material online, *Table S7*. Pooled estimates derived from imputation-based analysis according to the 'none had the event' assumption were largely similar to available case analysis for all outcomes with the exception of patency estimates for BMS vs. BA ± BMS, demonstrating no differences in patency at all follow-up times. Imputation according to best- and worst-case scenarios indicated potential uncertainty arising from missing participant data for the majority of outcomes (see Supplementary material online, *Table S7*). Sensitivity analysis incorporating only RCTs with self-expanding nitinol BMS

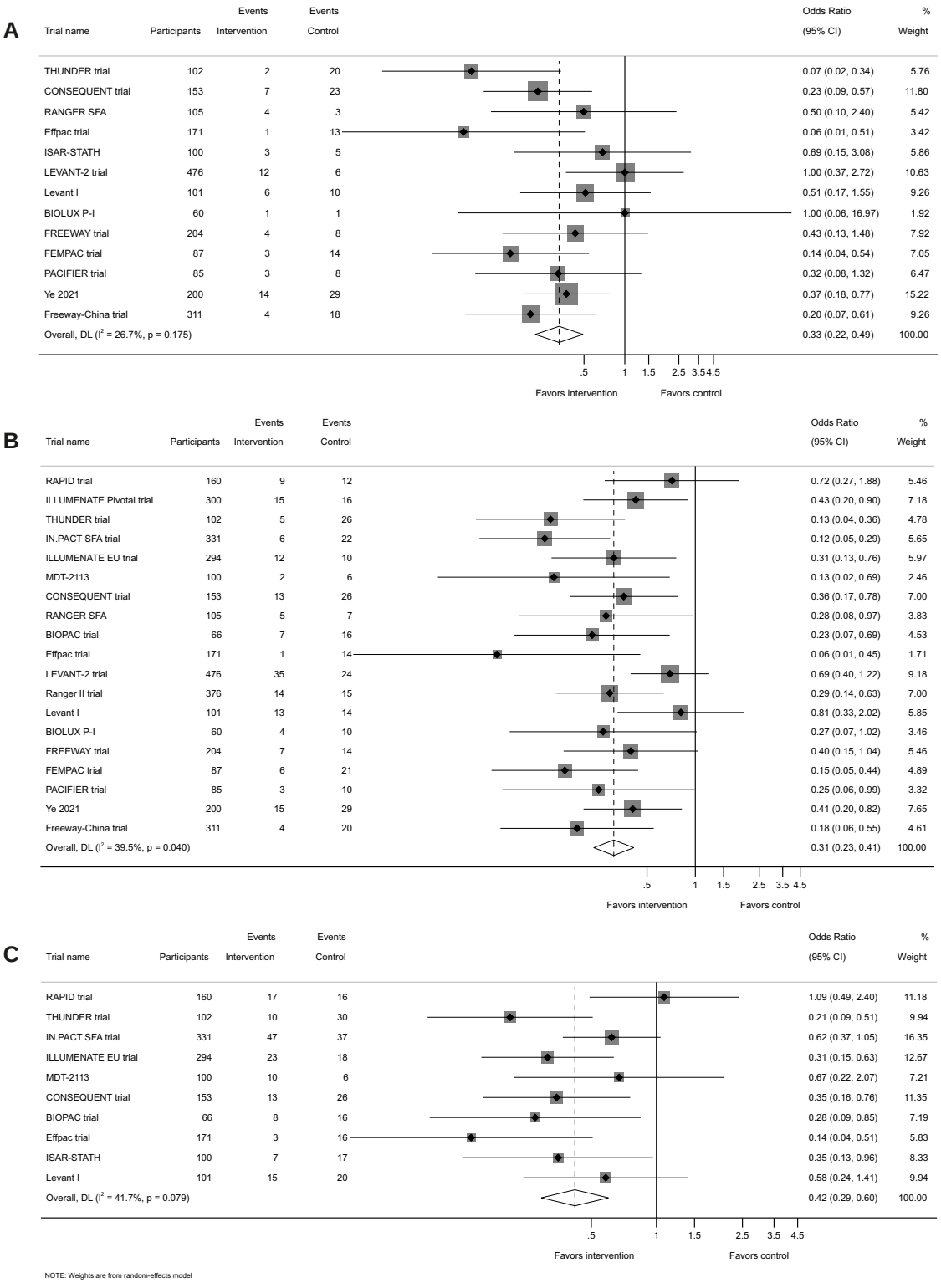


Figure 3 Effect estimates for target-lesion revascularization comparing drug-coated balloon ± bare-metal stents vs. balloon angioplasty ± BMS in femoropopliteal lesions at (*A*) short-term follow-up; (*B*) mid-term follow-up; and (*C*) long-term follow-up. The summary estimates presented were calculated using random-effects models (D + L). The sizes of the data markers are proportional to the inverse of the variance of the odds ratio; the confidence intervals are represented by the bars.

