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[Intervention Review]

Angioplasty versus stenting for infrapopliteal arterial lesions in chronic limb-threatening ischaemia

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ABSTRACT

Background

Chronic limb-threatening ischaemia (CLTI) is a manifestation of peripheral arterial disease (PAD) that includes chronic ischaemic rest pain or ischaemic skin lesions, ulcers, or gangrene for longer than two weeks. The severity of the disease depends on the extent of arterial stenosis and the availability of collateral circulation. Treatment for CLTI aims to relieve ischaemic pain, heal ischaemic ulcers, prevent limb loss, improve quality of life, and prolong survival. CLTI due to occlusive disease in the infrapopliteal arterial circulation (below-knee circulation) can be treated via an endovascular technique by a balloon opening the narrowed vessel, so called angioplasty, with or without the additional deployment of a scaffold made of metal alloy or other material, so called stenting. Endovascular interventions in the infrapopliteal vasculature may improve symptoms in patients with CLTI by re-establishing in-line blood flow to the foot. Controversy remains as to whether a balloon should be used alone to open the vessel, or whether a stent should also be deployed.

Objectives

To determine the efficacy and safety of percutaneous transluminal angioplasty (PTA) alone versus PTA with stenting of infrapopliteal arterial lesions (anterior tibial artery, posterior tibial artery, fibular artery (formerly known as peroneal artery), and common tibioperoneal trunk) for patients with chronic limb-threatening ischaemia (CLTI).

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and AMED databases, as well as World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 25 June 2018. We applied no language restrictions.

Selection criteria

We planned to include randomised or quasi-randomised controlled trials comparing PTA versus PTA with a stent and including patients aged 18 years or over with CLTI. We defined CLTI as Fontaine stage III (ischaemic rest pain) and IV (ischaemic ulcers or gangrene) or consistent with Rutherford category 4 (ischaemic rest pain), 5 (minor tissue loss), and 6 (major tissue loss), with stenotic (> 50% luminal loss) or occluded infrapopliteal artery, including tibiofibular trunk, anterior tibial artery, posterior tibial artery, and fibular artery. We included all types of stents irrespective of design (e.g. bare-metal, drug-eluting, bio-absorbable).

Data collection and analysis

Two review authors (CC-TH and GNCK) independently selected suitable trials, assessed trial quality, and extracted data. An additional third review author (MLvD) assessed trial quality and, when necessary, acted as arbiter for study selection and data extraction. Outcomes included technical success of the procedure, procedural complications, patency, major amputation, and mortality. We assessed the quality of evidence using the GRADE approach.

Main results

We included in the review seven trials with 542 participants. One trial randomised limbs to undergo PTA alone or PTA with stent placement, and the remaining studies randomised participants. Five trials with 476 participants show that the technical success rate was greater in the stent group than in the angioplasty group (odds ratio (OR) 3.00, 95% confidence interval (CI) 1.14 to 7.93; 476 lesions; 5 studies; $I^2 = 23\%$). Meta-analysis of three eligible trials with 456 participants did not show a clear difference in short-term (within six months) patency between infrapopliteal arterial lesions treated with PTA and those treated with PTA and stenting (OR 0.88, 95% CI 0.37 to 2.11; 456 lesions; 3 studies; $I^2 = 77\%$). Results also did not show clear differences between treatment groups in procedure complication rate (OR 0.87, 95% CI 0.01 to 53.60; 360 participants; 5 studies; $I^2 = 85\%$), rate of major amputations at 12 months (OR 1.34, 95% CI 0.56 to 3.22; 306 participants; 4 studies; $I^2 = 0\%$), and rate of mortality at 12 months (OR 0.71, 95% CI 0.43 to 1.17; 497 participants; 6 studies; $I^2 = 0\%$). Heterogeneity between studies was high for the outcomes procedure complications and primary patency. The overall methodological quality of the trials included in this review was moderate due to selection and performance bias. Studies used different regimens for pretreatment and post-treatment antiplatelet/anticoagulant medication. We downgraded the certainty of the overall evidence for all outcomes by one level to moderate due to inconsistency of results across studies and large confidence intervals (small numbers of trials and participants).

Authors' conclusions

Trials show that the immediate technical success rate of restoring luminal patency is higher in the stent group but reveal no clear differences in short-term patency at six months between infrapopliteal arterial lesions treated with PTA with stenting versus those treated with PTA without stenting. We ascertained no clear differences between groups in periprocedural complications, major amputation, and mortality. However, use of different regimens for pretreatment and post-treatment antiplatelet/anticoagulant medication and the duration of its use within and between trials may have influenced the outcomes. Limited currently available data suggest that high-quality evidence is insufficient to show that PTA with stent insertion is superior to use of standard PTA alone without stenting for treatment of infrapopliteal arterial lesions. Further studies should standardise the use of antiplatelets/anticoagulants before and after the intervention to improve the comparability of the two treatments.

PLAIN LANGUAGE SUMMARY

Angioplasty versus stenting for below-knee arterial disease in people with chronic limb-threatening ischaemia

Background

Chronic limb-threatening ischaemia (CLTI) is a manifestation of peripheral arterial disease that occurs as chronic ischaemic rest pain or ischaemic skin lesions, ulcers, or gangrene with symptoms present for longer than two weeks. The symptoms are a result of impaired blood flow to the leg and the foot due to narrowing of the arteries by atherosclerosis. Atherosclerosis is a disease of the arteries caused by a buildup of plaque composed of fat, cholesterol, calcium, and other substances in the blood; over time, the plaque narrows the artery. Patients can have narrowing of the artery in the thigh or below the knee. This review focusses on a subgroup of patients with below-knee arterial disease (infrapopliteal arterial disease) who might benefit from an intervention that re-establishes blood flow by inserting and inflating a balloon to re-open the narrowed artery (percutaneous transluminal angioplasty). This can be performed with or without additional placement of a stent (a scaffold made of metal alloy or other material). The types of stents used in this procedure vary from a simple bare-metal stent to a stent coated with medication. However, it is not clear whether deploying stents after ballooning in narrowed below-knee arteries (infrapopliteal arteries) provides any additional benefit for the patient.

Study characteristics and key results

We identified seven trials with a combined total of 542 participants comparing percutaneous transluminal angioplasty (PTA) alone versus PTA with stent placement (current until June 2018). One trial randomised limbs to PTA alone or PTA with stent placement, and the remaining studies randomised participants. Full analysis of five trials shows that the technical success rate of re-opening the narrowed artery was higher in the stent group than in the PTA group. However, we noted no clear differences in patency (opened vessel remaining open) of the treated vessel at six months. The complication rate of the procedure, the number of major amputations at 12 months, and the number of deaths at 12 months also did not differ greatly between treatment groups.

Certainty of the evidence

The overall certainty of evidence provided by the trials included in this review was moderate. Trials differed in their methods. Two studies reported poorly on the methods used to generate random numbers and to allocate participants to different groups. All studies were unblinded. All included studies were rated as direct in their relevance to the review question. Overall, we downgraded the certainty of

evidence for all outcomes by one level to moderate due to inconsistency of results across studies and the small numbers of studies and participants.

Conclusion

PTA with stent placement is better than PTA alone for restoring vessel patency immediately; however we found no clear difference in short-term patency at six months between the two groups. Trials show no clear differences between groups in complications at or around the time of the procedure, major amputation, and death. Currently available data suggest that high-certainty evidence is insufficient to show that PTA with stent placement is superior to PTA alone for treatment of infrapopliteal arterial lesions. Further studies should standardise the use of blood-thinning drugs (antiplatelets/anticoagulants) before and after both interventions to improve the comparability of the two treatments.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. PTA compared with stent for infrapopliteal arterial lesions in chronic limb-threatening ischaemia

PTA compared with stent for infrapopliteal arterial lesions in chronic limb-threatening ischaemia

Patient or population: people with infrapopliteal arterial lesions in chronic limb-threatening ischaemia

Setting: hospital and outpatient follow-up

Intervention: stent

Comparison: PTA

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Comments
		PTA	Stent	Difference		
Technical success ITT No. of limbs: 476 (5 RCTs)	OR 3.00 (1.14 to 7.93)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		93.3%	97.6% (94.0 to 99.1)	4.4% more (0.8 more to 5.8 more)		
Technical success TA No. of limbs: 474 (5 RCTs)	OR 2.78 (1.04 to 7.41)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		93.7%	97.6% (93.9 to 99.1)	4.0% more (0.2 more to 5.4 more)		
Procedural complications ITT No. of participants: 360 (5 RCTs)	OR 0.87 (0.01 to 53.60)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		7.4%	6.5% (0.1 to 81.1)	0.9% fewer (7.3 fewer to 73.7 more)		
Procedural complications TA No. of participants: 359 (5 RCTs)	OR 0.84 (0.01 to 47.70)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		7.4%	6.3% (0.1 to 79.3)	1.1% fewer (7.4 fewer to 71.9 more)		
Primary patency < 6 months ITT No. of lesions: 456 (3 RCTs)	OR 0.88 (0.37 to 2.11)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		33.3%	30.6% (15.6 to 51.3)	2.8% fewer (17.7 fewer to 18 more)		
Primary patency < 6 months TA No. of lesions: 309 (3 RCTs)	OR 0.97 (0.32 to 3.00)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		45.9%	45.2%	0.8% fewer		

		(21.4 to 71.8)	(24.6 fewer to 25.9 more)	
Mortality TA	OR 0.70	Study population		⊕⊕⊕⊖
No. of participants: 487	(0.42 to 1.15)			MODERATE ^a
(6 RCTs)		19.3%	14.3% (9.1 to 21.5)	5% fewer (10.2 fewer to 2.3 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; ITT: intention-to-treat; OR: odds ratio; PTA: percutaneous transluminal angioplasty; RCT: randomised controlled trial; TA: treatment analysis.