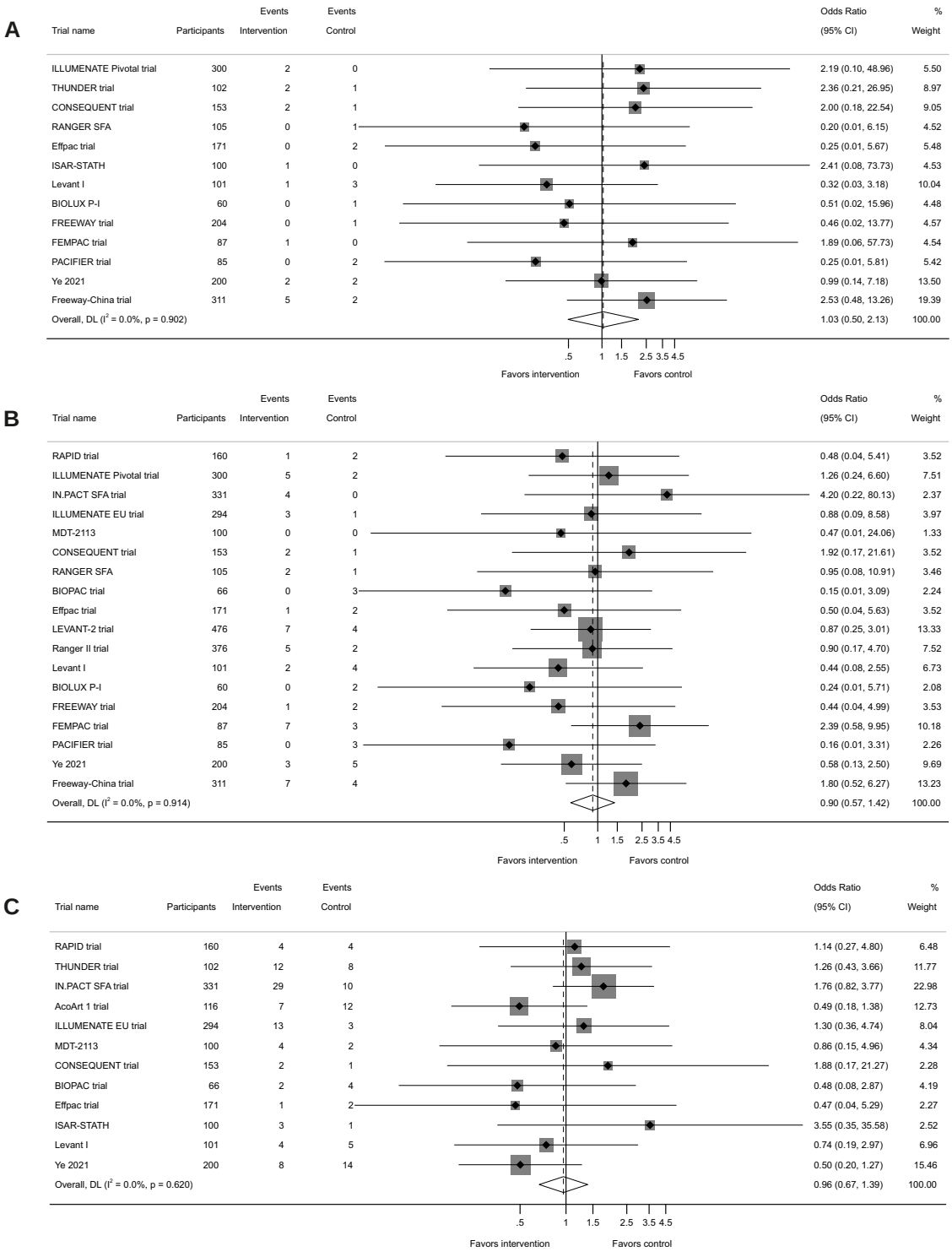


Figure 4 Effect estimates for all-cause mortality comparing drug-coated balloon ± bare-metal stents vs. balloon angioplasty ± bare-metal stent in femoropopliteal lesions at (*A*) short-term follow-up; (*B*) mid-term follow-up; and (*C*) long-term follow-up The summary estimates presented were calculated using random-effects models (D + L). The sizes of the data markers are proportional to the inverse of the variance of the odds ratio; the confidence intervals are represented by the bars.

technology produced patency estimates favouring primary stenting using BMS over provisional stenting at all follow-up durations, while TLR and all-cause mortality results remained unchanged (see Supplementary material online, *Table S8*). For primary patency comparing DCB vs. BA, confining analyses to studies using patients as the unit of observation and excluding one trial for short-,[54] mid-[37], and

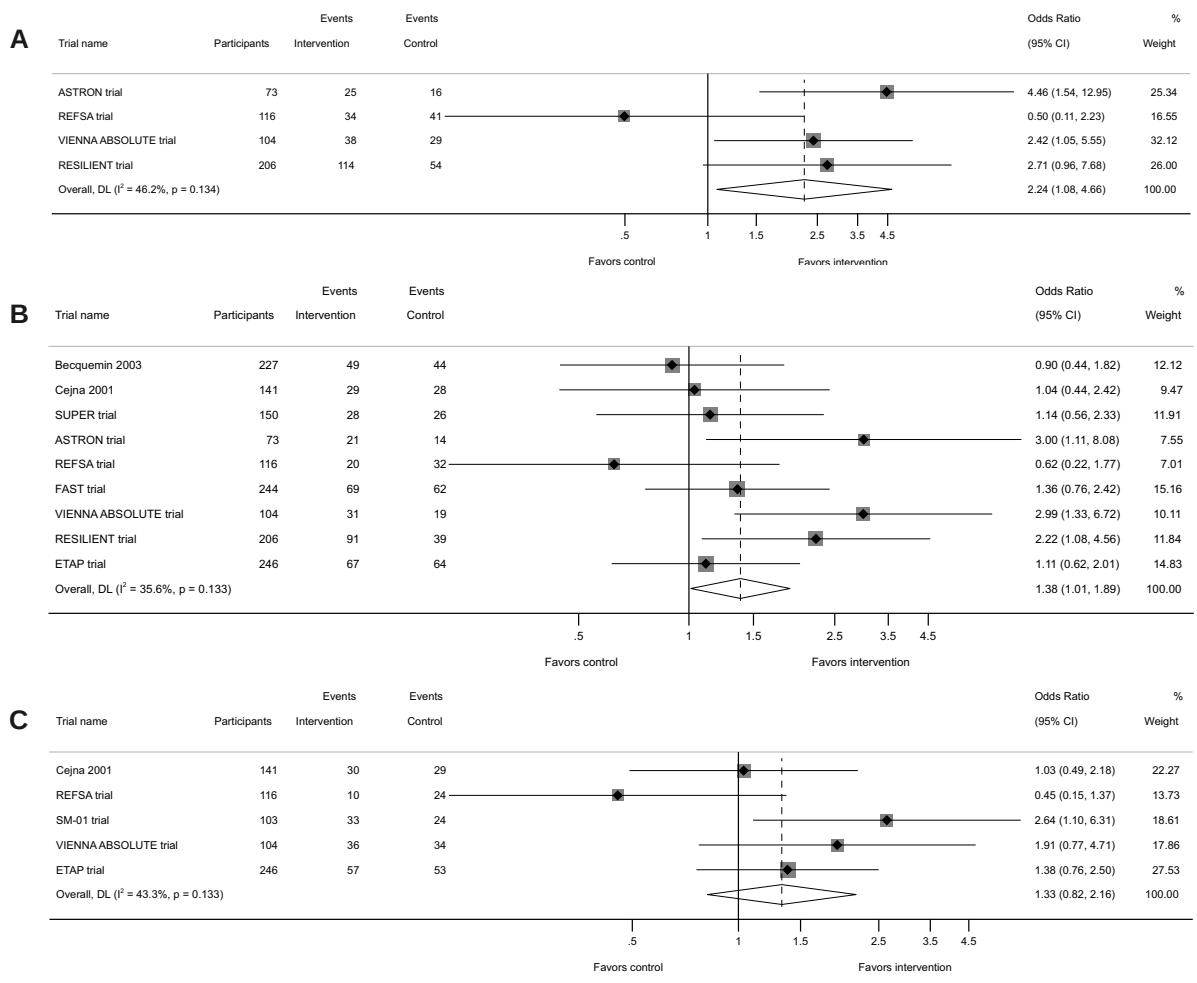


Figure 5 Effect estimates for primary patency comparing bare-metal stents vs. balloon angioplasty ± bare-metal stent in femoropopliteal lesions at (*A*) short-term follow-up; (*B*) mid-term follow-up; and (*C*) long-term follow-up. The summary estimates presented were calculated using random-effects models (D + L). The sizes of the data markers are proportional to the inverse of the variance of the odds ratio; the confidence intervals are represented by the bars.

long-term[38] follow-up provided similar results to main findings (see Supplementary material online, *Table S9*). For the comparison BMS vs. BA ± BMS, excluding two studies using lesion-based analysis[61,64] also produced mid-term patency estimates consistent with primary results (see Supplementary material online, *Table S10*). Similarly, restricting analysis to studies with core laboratory employment for patency assessment revealed consistency of results with primary findings (see Supplementary material online, *Tables S9/S10*).

Discussion

We conducted a systematic review and meta-analysis summarising evidence from RCTs for endovascular management of IC across all follow-up durations. The main findings are as follows: (i) substantial evidence gaps exist in aortoiliac disease; (ii) DCB angioplasty was associated with significantly higher primary patency and reduced TLR risk compared with BA in low-complexity, femoropopliteal lesions across all time points; (iii) primary BMS implantation was associated with statistically significant efficacy benefits over provisional stenting in non-complex femoropopliteal lesions at short- and mid-term follow-up, but these advantages were not sustained in the long-term; (iv) no statistically significant differences in mid-term efficacy were observed for DES over BMS in femoropopliteal arteries; and (v) there was no randomized evidence supporting stand-alone or adjunctive atherectomy over alternative endovascular strategies in IC and femoropopliteal disease (*Structured graphical abstract*).

The present study adds clinically relevant aspects and differs from previously published meta-analyses. Earlier meta-analyses focused on singular device groups, anatomic segments, or follow-up times, reducing their applicability to broader clinical settings.[3–5] Conversely, they did not define target populations based on LEAD severity, although treatment goals and expected outcomes fundamentally differ in IC and CLTI.[3,4,90] Most studies examining several device comparisons were conducted as network meta-analyses.[3,4,91] While network meta-analysis facilitates comparison of multiple treatment options in the

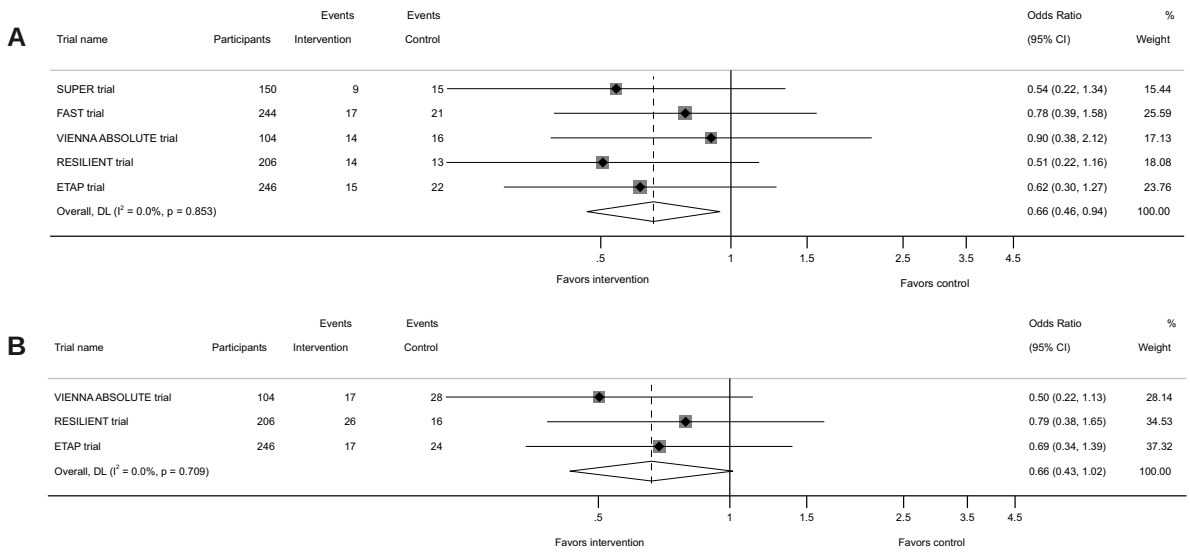


Figure 6 Effect estimates for target-lesion revascularization comparing bare-metal stents vs. balloon angioplasty ± BMS in femoropopliteal lesions at (*A*) mid-term follow-up; (*B*) long-term follow-up. The summary estimates presented were calculated using random-effects models (D + L). The sizes of the data markers are proportional to the inverse of the variance of the odds ratio; the confidence intervals are represented by the bars.

absence of head-to-head data, certain assumptions require fulfilment to ensure validity of results. However, variations in potential effect modifiers across studies, such as comorbidities, disease severity, and lesion characteristics, present obstacles to fully satisfying the transitivity assumption. Additionally, previous network meta-analyses were based on results from singular RCTs, resulting in low confidence around the accuracy of pooled effect estimates and complicating the interpretation of findings.[3,4,91] Lastly, and to the best of our knowledge, the present analysis has incorporated the largest number of unique RCTs, to date.