GRADE Working Group grades of evidence.

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

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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

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

^aDowngraded by one level due to inconsistency of results across different studies and imprecision (small numbers and wide confidence intervals).

BACKGROUND

Description of the condition

Atherosclerosis is the most common cause of peripheral arterial disease (PAD) of the lower extremities. Chronic limb-threatening ischaemia (CLTI), also known as critical limb ischaemia (CLI), is a manifestation of PAD that refers to the presence of chronic ischaemic rest pain or ischaemic skin lesions, ulcers, or gangrene, with symptoms present for longer than two weeks (Hirsch 2006; Norgren 2007). The severity of the disease depends on the extent of arterial stenosis and the availability of collateral circulation. Objective tests that support the diagnosis of CLTI include ankle-brachial index (ABI), toe systolic pressure, and transcutaneous oxygen tension (Hirsch 2006; Norgren 2007). CLTI is listed as stage III and IV in the Fontaine classification and as categories 4, 5, and 6 in the Rutherford classification (Table 1). The incidence of CLTI is between 500 and 1000 new cases every year in a European or North American population of one million (Norgren 2007). The diagnosis of CLTI is associated with a poor prognosis for both amputation-free survival and overall survival (Norgren 2007). The prognosis of a patient with CLTI one year after diagnosis is death in 20%, and the major amputation rate varies from around 10% to 40% (Dormandy 1999). Observational studies of patients with CLTI who are not candidates for revascularisation suggest that only about half of these patients will be alive without a major amputation a year after the onset of CLTI (Holdsworth 1997; Norgren 2007); some of them may still have rest pain, gangrene, or ulcers. Approximately 25% will have died, and 25% will have required a major amputation (Norgren 2007; Wolfe 1986).

Description of the intervention

Treatment for CLTI aims to relieve ischaemic pain, heal ischaemic ulcers, prevent limb loss, improve quality of life, and prolong survival (Norgren 2007). Interventions for CLTI may include conservative therapy, revascularisation, or amputation. Progressive gangrene, rapidly enlarging wounds, and continuous ischaemic rest pain often mandate the need for intervention. Although infrainguinal bypass surgery remains the cornerstone of CLTI treatment, not all patients are suitable candidates. Patients may lack a conduit or target, may be non-ambulatory, or may have an extensive soft tissue infection overlying a bypass target. Most commonly, patients have medical comorbidities that make them unacceptable surgical candidates, given that the associated mortality rate is approximately 2% (Conte 2001).

How the intervention might work

Endovascular interventions in the infrapopliteal vasculature involve additional challenges of small-calibre vessels and more diffuse atherosclerotic disease. Potential obstacles include early thrombosis and late luminal loss due to intimal hyperplasia formation, as well as complications of acute vessel occlusion, embolism, and vessel perforation during the procedure. A meta-analysis of infrapopliteal percutaneous transluminal angioplasty (PTA) compared to popliteal-to-distal vein bypass surgery shows that the bypass graft had better primary and secondary patency, but that limb salvage was comparable for the two treatments, suggesting the potential of PTA for treating CLTI (Romiti 2008). Trials are providing increasing evidence to support a recommendation for morbid PTA patients with CLTI as a result of infrapopliteal artery lesions, provided that in-line flow to the foot can be re-

established (Norgren 2007). Controversy remains as to whether primary stenting of infrapopliteal arteries should be performed in patients with CLTI to improve outflow or to increase patency of proximal endovascular interventions or bypass surgery. Currently, stenting is often reserved as a bailout option in cases of flow-limiting dissection, residual stenosis, or elastic recoil.

Why it is important to do this review

Recent advancements in stent design and growing expertise of interventionalists have made it possible to treat complex lesions that were previously known to have inferior outcomes, including long-segment lesions, those with eccentric calcification, unstable lesions, and occlusions. A variety of novel stent designs are available, ranging from bare-metal, metal-absorbable, carbofilm-coated, bio-absorbable stents to drug-eluting stents. In particular, the drug-eluting stent has demonstrated efficacy for inhibiting neo-intimal hyperplasia in the coronary arteries, thereby reducing repeat revascularisation procedures, as compared with the standard bare-metal coronary stent (Morice 2002; Moses 2003; Schofer 2003). Whether the efficacy of coronary technology can be translated to the infrapopliteal vasculature remains to be determined. We are interested to learn whether PTA with primary stenting offers advantages in improving outcomes compared with PTA alone. If sufficient data are available, this systematic review will also compare different stent designs.

OBJECTIVES

To determine the efficacy and safety of percutaneous transluminal angioplasty (PTA) alone versus PTA with stenting of infrapopliteal arterial lesions (anterior tibial artery, posterior tibial artery, fibular artery (formerly known as peroneal artery), and common tibioperoneal trunk) for patients with chronic limb-threatening ischaemia (CLTI).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised or quasi-randomised controlled trials comparing PTA devices versus PTA with a stent. We made the distinction between PTA with the primary intention of stent placement versus PTA with stent placement as a secondary intention. Quasi-randomised controlled trials use a method of allocating participants that is not truly random, for example, odd or even hospital number or date of birth, or they use alternation techniques to allocate treatment groups.

Types of participants

We included adults (aged 18 years or older) with chronic limb-threatening ischaemia (CLTI). We defined CLTI as Fontaine stage III (ischaemic rest pain) and IV (ischaemic ulcers or gangrene) or consistent with Rutherford categories 4 (ischaemic rest pain), 5 (minor tissue loss), and 6 (major tissue loss), with stenotic (> 50% luminal loss) or occluded infrapopliteal artery, including tibiofibular trunk, anterior tibial artery, posterior tibial artery, and fibular artery. This review includes participants with type 1 and type 2 diabetes.

Types of interventions

- Intervention: PTA with stenting
- Comparison: PTA alone (with bailout stenting after suboptimal or complicated PTA)

We included all types of stents, irrespective of design (e.g. bare-metal, drug-eluting, bio-absorbable).

Atherectomy was not permitted in either group.

Types of outcome measures

Primary outcomes

- Technical success defined as absence of residual stenosis < 30% and absence of flow-limiting dissection on final catheter angiogram
- Procedural complications, including death as a direct result of the procedure, vascular injury requiring vascular repair by surgical or non-surgical techniques, arterial dissection, major bleeding, stroke, myocardial infarction (MI), renal failure, retroperitoneal bleed, embolisation resulting in partial or total arterial occlusion, unplanned tibial or pedal bypass, major infection, compartment syndrome, acute renal failure, access site infection, groin haematoma, pseudoaneurysm, and arteriovenous fistula
- Primary patency defined as < 50% loss of luminal diameter at the treated site (determined by computerised tomography (CT) angiogram, magnetic resonance (MR) angiogram, or Doppler ultrasound) without re-intervention in the interim
- Secondary patency reflecting the fate of initial and subsequent PTA procedures combined, and determined by CT/MR angiogram or Doppler ultrasound as either the absence of a haemodynamically significant re-stenosis or > 50% re-stenosis

Secondary outcomes

- Major amputation
- Mortality
- Clinical outcome of the treated ischaemic leg based on Rutherford or Fontaine classification
- Healed or persistent ulcers
- Ankle-brachial index (ABI) or toe-brachial index (TBI)
- Quality of life assessment

Search methods for identification of studies

We applied no language restrictions to the search.

Electronic searches

The Cochrane Vascular Information Specialist first searched the following databases for relevant trials on 22 March 2017.