The *aortoiliac arteries* represent essential anatomical targets in IC, as the alleviation of proximal obstruction frequently provides symptomatic relief and satisfactory long-term patency, even in the presence of distal disease. Primary stenting has emerged as the first-line endovascular approach to iliac lesions, yet this paradigm is largely based on observational data.[92] We found no convincing evidence indicating that primary BMS placement outperforms provisional stenting in non-occlusive lesions. However, generalizability of the Dutch Iliac Stent Trial is limited by use of stainless steel stents, which were superseded by nitinol stents due to favourable biomechanical properties.[18–21] The STAG trial delineates potential safety advantages of primary stenting in reducing embolization rates for iliac occlusive disease, although premature trial termination reduced its power to identify differences in long-term efficacy endpoints.[22] Limited evidence suggests benefits for novel stent technologies over balloon-expandable BMS implantation. Covered stents may forestall neo-intimal hyperplasia through barrier formation, yet several methodological shortcomings hinder interpretation of the COBEST trial, including long-term post-hoc analysis, attrition to follow-up, and lack of core laboratory adjudication.[25] Mid-term efficacy advantages for self-expanding BMS reported by the ICE trial may be explained by circumferential stress amelioration due to reduced radial force application.[23] The absence of core laboratory adjudication within this open-label trial should be considered when applying findings to real-life cohorts.

While endovascular intervention has surpassed surgical revascularization for *femoropopliteal lesions* in everyday clinical practice, the optimal device-based approach in IC remains undefined.[11] Achieving therapeutic durability in this anatomic region is challenging due to high plaque burden, extensive lesion length and complex mechanical forces applied to vascular implants. Drug-coated balloons are designed to ameliorate neo-intimal hyperplasia through local paclitaxel delivery. Our findings indicate that DCB angioplasty is safe and associated with durable efficacy advantages compared with uncoated balloons in femoropopliteal disease of low-to-intermediate complexity, with general consistency of results following heterogeneity assessment and sensitivity analysis. While these encouraging findings solidify the role of DCB angioplasty as the first-line approach to non-complex femoropopliteal lesions in IC, deficits in evidence quality impede translation of results into routine treatment scenarios. Most analysed studies were small-scale, industry-sponsored RCTs formally powered for short-term surrogate endpoints and conducted for regulatory purposes in stringently selected populations.

Our findings also suggest temporary efficacy benefits for primary over provisional stenting in femoropopliteal arteries, without evidence for superiority beyond the mid-term. While vascular scaffolds may enhance short-term revascularization success by preventing constrictive arterial remodelling and recoil, lack of long-term benefits likely results from in-stent neo-intimal overgrowth. Sensitivity analysis for contemporary self-expanding nitinol stent technology diluted this catch-up effect for patency, yet long-term TLR risk remained unaffected. Imputation-based analysis exploring the influence of missing participant data demonstrated increased uncertainty surrounding patency results for this device comparison, but TLR estimates remained consistent. While transient efficacy improvements may be desirable, in-stent restenotic lesions are composed of fibrotic collagen matrix that poses considerable challenges to endovascular techniques with substantial failure and recurrence rates.[93]

Drug-eluting stents technology aims to forestall restenosis by combining vascular scaffolding and anti-proliferative agent delivery. We identified no significant mid-term benefits for DES over BMS placement, although sample size restrictions raise the possibility of a Type II error.