- Cochrane Vascular Specialised Register.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), in the Cochrane Library, via the Cochrane Register of Studies (<http://www.metaxis.com/CRSWeb/Index.asp>).

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

The Cochrane Vascular Information Specialist also searched the following trials registries on 22 March 2017 for details of ongoing and unpublished studies, using the terms 'popliteal' and 'stent'.

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

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

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched from 1 January 2017 to 25 June 2018).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Register of Studies Online (CRSO; 2018, Issue 5).
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, and Ovid MEDLINE®) (searched from 1 January 2017 to 25 June 2018).
- Embase Ovid (searched from 1 January 2017 to 25 June 2018).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Ebsco (searched from 1 January 2017 to 25 June 2018).
- Allied and Complementary Medicine Database (AMED) Ovid (searched from 1 January 2017 to 25 June 2018).

The Information Specialist modelled search strategies for the listed databases on the search strategy designed for CENTRAL. When appropriate, review authors combined these strategies with adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials (RCTs) and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 6; [Lefevbre 2011](#)). We have provided search strategies for the major databases in [Appendix 2](#).

The Information Specialist also performed top-up searches of the following trials registries on 25 June 2018.

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

Searching other resources

We also searched citations within identified studies.

Data collection and analysis

We identified all randomised or quasi-randomised trials that compare PTA devices versus PTA with stenting of infrapopliteal arterial lesions (anterior tibial artery, posterior tibial artery, fibular artery, and common tibioperoneal trunk) for patients with chronic limb-threatening ischaemia. We assessed outcome measures as follows: outcomes concerning technical success, long-term occlusions, and adverse events. We assessed the primary outcome measures technical success and procedural complications within 30 days of the index intervention. We assessed the remaining outcome measures at intervals up to three months, up to six months, up to one year, and annually thereafter, when data were

available. If researchers reported different time points, we also considered these.

Selection of studies

Two review authors (CC-TH and GNCK) independently assessed studies identified for inclusion in this review using the criteria stated above. In the case of disagreement, a third review author (MLvD) acted as arbiter.

Data extraction and management

Two review authors (CC-TH and GNCK) independently extracted data from the studies included in this review using a standard data extraction form. In cases of disagreement, a third review author (MLvD) acted as arbiter.

Assessment of risk of bias in included studies

Three review authors (CC-TH, GNCK, and MLvD) assessed the risk of bias for each study as described in the *Cochrane Handbook for Systematic Reviews of Interventions* for each of the following domains (Higgins 2011).

- Random sequence generation.
- Allocation concealment.
- Blinding (of participants, personnel, and outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Other sources of bias.

We expressed judgements for each 'Risk of bias' domain as low, high, or unclear risk of bias. If researchers described and used appropriate and adequate methods, we assessed the risk as 'low'. We assessed the risk of bias as 'high' when available information described or suggested inadequate methods (e.g. non-random methods of allocation). An 'unclear' risk of bias indicates that study authors provided insufficient information.

Measures of treatment effect

When dealing with dichotomous outcome measures, we calculated a pooled estimate of the treatment effect for each outcome across trials using the odds ratio (OR) (the odds of an outcome among treatment-allocated participants to the corresponding odds among control participants) and the 95% confidence interval (CI). For continuous outcomes, we recorded either mean change from baseline for each group or mean post-intervention values and standard deviations for each group. When appropriate, we then calculated a pooled estimate of treatment effect by calculating the mean difference and the 95% CI.

Unit of analysis issues

We did not include cross-over trials in this review because researchers designated only a single treatment to each group. If treatment by percutaneous transluminal angioplasty (PTA) is successful, it is inappropriate to expose study participants to other forms of intervention (i.e. stenting). We considered cluster-randomised trials, but, as the unit of analysis is the patient, we planned to make adjustments for clustering in the final analysis according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

In case of randomisation at the level of the limb, we considered outcome data for each limb separately. In case of randomisation per patient, we adjusted for clustering when considering outcome data per limb. As per guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we conducted the analysis at the same level as the allocation, using a summary measurement from each cluster when individual participant data were available.

Dealing with missing data

To enable an intention-to-treat (ITT) analysis, we sought data on the number of participants with each outcome event by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or was otherwise excluded from treatment or follow-up. Review authors requested missing data from the original investigators, when necessary.

Assessment of heterogeneity

We assessed statistical heterogeneity in the meta-analysis using the I^2 statistic and explored reasons for heterogeneity (Higgins 2011). Thresholds for interpretation of I^2 can be misleading because the importance of inconsistency depends on several factors. We used the rough guide to interpretation as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered a level of heterogeneity of 50% or greater as significant.

We planned to assess clinical heterogeneity by conducting subgroup analyses to stratify available data (see [Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

We planned to investigate publication bias (referring to the phenomenon that studies with a positive outcome are more likely to be published) by using funnel plots if we identified 10 or more studies for inclusion in the review (Higgins 2011). We captured selective reporting of outcomes under [Assessment of risk of bias in included studies](#).

Data synthesis

We planned to use a fixed-effect model in our analysis. In cases of significant heterogeneity ($I^2 > 50%$), we pooled the data using a random-effects model (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses with participants stratified by the following factors, if we had included five or more studies in the meta-analysis.

- Age 18 to 65 years and 65 years or older.
- Gender.
- Type 1 or type 2 diabetes.
- Different stent designs: stents can be classified by the four parameters proposed by Nelken 2004 according to method of deployment, geometry, construction materials, and treated stents (coated stents and drug-eluting stents) (Table 2).
- Severity and extent of disease based on the TransAtlantic Inter-Society Consensus II classification.

Sensitivity analysis

We planned to undertake sensitivity analysis to explore the impact of risk of bias on meta-analysis of the overall estimate of effect by first entering only trials with adequate allocation concealment and blinding, and then gradually adding trials with high(er) risk of bias.

'Summary of findings'

We presented the main findings of the review concerning certainty of evidence, magnitude of effect of the interventions examined, and sum of available data for the outcomes technical success intention-to-treat analysis (ITT) and treatment analysis (TA), procedural complications ITT and TA, primary patency less than six months

ITT and TA, and mortality TA in a 'Summary of findings' table, according to the GRADE principles, as described by [Higgins 2011](#) and [Atkins 2004](#). We evaluated evidence based on risk of bias of the included studies, inconsistency, indirectness and imprecision of the data, and publication bias. We used GRADEprofiler (GRADEpro) software to assist in preparation of the 'Summary of findings' table (www.gradepro.org).