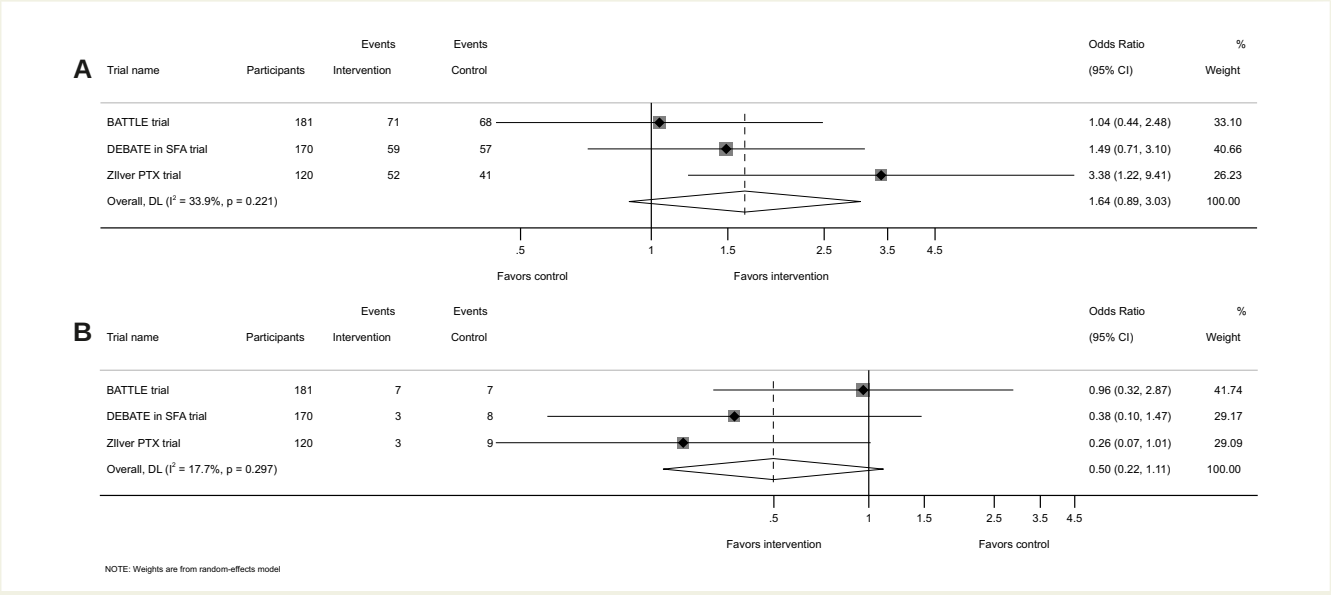


Figure 7 Effect estimates for (*A*) mid-term primary patency and (*B*) mid-term target-lesion revascularization comparing drug-eluting stents vs. bare-metal stents in femoropopliteal lesions. The summary estimates presented were calculated using random-effects models (D + L). The sizes of the data markers are proportional to the inverse of the variance of the odds ratio; the confidence intervals are represented by the bars.

Similarly, the REAL-PTX and DRASTICO (subgroup) studies reported equivocal efficacy results for DES and DCB use, albeit that both analyses were insufficiently powered for detection of long-term differences.[77,78]

Data for covered stenting in femoropopliteal lesions are equally conflicting. Patency benefits over BA with bailout stenting are reported by a study terminated early following device modification and endpoint redefinition.[86] Covered and uncovered stenting yielded equivalent, yet disappointing results in the VIBRANT trial with merely a quarter of deployed stents remaining patent at 3 years.[87] Employing updated Viabahn stents with heparin-bonded surfaces, the VIASTAR trial identified promising patency outcomes at 2 years, yet this did not translate into lower TLR rates.[89] Although covered stents may have a niche in long, complex femoropopliteal lesions by preventing neointimal ingrowth, edge restenosis may still limit revascularization durability. In light of inconsistent findings and methodological limitations, presented results for covered stents should be merely viewed as hypothesis generating.

Atherectomy aims to debulk atherosclerotic plaques to minimize barotrauma and ameliorate adverse tissue remodelling. However, cumulative randomized evidence does not indicate that atherectomy, whether used independently or adjunctively, offers efficacy advantages in IC populations. Furthermore, safety concerns were raised by distal embolization events, necessitating additional equipment costs of embolic capture devices.[81]

Collectively, none of the included studies identified a significant difference in QoL parameters across all device comparisons, anatomic segments, and follow-up durations. However, the comparative value of available QoL data is diminished by the ubiquitous lack of adjustment for the occurrence of reintervention prior to QoL assessment, thereby hindering the identification of any potential effects related to the index revascularization procedure. Consistent failure to adjust for reintervention events also extended to other functional endpoints, such as walking distance. This methodological flaw in functional and QoL endpoint assessment makes the findings of the present analysis unsurprising.

Limitations

While the primary target population was patients with IC, the vast majority of RCTs consisted of mixed populations. *A priori*, we decided to exclude studies comprising < 70% of patients with IC to maintain sufficient power for device comparisons and ensure applicability to broader IC populations. Additionally, results remained consistent when restricting the analysis to trials with IC proportions of 90% and above (see Supplementary material online, *Table S5*). Underlying study quality further limits this analysis, reflecting the abundance of small-scale, industry-sponsored, open-label trials with extensive attrition to follow-up and insufficient power for long-term, clinical endpoint assessment. Substantial losses to follow-up were encountered by the majority of included trials, introducing potential uncertainty due to missing participant data, especially with regards to patency estimates for primary vs. provisional bare-metal stenting. However, available case analysis, imputation-based sensitivity analysis, and stratified analysis by percentage loss to follow-up provided generally consistent results across outcomes. There was clinical and methodological heterogeneity between studies regarding comorbidities, lesion characteristics, device features, and endpoint definitions. For example, the endpoint of TLR was subject to varying definitions, with some studies requiring symptom recurrence to justify reintervention and other studies basing reintervention solely on imaging evidence for restenosis, or a mixture of both. Furthermore, calculation and synthesis of event rates were not feasible, as follow-up durations per treatment arm were rarely described. Use of ORs, also considering limitations of approaches we applied to derive estimates, could have introduced biases inherited from individual studies. Meta-analysis of amputation risk was not performed due to low event numbers, while quantitative synthesis of QoL outcomes was precluded by paucity of data and significant inter-study variability regarding questionnaire types, versions and reporting. Lastly, we evaluated endpoints for all available follow-up durations, yet long-term outcome assessment is limited by the small proportion of studies reporting results beyond 2 years.

Implications for clinical practice and future directions

This review highlights substantial evidence gaps for endovascular treatment of IC in aortoiliac disease with no single-device-based approach displaying conclusive advantages over standard care (BA with bailout stenting). Primary stenting may reduce distal macroembolization in iliac occlusive disease, but whether it provides significant benefits in iliac stenosis remains uncertain. Although our findings strengthen the role of DCB angioplasty as the primary endovascular approach to non-complex femoropopliteal lesions in IC, translation of findings to real-life patient cohorts is not straight forward, given the limitations inherent to presented studies. These deficiencies are symptomatic for the general state of evidence in endovascular therapy for LEAD, highlighting the urgent need for pragmatic, investigator-initiated trials adequately powered for long-term, patient-centred outcomes and considering IC and CLTI as disease entities with fundamentally different treatment goals. Our findings do not support routine primary bare-metal stenting in IC and femoropopliteal disease given the transient nature of observed efficacy benefits, the statistical uncertainty surrounding derived patency estimates, and the poor prognosis associated with in-stent restenosis. Randomized data for DES and covered stent technologies in femoropopliteal arteries are conflicting, underpowered and limited by methodological shortcomings, preventing identification of clear treatment effects for either approach. As a consequence of higher equipment costs and deficient evidence for efficacy advantages, atherectomy currently has no role in endovascular treatment of femoropopliteal lesions causing IC. Paucity of data, non-standardized reporting and methodologically flawed assessment of functional and QoL endpoints are further notable disappointments for the current state of evidence in the field, given that improvements in these domains represent central therapeutic goals in IC management.