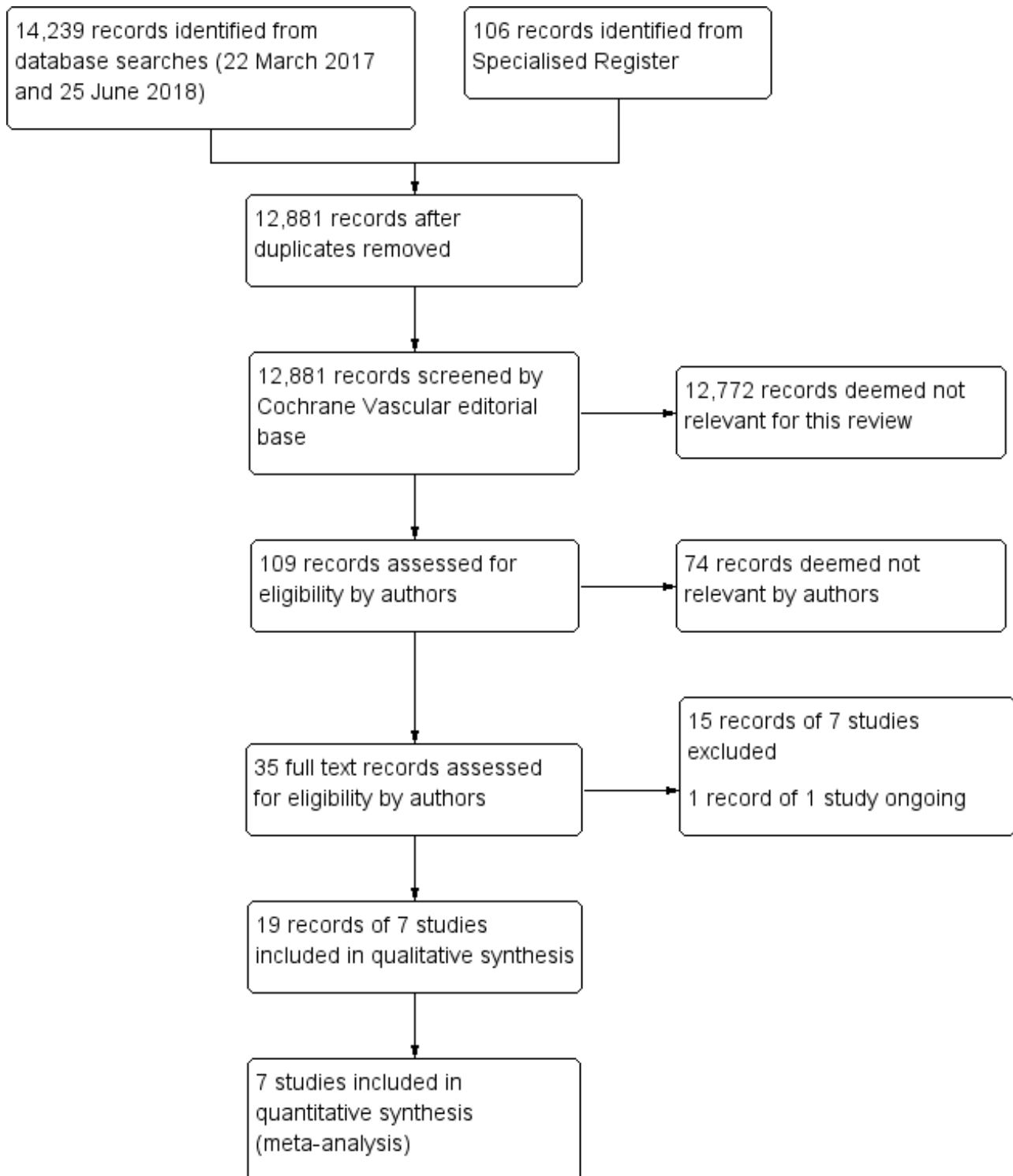
RESULTS

Description of studies

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram.



Included studies

Seven randomised controlled trials met the criteria for inclusion (Bosiers 2009; Brodmann 2011; Rand 2006; Rand 2011; Randon 2010; Spreen 2016; Tepe 2010). All studies were performed at tertiary hospitals or through multi-centre collaboration. The study population consisted of patients with symptomatic chronic limb ischaemia Fontaine stage III and IV (Rand 2006), Rutherford stage 4

to 5 (Bosiers 2009; Rand 2011), Rutherford stage 4 to 6 (Brodman 2011; Randon 2010; Spreen 2016), and Rutherford stage 5 to 6 (Tepe 2010). Rand 2011 randomised limbs for treatment, and all remaining trials randomised participants but reported event rates at the level of arterial lesions or limbs. Age, gender, and risk factors of participants in the included trials were comparable. The stent material used in the stenting group was variable between

studies but can be separated into drug-eluting stents - [Spreen 2016](#) and [Tepe 2010](#) - versus non-drug-eluting stents - [Bosiers 2009](#), [Brodmann 2011](#), [Rand 2006](#), [Rand 2011](#), and [Randon 2010](#). Types of non-drug-eluting stents used in these trials also varied in terms of stent design and material: absorbable metal stent ([Bosiers 2009](#)), silicon-carbide coating stent ([Brodmann 2011](#)), carbostent ([Rand 2006](#); [Rand 2011](#)), and self-expandable stent ([Randon 2010](#)). Also, use of dual antiplatelet therapy varied between control and experimental groups in individual trials and between trials. See [Characteristics of included studies](#) for further details.

Excluded studies

We excluded seven trials ([Bosiers 2012](#); [Bradbury 2010](#); [Rastan 2011](#); [Scheinert 2012](#); [Schulte 2015](#); [Siablis 2007](#); [Siablis 2014](#)).

[Bosiers 2012](#) and [Rastan 2011](#) compared two different stents. [Bradbury 2010](#) presented a description of severity and extent of disease using the Bollinger angiogram scoring method and the TransAtlantic Inter-Society Consensus II classification in the BASIL trial. [Scheinert 2012](#), [Schulte 2015](#), and [Siablis 2014](#)

included patients with symptomatic peripheral arterial disease and Rutherford stage 3 to 5 manifested in the infrapopliteal arterial territory, whereas in this review, we planned to include only patients with stage 4 disease and above. These studies did not provide data on the subgroup of patients with stage 4 or above disease; therefore we excluded them from the review. [Siablis 2007](#) performed stenting as a bailout procedure for suboptimal angioplasty, and outcomes reflected a comparison between two different types of stents, which is not within the scope of this review.

See [Characteristics of excluded studies](#).

Ongoing studies

We identified one ongoing study ([NCT01644487](#)).

See [Characteristics of ongoing studies](#).

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#).

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

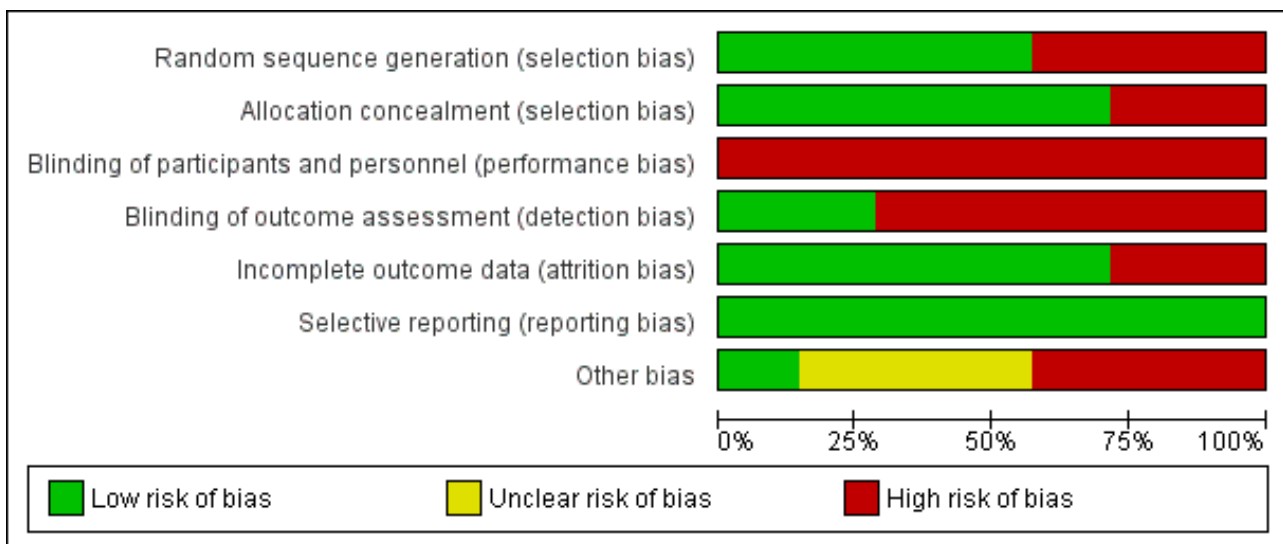


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bosiers 2009	+	+	-	-	+	+	-
Brodmann 2011	+	+	-	-	-	+	-
Rand 2006	-	+	-	+	+	+	?
Rand 2011	-	-	-	-	+	+	+
Randon 2010	+	+	-	+	+	+	?
Spreen 2016	+	+	-	-	+	+	?
Tepe 2010	-	-	-	-	-	+	-

Allocation

Four studies used computer-generated randomisation procedures (Bosiers 2009; Brodmann 2011; Randon 2010; Spreen 2016). The others did not describe the generation process, and we classified them as having high risk of selection bias (Rand 2006; Rand 2011; Tepe 2010).

Five studies described concealment of allocation as using sealed envelopes (Bosiers 2009; Brodmann 2011; Rand 2006; Randon 2010; Spreen 2016). Two studies did not describe the allocation concealment process; we therefore classified them as having high risk of bias for this criterion (Rand 2011; Tepe 2010).

Blinding

None of the included studies described blinding of participants or doctors performing the intervention. Although blinding of the treating doctor is not possible in this context, blinding of participants could have been considered. Given the potential impact on the overall effect estimate associated with non-blinding, even if this is not feasible in a given setting, we classified all studies as having high risk of bias in this domain.

Blinding of outcome assessment is feasible in the context of the studied interventions; however only two studies described blinding of the person assessing outcomes (Rand 2006; Randon 2010). We classified the remaining studies as having high risk of bias.

Incomplete outcome data

All included studies, except two (Brodmann 2011; Tepe 2010), accounted for all participants randomised in the study. We therefore classed these as having high risk of bias. Three studies performed ITT analysis (Bosiers 2009; Rand 2011; Spreen 2016), one study performed survival analysis (Rand 2006), and one study reported no losses to follow-up (Randon 2010).

Selective reporting

All included studies reported on the outcomes they intended to measure; we therefore classed them as having low risk of reporting bias.