Author contributions

I.B. conceived the project alongside T.M. and D.K. D.K. is the primary author of the manuscript with S.B., J.B., A.L., S.Z., C.A.B., J.N., T.M., and I.B. providing revisions for subsequent drafts. C.N., T.M., and D.K. conducted the literature search. D.K., P.F.R., L.K., A.C.Q.C., H.R.D., and F.K. performed abstract screening and full text review. Data extraction and risk of bias assessment were conducted by D.K., P.F.R., and L.K. Statistical analysis was performed by T.M. All authors approved the manuscript prior to submission.

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Supplementary data

Supplementary data is available at *European Heart Journal* online.

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Conflict of interest: D.K., T.M., Z.S., S.B., A.C.Q.C, C.A.B., F.K., C.N., and A.L. declare that there is no conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix 1: Search strategy

Date search performed: 11-11-2021

Database searched via Years of coverage Records Records after duplicates removed

Embase Embase.com 1971 - Present 5786 5712

Medline ALL Ovid 1946 - Present 1828 276

Web of Science Core Collection* Web of Knowledge 1975 - Present 3957 481

Cochrane Central Register of Controlled Trials Wiley 1992 - Present 646** 185

Total 12217 6654

Other sources: Google Scholar 200 70

*Science Citation Index Expanded (1975-present); Social Sciences Citation Index (1975-present); Arts & Humanities Citation Index (1975-present); Conference Proceedings Citation Index- Science (1990-present); Conference Proceedings Citation Index- Social Science & Humanities (1990-present); Emerging Sources Citation Index (2015-present)

**This is excluding 145 trials

Embase

('femoropopliteal obstruction'/de OR 'femoropopliteal lesion'/de OR 'femoropopliteal disease'/de OR 'femoropopliteal obstruction'/de OR 'superficial femoral artery lesion'/de OR 'superficial femoral artery disease'/de OR 'popliteal artery'/de OR 'iliac artery disease'/de OR 'iliac artery obstruction'/de OR 'Leriche syndrome'/de OR 'infrapopliteal lesion'/de OR 'infrapopliteal artery disease'/de OR (infrainguinal* OR infra-inguinal* OR ((femoropopliteal*) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((superficial* OR common*) NEAR/3 (femor*) NEAR/3 (arter* OR aort*) NEAR/6 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((SFA) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((popliteal*) NEAR/3 (arter* OR aort*) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((iliac OR aortoiliac* OR infrapopliteal* OR crural*) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((aortoiliac*) NEAR/3 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((Leriche*) NEAR/2 (syndrome* OR diseas* OR fontain*)) OR ((arter* OR vascul*) NEAR/3 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*) NEAR/3 (lower-extrem* OR below-the-knee* OR leg OR legs)) OR ((femoropopliteal*) NEAR/3 (arter*) NEAR/3 (revascular*)) OR ((atheroscler*) NEAR/2

(femoropopliteal*))):ab,ti,kw) AND ('endovascular surgery'/exp OR 'endovascular therapy'/de OR 'endovascular intervention'/de OR 'percutaneous vascular intervention'/de OR 'percutaneous transluminal angioplasty'/de OR 'stent'/exp OR 'cryoplasty'/de OR 'atherectomy'/exp OR 'balloon'/exp OR (endovascular OR evt OR endotherap* OR ((percutaneous* OR transluminal*) NEAR/3 (angioplas*)) OR balloon* OR stent OR stenting OR stents OR cryoplast* OR atherectom*):ab,ti,kw) AND ('vascular patency'/de OR 'revascularization'/exp OR 'walking distance'/exp OR 'walking impairment questionnaire'/de OR 'ankle brachial index'/de OR 'quality of life'/exp OR 'mortality'/exp OR 'survival'/exp OR 'limb salvage'/de OR 'Rutherford backscattering spectrometry'/de OR 'restenosis'/de OR 'leg amputation'/exp OR (((hemodynamic* OR haemodynamic*) NEAR/3 (success* OR outcome*)) OR patenc* OR revasculari* OR recanali* OR mortali* OR death OR surviv* OR Rutherford* OR restenos* OR amputat* OR ((technical*) NEAR/3 (success* OR procedur*)) OR ((repeat*) NEAR/3 (intervent*)) OR ((walk*) NEAR/3 (distan*)) OR ((walk*) NEAR/3 (impair*) NEAR/3 (questionn* OR scor* OR index)) OR ((ankle*) NEAR/3 (brachial*) NEAR/3 (index OR scor*)) OR ((limb*) NEAR/3 (salv* OR save*)) OR ((qualit* OR experience*) NEAR/3 (life OR living)) OR hrql OR hrqol OR qol):ab,ti,kw) NOT ([Conference Abstract]/lim) AND [ENGLISH]/lim

Medline

('Popliteal Artery'/ OR 'Leriche Syndrome'/ OR (infrainguinal* OR infra-inguinal* OR ((femoropopliteal*) ADJ3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((superficial* OR common*) ADJ3 (femor*) ADJ3 (arter* OR aort*) ADJ6 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((SFA) ADJ3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((popliteal*) ADJ3 (arter* OR aort*) ADJ3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((iliac OR aortoiliac* OR infrapopliteal* OR crural*) ADJ3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((aortoiliac*) ADJ3 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((Leriche*) ADJ2 (syndrome* OR diseas* OR fontain*)) OR ((arter* OR vascul*) ADJ3 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*) ADJ3 (lower-extrem* OR below-the-knee* OR leg OR legs)) OR ((femoropopliteal*) ADJ3 (arter*) ADJ3 (revascular*)) OR ((atheroscler*) ADJ2 (femoropopliteal*))).ab,ti,kf.) AND (exp 'Endovascular Procedures'/ OR exp 'Stents'/ OR exp 'Atherectomy'/ OR exp 'Angioplasty, Balloon'/ OR (endovascular OR evt OR endotherap* OR ((percutaneous* OR transluminal*) ADJ3 (angioplas*)) OR balloon* OR stent OR stenting OR stents OR cryoplast* OR atherectom*).ab,ti,kf.) AND ('Vascular Patency'/ OR 'Quality of Life'/ OR 'Ankle Brachial Index'/ OR 'Mortality'/ OR 'Survival'/ OR mo.fs OR 'Limb Salvage'/ OR 'Coronary Restenosis'/ OR 'Amputation'/ OR (((hemodynamic* OR haemodynamic*) ADJ3 (success* OR outcome*)) OR patenc* OR revasculari* OR recanali* OR mortali* OR death OR surviv* OR Rutherford* OR restenos* OR amputat* OR ((technical*) ADJ3 (success* OR procedur*)) OR ((repeat*) ADJ3 (intervent*)) OR ((walk*) ADJ3 (distan*)) OR ((walk*) ADJ3 (impair*) ADJ3 (questionn* OR scor* OR index)) OR ((ankle*) ADJ3 (brachial*) ADJ3 (index OR scor*)) OR ((limb*) ADJ3 (salv* OR save*)) OR ((qualit* OR experience*) ADJ3 (life OR living)) OR hrql OR hrqol OR qol).ab,ti,kf.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND (english).lg

Web of science

TS=(((infrainguinal* OR infra-inguinal* OR ((femoropopliteal*) NEAR/2 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((superficial* OR common*) NEAR/2 (femor*) NEAR/2 (arter* OR aort*) NEAR/5 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((SFA) NEAR/2 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((popliteal*) NEAR/2 (arter* OR aort*) NEAR/2 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((iliac OR aortoiliac* OR infrapopliteal* OR crural*) NEAR/2 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((aortoiliac*) NEAR/2 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((Leriche*) NEAR/2 (syndrome* OR diseas* OR fontain*)) OR ((arter* OR vascul*) NEAR/2 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*) NEAR/2 (lower-extrem* OR below-the-knee* OR leg OR legs)) OR ((femoropopliteal*) NEAR/2 (arter*) NEAR/2 (revascular*)) OR ((atheroscler*) NEAR/2 (femoropopliteal*)))) AND ((endovascular OR evt OR endotherap* OR ((percutaneous* OR transluminal*) NEAR/2 (angioplas*)) OR balloon* OR stent OR stenting OR stents OR cryoplast* OR atherectom*)) AND ((((hemodynamic* OR haemodynamic*) NEAR/2 (success* OR outcome*)) OR patenc* OR revasculari* OR recanali* OR mortali* OR death OR surviv* OR Rutherford* OR restenos* OR amputat* OR ((technical*) NEAR/2 (success* OR procedur*)) OR ((repeat*) NEAR/2 (intervent*)) OR ((walk*) NEAR/2 (distan*)) OR ((walk*) NEAR/2 (impair*) NEAR/2 (questionn* OR scor* OR index)) OR ((ankle*) NEAR/2 (brachial*) NEAR/2 (index OR scor*)) OR ((limb*) NEAR/2 (salv* OR save*)) OR ((qualit* OR experience*) NEAR/2 (life OR living)) OR hrql OR hrqol OR qol))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(English)

Cochrane

((infrainguinal* OR infra-inguinal* OR ((femoropopliteal*) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((superficial* OR common*) NEAR/3 (femor*) NEAR/3 (arter* OR aort*) NEAR/6 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((SFA) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((popliteal*) NEAR/3 (arter* OR aort*) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((iliac OR aortoiliac* OR infrapopliteal* OR crural*) NEAR/3 (obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((aortoiliac*) NEAR/3 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*)) OR ((Leriche*) NEAR/2 (syndrome* OR diseas* OR fontain*)) OR ((arter* OR vascul*) NEAR/3 (obliter* OR obstruct* OR occlus* OR stenosis* OR lesion* OR diseas*) NEAR/3 (lower-extrem* OR below-the-knee* OR leg OR legs)) OR ((femoropopliteal*) NEAR/3 (arter*) NEAR/3 (revascular*)) OR ((atheroscler*) NEAR/2 (femoropopliteal*))):ab,ti,kw) AND ((endovascular OR evt OR endotherap* OR ((percutaneous* OR transluminal*) NEAR/3 (angioplas*)) OR balloon* OR stent OR stenting OR stents OR cryoplast* OR atherectom*):ab,ti,kw) AND ((((hemodynamic* OR haemodynamic*) NEAR/3 (success* OR outcome*)) OR patenc* OR revasculari* OR recanali* OR mortali* OR death OR surviv* OR Rutherford* OR restenos* OR amputat* OR ((technical*) NEAR/3 (success* OR procedur*)) OR ((repeat*) NEAR/3 (intervent*)) OR ((walk*) NEAR/3 (distan*)) OR ((walk*) NEAR/3 (impair*) NEAR/3 (questionn* OR scor* OR index)) OR ((ankle*) NEAR/3 (brachial*) NEAR/3 (index OR scor*)) OR ((limb*) NEAR/3 (salv* OR save*)) OR ((qualit* OR experience*) NEAR/3 (life OR living)) OR hrql OR hrqol OR qol):ab,ti,kw)

Google Scholar

Femoropopliteal|popliteal|iliac|aortoiliac|infrapopliteal obstruction|occlusion|stenosis|lesion|diseaseballoon|stent|endovascular patency|revascularization|revascularization|'quality of life'|mortality|survival|restenosis 'lower extremity'