Other potential sources of bias

Conflicts of interest and funding

Bosiers 2009 was funded totally by BIOTRONIK AG, which was responsible for administration and monitoring of the study. Therefore, we classed this study as having high risk in this domain. Rand 2011 also received funding from the manufacturer of stents, but study authors described that they were completely in control of data analysis and publication; therefore, we classified this study as having low risk in this domain. Randon 2010 does not mention any support or conflict of interest; we therefore classified it as having unclear risk. Tepe 2010 mentioned that the study was supported by Eli Lilly but did not explicitly mention the independence of the research team; we therefore classified this study as having high risk.

Comparability of participants in groups

In Brodmann 2011, the two intervention groups were not comparable. This study was originally conceived as a multi-centre trial, but it included participants from only one centre. Brodmann 2011 reported an imbalance in cardiovascular risk factors, with a higher percentage of baseline cardiovascular risk factors in the stent group than in the PTA group. This imbalance could reflect high risk of bias. Rand 2006 described administration of clopidogrel only to participants who received stents - not to participants who underwent PTA alone. Study authors stated: "We also observed a higher incidence of PTAs than stent applications per patient. This might be due to a certain degree of investigator bias, as potentially one balloon can be used for several lesions in contrast to the necessity of one stent per lesion." We therefore judged Rand 2006 to be at unclear risk of other bias.

Effects of interventions

See: [Summary of findings for the main comparison PTA compared with stent for infrapopliteal arterial lesions in chronic limb-threatening ischaemia](#)

Primary outcomes

Technical success

Technical success: ITT

The event rate for technical success is defined by success of treated infrapopliteal arterial lesions, with the exception of two trials (Brodmann 2011; Spreen 2016), which counted limbs - Spreen 2016 - and numbers of participants - Brodmann 2011 - respectively. Although Spreen 2016 provided data on participants, limbs, and lesions, Spreen 2016 excluded several participants post randomisation before they received the allocated treatment. Therefore, we report technical success in the ITT analysis with the limb as the unit of analysis. We included in the meta-analysis five trials with a total of 476 lesions (Bosiers 2009; Rand 2006; Rand 2011; Randon 2010; Tepe 2010). The primary success rate was higher among stented lesions (odds ratio (OR) 3.00, 95% confidence interval (CI) 1.14 to 7.93; $P = 0.03$; 5 studies; $I^2 = 23%$; moderate-certainty evidence). Research results are heavily weighted by one trial in which seven PTA without stenting group participants (7/57) with 11 lesions (11/75) crossed over to the PTA with stenting arm due to dissection in at least one of the lesions and, in the case of one participant, due to significant residual stenosis (Bosiers 2009). See [Analysis 1.1](#).

In Brodmann 2011, the procedure was successful in 94% (31/33) of participants treated with PTA alone and in 100% (21/21) of those treated with PTA with stents. Two participants in the PTA alone group encountered extended dissections in the treated vessels requiring secondary stent placement.

Spreen 2016 provided data on participants, limbs, and numbers of lesions; however investigators excluded several participants from the study post randomisation. Therefore, we report technical success in the ITT analysis with limb as the unit of analysis. Spreen 2016 randomised 69 limbs to the PTA alone group and 75 limbs to the PTA with stent group. This study excluded three participants/three limbs post randomisation to the PTA alone group and one participant/one limb post randomisation to the PTA with stent group. Spreen 2016 treated 14 limbs in the PTA alone group with a bailout stent. Seven participants in the PTA alone group had > 50% stenosis or occlusion, and six in the stent group had > 50% stenosis or occlusion. Hence the success rate was 65% (45/69) in the PTA alone group and 91% (68/75) in the PTA with stent group.

Technical success: TA

The event rate for technical success is defined by success of treated infrapopliteal arterial lesions, with the exception of two trials (Brodmann 2011; Spreen 2016), which counted limbs - Spreen 2016 - and numbers of participants - Brodmann 2011 - respectively. Although Spreen 2016 provided data on participants, limbs, and lesions, study authors did not specify the number of lesions in the PTA alone group requiring bailout stenting. Therefore, we report technical success in the treatment analysis with the limb as the unit of analysis.

We included five trials with a total of 474 lesions reporting this outcome ([Bosiers 2009](#); [Rand 2006](#); [Rand 2011](#); [Randon 2010](#); [Tepe 2010](#)). The primary success rate was higher among stented lesions (OR 2.78, 95% CI 1.04 to 7.41; $P = 0.04$; 5 studies; $I^2 = 15\%$; moderate-certainty evidence). See [Analysis 1.2](#).

[Brodmann 2011](#) reported a technical success rate of 94% (31/33) in the PTA alone group and 100% (21/21) in the PTA with stenting group. Two participants from the PTA alone group crossed over to the stent group due to arterial dissection of the treated vessels requiring stent placement.

[Spreen 2016](#) randomised 69 limbs to the PTA alone group and 75 limbs to the PTA with stent group. Investigators excluded three participants/three limbs post randomisation to the PTA alone group and one participant/one limb post randomisation to the PTA with stent group. They treated 14 limbs in the PTA group with a bailout stent. Seven participants in the PTA alone group had > 50% stenosis or occlusion, and six in the PTA plus stent group had > 50% stenosis or occlusion. Hence the success rate was 65% (45/69) in the PTA alone group and 90% (68/75) in the PTA with stent group.

Procedural complications

Procedural complications: ITT

Procedural complications are reported per individual participant. We analysed five trials with 360 participants ([Bosiers 2009](#); [Brodmann 2011](#); [Rand 2011](#); [Randon 2010](#); [Tepe 2010](#)). [Bosiers 2009](#), [Rand 2011](#), and [Tepe 2010](#) reported no procedural complications and found no clear differences between participants in PTA alone and PTA with stenting groups (OR 0.87, 95% CI 0.01 to 53.60; 360 participants; 5 studies; $I^2 = 85\%$; moderate-certainty evidence). See [Analysis 1.3](#).

[Spreen 2016](#) reported procedural complications per limb: 22% (15/69 limbs) in the PTA group and 27% (20/75 limbs) in the stenting group. These complications included haematoma, material dysfunction, acute thrombosis, distal embolus, and pseudoaneurysm. Serious adverse events occurred in 22% (15/69 limbs) in the PTA alone group and in 20% (15/75 limbs) in the PTA with stenting group. These included gastrointestinal bleeding, ischaemic cerebral event and cerebral haemorrhage, pneumonia, cardiac disease, renal failure, and non-CLTI-related infection. [Spreen 2016](#) reported that overall, the incidence of periprocedural complications and serious adverse events did not differ significantly between the two groups.

[Rand 2006](#) reported one puncture site haematoma and one case of post-procedural sepsis but did not specify in which group these complications occurred.

Procedural complications: TA

Procedural complications are reported per individual participant. We analysed five trials with 359 participants ([Bosiers 2009](#); [Brodmann 2011](#); [Rand 2011](#); [Randon 2010](#); [Tepe 2010](#)). We found no clear difference between participants in PTA alone and PTA with stenting groups (OR 0.84, 95% CI 0.01 to 47.70; moderate-certainty evidence). Heterogeneity was significant ($I^2 = 84\%$). [Bosiers 2009](#), [Rand 2011](#), and [Tepe 2010](#) reported no cases of procedural complications. See [Analysis 1.4](#).

[Spreen 2016](#) reported procedural complications per limb: 23% (15/66 limbs) in the PTA group and 27% (20/74 limbs) in the stenting

group. Serious adverse events occurred in 23% (15/66 limbs) in the PTA group and in 20% (15/74 limbs) in the stenting group. We have reported details of these complications and serious adverse events in the section above.

Primary patency at six months

Primary patency at six months: ITT

We included three trials with a total of 456 lesions ([Bosiers 2009](#); [Rand 2006](#); [Spreen 2016](#)). We found no clear differences between PTA alone and PTA with stenting groups (OR 0.88, 95% CI 0.37 to 2.11; moderate-certainty evidence). Heterogeneity was significant ($I^2 = 77\%$). See [Analysis 1.5](#).

[Randon 2010](#) reported patency outcomes with the participant as the unit of measurement, and we did not include this study in the meta-analysis. Cumulative primary and secondary patency rates were 76% and 85% at six months for the PTA alone group, and 80% and 91% at six months for the PTA with stenting group. [Randon 2010](#) reported no significant differences in primary or secondary patency between the two treatment groups.