Appendix 2: Formulae for estimating sample size from Kaplan–Meier proportions

For studies solely providing estimated Kaplan–Meier proportions along with standard errors or 95% confidence intervals, sample sizes were estimated using the following formulae:

(1) When Kaplan–Meier proportions along with standard errors were provided:
SE = sqrt[P(1−P)/N]
(2) When Kaplan–Meier proportions along with 95% confidence intervals were provided:
(a) Calculating standard errors from 95% confidence intervals
SE = (upper limit—lower limit)/1.96
(b) Calculating sample size from given proportions and calculated SE
SE = sqrt[P(1-P)/N]

Appendix 3: Legend for trial name abbreviations

AcoArt 1 (NCT01850056): Prospective, Multi-centre and Randomized Controlled Clinical Study to Verify Effectiveness and Safety of Drug-eluting Balloon in PTA Procedure

ASTRON (trial identifier not found): Balloon Angioplasty vs. Stenting with Nitinol Stents in Intermediate Length Superficial Femoral Artery Lesions

BATTLE (NCT02004951): Bare Metal Stent vs. Paclitaxel Eluting Stent in the Setting of Primary Stenting of Intermediate Length Femoropopliteal Lesions

BIOLUX P-1 (NCT01056120): NA

BIOPAC (NCT02145065): Prospective, Pivotal, First - in Man Clinical Trial of the Safety and Efficacy of a Novel Microcrystalline Paclitaxel Coated Balloon for Treatment of Femoropopliteal Artery Disease

COBEST (ISRCTN89458845): COvered Balloon Expandable Stent Trial

COMPLIANCE 360 (trial identifier not found): NA

CONSEQUENT (NCT01970579): Clinical Trial on Peripheral Arteries Treated With SeQuent® Please P Paclitaxel Coated Balloon Catheter

DEBATE-IN-SFA (UMIN000010071): Drug Eluting stent implantation vs BAre metal sTEnt implantation in treatment of SFA

DEFINITIVE-AR (NCT01366482): Directional AthErectomy Followed by a PacItaxel-Coated BallooN to InhibiT RestenosIs and Maintain Vessel PatEncy: A Pilot Study of Anti-Restenosis Treatment

DRASTICO (NCT01969630): Drug-Eluting Balloon vs. Drug-Eluting Stent for Complex Femoropopliteal Arterial Lesions

Dutch Iliac Stent trial (trial identifier not found): NA

EFFPAC (NCT02540018): Effectiveness of Paclitaxel-coated Luminor® Balloon Catheter vs. Uncoated Balloon Catheter in the Arteria Femoralis Superficialis

ETAP (NCT00712309): Endovascular Treatment of Popliteal Artery - Balloon Angioplasty vs. Primary Stenting

FAST (trial identifier not found): The Femoral Artery Stenting Trial

FEMPAC (NCT00472472): Femoral Paclitaxel Randomized Pilot Trial

FREEWAY (trial identifier not found): The Randomized Freeway Stent Study

FREEWAY-CHINA (trial identifier not found): NA

ICE (NCT01305174): Iliac, Common and External Artery Stent Trial

ILLUMENATE-EU (NCT01858363): CVI Drug-Coated Balloon European Randomized Clinical Trial

ILLUMENATE-PIVOTAL (NCT01858428): Prospective, Randomized, Single-Blind, U.S. Multi-Centre Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With A Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon

IN.PACT SFA (NCT01175850): Randomized Trial of IN.PACT Admiral® Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease

ISAR-STATH (NCT00986752): Efficacy Study of Stenting, Paclitaxel Eluting Balloon or Atherectomy to Treat Peripheral Artery Disease

LEVANT 1 (NCT00930813): The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis

LEVANT 2 (NCT01412541): Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries

MDT-2113 (NCT01947478): Drug-Eluting Balloon vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery

PACIFIER (NCT01083030): Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis

RANGER 2 (NCT03064126): RANGER™ Paclitaxel Coated Balloon vs Standard Balloon Angioplasty

RANGER-SFA (NCT02013193): Comparison of the Ranger™ Paclitaxel-Coated PTA Balloon Catheter and Uncoated PTA Balloons in Femoropopliteal Arteries

RAPID (ISRCTN47846578): Randomized trial of Legflow(®) paclitaxel eluting balloon and stenting vs. standard percutaneous translumenal angioplasty and stenting for the treatment of intermediate and long lesions of the superficial femoral artery

REAL-PTX (NCT01728441): Randomized Evaluation of the Zilver PTX Stent vs. Paclitaxel-Eluting Balloons for Treatment of Symptomatic Peripheral Artery Disease of the Femoropopliteal Artery

REFSA (trial identifier not found): NA

RESILIENT (NCT00673985): Edwards Lifesciences Self-Expanding Stent Peripheral Vascular Disease Study

SM-01 (NCT01183117): A Clinical Investigation of SM-01 Stenting vs. PTA for the Treatment of Superficial Femoral Artery Disease

STAG (ISRCTN48145465): Stents vs. Angioplasty Trial

SUPER (trial identifier not found): Randomized Trial of the SMART Stent vs. Balloon Angioplasty in Long Superficial Femoral Artery Lesions

THUNDER (NCT00156624): Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries

VIASTAR (ISRCTN48164244): Viabahn Endoprosthesis With PROPATEN Bioactive Surface [VIA] vs. Bare Nitinol Stent in the Treatment of Long Lesions in Superficial Femoral Artery Occlusive Disease

VIBRANT (NCT00228384): GORE VIABAHN Endoprosthesis vs. Bare Nitinol Stent in the Treatment of Long Lesion (>8 cm) Superficial Femoral Artery Occlusive Disease

VIENNA-ABSOLUTE (NCT00281060): Balloon Angioplasty vs. Stenting With Nitinol Stents in the Superficial Femoral Artery

ZILVER-PTX (NCT00120406): Evaluation of the Zilver PTX Drug-Eluting Stent in the Above-the-Knee Femoropopliteal Artery

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