Primary patency at six months: TA

We included three trials with a total of 309 lesions ([Bosiers 2009](#); [Rand 2006](#); [Spreen 2016](#)). We found no clear differences between participants in PTA alone and PTA with stenting groups (OR 0.97, 95% CI 0.32 to 3.00; moderate-certainty evidence). Heterogeneity was significant ($I^2 = 82\%$). See [Analysis 1.6](#).

[Brodmann 2011](#) reported primary patency per participant at six months, with 60.7% patency in the PTA alone group and 52.6% in the PTA with stent group.

Primary patency at 12 months: ITT

Most trials did not report data on patency of treated lesions beyond six months.

[Brodmann 2011](#) reported primary patency per participant at 12 months, with 48.1% patency in the PTA alone group and 35.3% in the PTA with stent group.

[Rand 2011](#) reported patency results at nine months: the minimal lumen diameter after nine months was not significantly different between the PTA alone group and the PTA with stent group. The percentage of residual diameter stenosis also was not significantly different: 43% in the PTA alone group versus 39% in the PTA with stent group. In addition, binary re-stenosis for a 50% and a 70% threshold was not significantly different: 34.6% in the PTA alone group versus 23.8% in the PTA with stent group, and 15.4% in the PTA alone group versus 9.5% in the PTA with stent group, respectively.

[Randon 2010](#) defined primary patency as clinical primary patency: this means freedom from re-stenosis; occlusion with recurrence of ischaemic rest pain or recurrence of ulceration, leading to redo angioplasty; bypass surgery; or major amputation. [Randon 2010](#) defined secondary patency as freedom from redo angioplasty until recurrence of symptoms. [Randon 2010](#) reported that cumulative primary and secondary patency rates for the PTA alone group were 66% and 79.5% at 12 months, and primary and secondary patency rates for the PTA with stenting group were 56% and 64% at 12 months. Results show no clear differences in primary or secondary patency between the two groups.

Secondary patency

Two trials reported secondary patency after repeat angioplasty for re-stenosis or recurrence of symptoms (Randon 2010; Brodmann 2011). In Randon 2010, cumulative secondary patency rates for the PTA alone group were 85% at six months and 79.5% at 12 months. Secondary patency rates for the PTA with stenting group were 91% at six months and 64% at 12 months. Results show no clear differences in primary or secondary patency between the two treatment groups. Brodmann 2011 also reported on secondary patency, with no reported differences between PTA alone and PTA with stenting groups at six months, but at 12 months, patency rates were 70.4% in the PTA alone group and 52.9% in the PTA with stent group.

Secondary outcomes

Major amputations < 12 months after the index intervention

Major amputations < 12 months after the index intervention: ITT

We analysed four trials with 306 participants (Bosiers 2009; Rand 2011; Randon 2010; Tepe 2010); we found no clear differences in major amputations between PTA alone and PTA with stenting groups (OR 1.34, 95% CI 0.56 to 3.22).

Spreen 2016 reported a major amputation rate of 38% (13/69 limbs) in the PTA alone group and 20% (8/75 limbs) in the PTA with stenting group. Brodmann 2011 reported minor amputations only. Rand 2006 reported one major amputation in a participant undergoing stent application.

Major amputations < 12 months after the index intervention: TA

We analysed four trials with 252 participants (Bosiers 2009; Rand 2011; Randon 2010; Tepe 2010); we found no clear differences in major amputations between PTA alone and PTA with stenting groups (OR 1.41, 95% CI 0.59 to 3.40).

Mortality within 12 months after the index intervention

Mortality within 12 months after the index intervention: ITT

We analysed six trials with 497 participants (Bosiers 2009; Brodmann 2011; Rand 2011; Randon 2010; Spreen 2016; Tepe 2010); we noted no clear differences in mortality between PTA alone and PTA with stenting groups (OR 0.71, 95% CI 0.43 to 1.17; moderate-certainty evidence).

Rand 2006 reported one death but did not specify the treatment group in which this occurred.

Mortality within 12 months after the index intervention: TA

We analysed six trials with 487 participants (Bosiers 2009; Brodmann 2011; Rand 2011; Randon 2010; Spreen 2016; Tepe 2010); we found no clear differences between participants in PTA alone and PTA with stenting groups (OR 0.7, 95% CI 0.42 to 1.15).

Clinical outcome of the treated ischaemic leg using the Rutherford or Fontaine classification at < six months and at < 12 months

Brodmann 2011 reported improvement by at least one Rutherford category in a total of 33 (75.0%) participants at 12 months: 22 (81.5%) in the PTA alone group and 11 (64.7%) in the PTA with stent group (P value as reported by study authors = NS).

Bosiers 2009 reported six-month clinical status of participants by the evolution of the Rutherford category. Investigators reported improvement by at least one Rutherford category in 65.9% (27/41) in the PTA alone group and in 69.2% (27/39) in the PTA with stent group with no statistically significant differences between groups by either ITT or treatment analysis.

In Rand 2011, clinical results based on the American Heart Association Clinical Improvement Score show clinical improvement at three months in 20 of 32 participants (62.5%) in the PTA alone group. Twelve of the 32 participants (37.5%) had clinical worsening or remained stable. The PTA with stent group shows clinical improvement in 27 of 33 participants (81.8%) and clinically worsening or stable disease in six participants (18.2%). At nine months' follow-up, the PTA alone group included 24 participants and the PTA with stent group included 19 participants. At nine months, 14 of 24 participants (58.3%) in the PTA alone group show improved clinical status, and the remaining 10 participants (41.7%) show clinical worsening or remain stable. The PTA with stent group shows nine of 19 participants (47.4%) with clinical improvement and 10 of 19 participants (52.6%) with clinically worsening or stable disease.

The remaining included studies did not report on the clinical outcome of the treated ischaemic leg using the Rutherford or Fontaine classification at < six months and at < 12 months.

Healed or persistent ulcers at < six months' and at < 12 months' follow-up

Brodmann 2011 reported that complete ulcer healing at 12 months was evident in 21 (63.6%) participants: 16 (80.0%) treated with PTA alone and five (38.5%) treated with PTA with stenting became ulcer free (P as reported by study authors = 0.006).

Tepe 2010 described general reduction in mean ulcer size (cm²) in both PTA alone and PTA with stent groups without performing statistical analysis. In the PTA alone group (PTA with or without abciximab), mean ulcer sizes were 8.4 cm² and 15 cm², respectively, at baseline; 2.9 cm² and 13 cm² at two months; and 0.63 cm² and 1 cm² at nine months. In the PTA with stent group (bare-metal stent and drug-eluting stent), mean ulcer sizes were 48.7 cm² and 11.6 cm², respectively, at baseline; 39.1 cm² and 5.3 cm² at two months; and 32.1 cm² and 2.9 cm² at nine months.

The remaining included studies did not report on healed or persistent ulcers at < six months' and < 12 months' follow-up.

Ankle-brachial index (ABI) or toe-brachial index (TBI) at < six months' and < 12 months' follow-up

Rand 2011 reported that ABIs at three months were 0.7 ± 0.3 for the PTA alone group and 0.9 ± 0.1 for the PTA with stent group (no significant difference). At nine months, they were 0.8 ± 0.3 for the PTA alone group and 0.8 ± 0.1 for the PTA with stent group (no significant differences).

Spreen 2016 reported significant improvement in mean ABIs and toe pressure after six months and after 12 months among survivors of both treatment groups compared with baseline (P ≤ 0.005). Spreen 2016 also reported that these improvements were comparable in both treatment groups.

[Bosiers 2009](#) reported that ABIs at baseline were 0.7 ± 0.3 for the PTA alone group and 0.8 ± 0.5 for the PTA with stent group. At 24 hours after endovascular treatment, ABIs increased significantly to 1.0 ± 0.2 in the PTA alone group and 1.0 ± 0.4 in the PTA with stent group. At six months, they were 0.9 ± 0.3 for the PTA alone group and 0.9 ± 0.4 for the PTA with stent group (no significant differences).

Quality of life assessment

Included trials did not perform this assessment.

Long-term follow-up

Very limited follow-up data are available beyond the 12-month period. [Spreen 2017](#) published long-term clinical outcomes of the PADI trial ([Spreen 2016](#)). Unfortunately, [Spreen 2017](#) did not separate out participants who had only PTA and those who had PTA with bailout bare-metal stent. Nevertheless, limited available results show higher primary patency rates after the drug-eluting stent compared with PTA with or without a bailout bare-metal stent at one, three, and four years' follow-up. The five-year major amputation rate was lower in the drug-eluting stent group than in the PTA with or without bailout bare-metal stent group (19.3% vs 34.0%; $P = 0.091$). Overall survival rates were comparable ([Spreen 2017](#)).

Subgroup analyses, sensitivity analyses, and assessment of publication bias

We did not perform subgroup analyses, as included trials did not provide data specific for age, gender, diabetes status, or TransAtlantic Inter-Society Consensus II classification. However, we did perform sensitivity analysis by removing studies deemed at high risk of bias, such as [Rand 2011](#) and [Tepe 2010](#). However, this did not change the conclusion for relevant outcomes.

We did not perform subgroup analysis for different types of stents. Although stents used in the trial can be broadly separated into drug-eluting stents - [Spreen 2016](#) and [Tepe 2010](#) - and non-drug-eluting stents - [Bosiers 2009](#), [Brodmann 2011](#), [Rand 2006](#), [Rand 2011](#), and [Randon 2010](#) - the types of non-drug-eluting stents used vary significantly in material and design, and included absorbable metal stents ([Bosiers 2009](#)), silicon-carbide coating stents ([Brodmann 2011](#)), carbostents ([Rand 2006](#); [Rand 2011](#)), and self-expandable stents ([Randon 2010](#)). Pooling these varied types of non-drug-eluting stents into a single group was not considered appropriate. Last, the small number of participants included in these trials limits the ability of researchers to detect subgroup effects.

DISCUSSION

Summary of main results

Our review shows that technical success is significantly greater in the percutaneous transluminal angioplasty (PTA) with stent group than in the PTA alone group. This may be due in part to the use of stenting as a bailout solution to arterial dissection, which is a complication of PTA, as demonstrated in the heavily weighted [Bosiers 2012](#) trial. Overall, we found no clear differences in complication rates between PTA with stent and PTA alone groups, but heterogeneity between studies was significant. Similarly, we observed no clear differences in short-term patency at six months between the two treatment groups. Very few trials reported longer-term follow-up (up to 12 months), and only [Brodmann 2011](#), [Rand 2011](#), and [Randon 2010](#) provide data on patency at 12 months.

These studies do not show a clear difference in patency between the two treatment groups. Rates of major amputation and mortality were not significantly different between the two treatment groups. We performed sensitivity analysis by removing studies at high risk of bias, such as [Rand 2011](#) and [Tepe 2010](#), but this analysis did not alter our overall conclusions.

Overall completeness and applicability of evidence

Most of the trials included in this review provided only short-term follow-up of up to six months. Only three trials provided follow-up data on long-term patency extending to 12 months. Although long-term durability of the stent and long-term patency of the treated lesion remain unknown due to the inherent high morbidity and mortality of cardiovascular risk factors associated with chronic limb-threatening ischaemia, the benefit of achieving short-term vessel patency may still be clinically relevant. Last, trials show inconsistency in the use of periprocedural anticoagulation and the use of oral anticoagulation or antiplatelet medications post treatment. The PTA with stenting group was more likely to receive antiplatelet medications post treatment, as clinicians have the added burden of preventing stent re-stenosis in these patients compared to those treated with PTA alone. These confounding variables could influence the outcome of patency.

Not all studies reported on all outcomes, and pooled analysis was not always possible, for example, for secondary patency.

Quality of the evidence

The overall methodological quality of the included studies was moderate. Studies generally reported poorly on methods used to allocate participants to different study groups. All studies were unblinded, but this can be justified by the nature of the intervention, as it is not possible to ensure blinding of doctors performing the angioplasty or placing the stent. Theoretically, it could be possible to blind participants or outcome assessors to the intervention performed; however, none of the included studies described blinding of participants and/or outcome assessors. Most trials poorly reported conflicts of interest and details of financial support.

Outcomes of the included studies are relevant and are generalisable to the clinical population, hence we found no serious indirectness. We considered moderate to severe heterogeneity as inconsistency of results, and we found serious inconsistency for outcomes concerning technical success rate, complications, and six-month patency. We therefore downgraded the certainty of evidence by one level to moderate for all outcomes due to inconsistency of results across different studies and imprecision (small numbers and wide confidence intervals).

A major confounder is inconsistency in the use of anticoagulation and antiplatelet medications between PTA alone and PTA with stenting groups, as well as between trials. Established evidence suggests that patients with peripheral vascular disease treated by angioplasty or stenting would benefit from receiving aspirin at a dose of 50 mg to 300 mg daily, started before angioplasty or stenting and continued for at least two years or given lifelong ([Robertson 2012](#)). On the other hand, proven benefit of clopidogrel or dual antiplatelet or anticoagulant use in patients undergoing peripheral vascular interventions has not been definitively established.

Last, only [Rand 2011](#) randomised limbs; all other included trials randomised at the participant level but reported outcomes at the level of arterial lesions or limbs. Such trials do not adjust for the non-independence between arterial lesions within the same patient (e.g. by applying cluster analysis). In our meta-analysis, we did not use generalised estimated equations, as individual participant data were not available to us. Therefore, we may have overestimated the estimated effects of treatments. However, given that the number of participants with bilateral lesions is small, we assume that the unit of analysis error does not have a major impact on the overall result. Please refer to [Characteristics of included studies](#) for details on bilateral lesions.

Potential biases in the review process

The Cochrane Vascular Information Specialist searched multiple databases and trials registers to identify trials for this review. The review authors also independently searched references lists in other studies and reviews, and it is likely that we have included in this review all major trials on this subject matter. However, it is possible that despite extensive searches in multiple databases, we may have missed relevant studies for inclusion.

Two review authors independently performed all data selection and extraction with consultation from a third review author to ensure completeness and to exclude bias and error.

Different trials reported outcomes at different time intervals, and to allow meta-analysis, we have pooled data from various time frames within the prespecified periods of six months and 12 months. For example, researchers assessed primary vessel patency at two, three, six, nine, and 12 months. We pooled the data into two separate time frames - six months and 12 months. Similarly, we assessed cumulative mortality and major amputation for all trials at 12 months. This may have created bias in favour of studies reporting outcomes at earlier time points, as it is possible that adverse or unintended outcomes might have occurred later and would not have been captured.

Agreements and disagreements with other studies or reviews

We identified an existing systematic review and meta-analysis that compared the role of drug-eluting stents versus angioplasty or bare-metal stents in infrapopliteal arterial disease ([Fusaro 2013](#)). This review identified five trials, but four of these trials compared drug-eluting stents versus bare-metal stents, and this comparison is not relevant to the objective of our review. The only trial that is relevant to our objective is [Tepe 2010](#), which we included in our analysis.

The [Yang 2014](#) review included 16 studies, nine of which were retrospective studies, four prospective non-randomised studies, and three randomised controlled trials (RCTs). Two of the included RCTs are not relevant to our topic, as investigators compared drug-eluting stents versus bare-metal stents ([Bosiers 2012](#); [Rastan 2011](#)). We identified one of the included RCTs through our search, but we excluded it from our analysis ([Scheinert 2012](#)). This trial included Rutherford stage 3 to 5 infrapopliteal arterial disease without providing data for stages 2, 4, and 5 separately. In our review, we planned to include only patients with stage 4 disease and above.

Another systematic review and meta-analysis shows close resemblance to our review ([Wu 2014](#)). [Wu 2014](#) included six

prospective RCTs ([Bosiers 2009](#); [Brodmann 2011](#); [Rand 2006](#); [Rand 2011](#); [Randon 2010](#); [Scheinert 2012](#)). Our review includes these trials and has added two other trials ([Spreen 2016](#); [Tepe 2010](#)), although we excluded [Scheinert 2012](#) for the reasons mentioned above. Outcomes assessed in the [Wu 2014](#) review include immediate technical success, primary and secondary patency, limb salvage, and patient survival (assessed at six-month and 12-month intervals). However, [Wu 2014](#) did not include procedural complications in its analysis and found that immediate technical success was greater in the PTA with stent group (96.2%) than in the PTA alone group (93.3%), but this finding was not statistically significant (odds ratio (OR) 0.59, 95% confidence interval (CI) 0.24 to 1.47). In contrast, we found a difference in the immediate technical success rate. The difference in conclusions between these reviews is likely to be influenced by differences among included trials. In relation to patency at six months, [Wu 2014](#) analysed four studies and showed no significant differences between the PTA alone group of 73.4% and the PTA with stent group of 75.9% (OR 0.94, 95% CI 0.48 to 1.8) ([Bosiers 2009](#); [Rand 2006](#); [Rand 2011](#); [Randon 2010](#)). We analysed [Bosiers 2009](#), [Rand 2006](#), and [Spreen 2016](#) and revealed a similar result of no clear differences in primary patency at six months. In our review, we analysed cumulative mortality at 12 months, whereas [Wu 2014](#) analysed patient survival at six months and 12 months; both reviews found no clear differences between the two treatment groups.

AUTHORS' CONCLUSIONS

Implications for practice

Our meta-analysis of five trials (four trials with estimable data) including participants with chronic limb-threatening ischaemia (CLTI) shows a greater technical success rate in the PTA with stent group than in the PTA alone group but no clear differences in short-term patency (at six months) between infrapopliteal arterial lesions treated with PTA alone and those treated with PTA in combination with stenting. We found no clear differences in complication rates between PTA and PTA with stent groups. Overall, the 12-month major amputation rate and the mortality rate are not clearly different between PTA and PTA with stent groups. However, the use of different regimens for pretreatment and post-treatment antiplatelet medication, such as clopidogrel, and the duration of its use within and between trials may have influenced the outcome. Based on limited currently available data and on the results of this meta-analysis, high-quality evidence is insufficient to suggest that stent insertion is superior to standard PTA alone without stenting for treatment of infrapopliteal arterial lesions. Stent insertion could be reserved for use as a 'bailout' procedure when arterial dissection is encountered.

Implications for research

More consistent trial reporting is needed on both randomisation of limbs as the unit of analysis and use of antiplatelet and anticoagulant treatment before and after the intervention. Future trials should use limbs as the unit of allocation and reporting, and use of antiplatelet and anticoagulant treatment before and after the intervention should be standardised in upcoming trials. Future trials also must implement standardised reporting of outcomes and time intervals for re-assessment; this will allow better comparison of data between trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bosiers 2009

Methods	<p>Country: Absorbable Metal Stents (AMS) INSIGHT investigators (13 clinical sites in Austria, Belgium, Germany, and The Netherlands)</p> <p>Setting: multi-centre tertiary hospital</p> <p>Study design: RCT</p> <p>Level of randomisation: participant</p>
Participants	<p>No. of participants randomised: 57 were randomised to the percutaneous transluminal angioplasty (PTA) group, and 60 to the AMS group. In total, 149 lesions were treated in 117 participants, which resulted in a total of 74 lesions in the AMS arm and 75 lesions in the PTA control arm</p> <p>Exclusions post randomisation: none</p> <p>Shifted to another treatment arm: if stenosis persisted to be > 50% or a flow-limiting dissection occurred, the participant underwent implantation of the AMS study stent and ended up in the cross-over group. Seven PTA group participants (7/57) with 11 lesions (11/75) crossed over to the other treatment arm due to dissections in at least 1 of the lesions and, in the case of 1 participant, due to significant residual stenosis</p> <p>Number of participants evaluated: 7 PTA group participants (7/57) with 11 lesions (11/75) crossed over to the other treatment arm due to dissection in at least 1 of the lesions and, in the case of 1 patient, due to significant residual stenosis. These participants were included in the PTA + AMS group, which was not considered in the on-treatment data analysis performed by study authors. One participant randomised for stenting (1/60) with a double lesion (2/74) underwent implantation of a non-study stent (self-expanding) due to severe tortuosity of the iliac artery. Therefore, this participant was not considered in the on-treatment analysis performed by study authors. The final on-treatment cohort consisted of 50 participants with 64 lesions treated with PTA only and 59 participants with 72 lesions who underwent implantation of the study stent. Therefore, according to the study authors, ITT technical success, which was based on visual assessment, was achieved in 60 of 60 participants in the AMS group (100%), and in 55 of 57 participants in the PTA group (96.4%). For one PTA lesion, data on technical success were not provided by the investigator, and this participant's treatment was considered a non-success</p> <p>Age (mean), years: PTA only 73.1, AMS 74.7</p> <p>Gender: PTA group: 41 male/16 female, AMS stent group: 31 male/29 female</p> <p>Inclusion criteria: stenotic (> 50%) or occlusive atherosclerotic disease of the infrapopliteal arteries, length of lesion < 15 mm (< 1 stent length), reference vessel diameter 3.0 mm to 3.5 mm, maximum of 2 lesions in 1 infrapopliteal vessel treated in the study or in 2 vessels of 2 different legs, symptomatic critical limb ischaemia (Rutherford 4 and 5), patient ≥ 50 years of age, life expectancy > 6 months, no child-bearing potential or negative serum pregnancy test within 7 days of the index procedure, participant willing and able to return at appropriate follow-up times for the duration of the study, patient provision of written patient informed consent that is approved by the ethics committee</p> <p>Exclusion criteria: patient refusal of treatment; reference segment diameter not suitable for available stent design; length of lesion requiring more than 1 stent implantation; previously implanted stent(s) or PTA at the same lesion site; lesion lying within or adjacent to an aneurysm; inflow-limiting arterial lesions left untreated; known allergy to heparin, aspirin, or other anticoagulant/antiplatelet therapies or bleeding diatheses, or unable or unwilling to tolerate such therapies; taking phenprocoumon (Marcumar); history of prior life-threatening contrast medium reaction; currently enrolled in another investigational device or drug trial; currently breastfeeding, pregnant, or intending to become pregnant; mentally ill or retarded; liable for military or civilian service</p>
Interventions	<p>AMS stenting group:</p> <ul style="list-style-type: none"> Target lesion was pre-dilated with the Pleon Explorer balloon mandatory in this study. After dilatation, the stenosed area was treated with 1 AMS implant. Post-dilatation was allowed at the discretion of

Bosiers 2009 (Continued)

the physician, for cases where angiographic control revealed suboptimal apposition of the AMS to the vessel wall or flow-limiting residual stenosis

PTA group (control):

- Pleon Explorer balloon

Medication:

- Clopidogrel saturation was obtained before the procedure
- Heparin was administered during the procedure according to standard practice
- Post-procedure antithrombotic regimen was that used according to the protocol (clopidogrel 75 mg daily for 1 month and aspirin 75 to 300 mg daily lifelong)

Outcomes

Primary outcomes:

- Absence of clinical complications at 1 month post procedure. Complications were defined as major amputations or any cause of death. Major amputations were defined as amputations at or above the ankle
- 6-month angiographic patency rate after PTA alone or PTA followed by AMS implantation in patients with stenotic or occlusive atherosclerotic disease of the infrapopliteal arteries. Patency was defined as the absence of a haemodynamically significant re-stenosis (50%) documented by digital subtraction angiography and confirmed by core-lab QVA

Secondary outcomes:

- Immediate angiographic technical success, which was defined in both therapy groups as 30% final residual diameter stenosis of the target segment based on visual assessment of the planned treatment area
- Late lumen loss (LLL) as diagnosed at 6-month angiographic control and defined by the difference between in-stent minimal lumen diameter (MLD) post procedure and MLD at follow-up measured by angiography
- Limb salvage rate, defined as lack of major amputations at different prescheduled follow-up visits until 12 months after index intervention
- Primary patency rates at each visit as determined by colour flow Doppler ultrasound (CFDU) and defined as the absence of a haemodynamically significant re-stenosis (50%) derived from the ratio of peak systolic velocity (PSV) at the lesion segment to that at the proximal part, a major amputation, or a TLR

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to either PTA or AMS implantation. The randomization list was generated using PROC PLAN of SAS (Statistical Analysis Software)"
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered sealed envelopes contained information on the treatment to be applied. The sealed envelopes were opened only after the lesion was successfully crossed with the guidewire, and then patients were allocated either to stent or to PTA alone"
Blinding of participants and personnel (performance bias) All outcomes	High risk	None

Bosiers 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Primary safety endpoint at 1 month reported for 57/57 in the PTA group and for 59/60 in the AMS group</p> <p>Primary efficacy endpoint at 6 months reported for 40/57 in the PTA group and for 37/60 in the AMS group</p> <p>7 participants in the PTA group crossed over to other treatment (included in PTA + AMS group for on-treatment analysis)</p> <p>1 participant in the AMS group underwent implantation of a non-study stent (not included in on-treatment analysis)</p> <p>Sudy authors provide on-treatment and ITT analyses</p>
Selective reporting (reporting bias)	Low risk	None
Other bias	High risk	Quote: "The devices used in the study were the first-generation AMS and the Pleon Explorer angioplasty balloon catheter, both developed by BIOTRONIK AG (Switzerland). The sponsor, BIOTRONIK AG, funded the total study costs and was responsible for the study administration and monitoring of the study"

Brodmann 2011

Methods	<p>Country: Austria</p> <p>Setting: monocentre university hospital</p> <p>Study design: RCT</p> <p>Level of randomisation: participant</p>
Participants	<p>No. of participants randomised: 54 patients were randomised to primary stenting (balloon expandable stent) or PTA alone</p> <p>Exclusions post randomisation: not mentioned; assumed none</p> <p>Shifted to another arm: 2 participants in PTA group with dissection in treated vessels required secondary stent, and total of 3 stents were placed</p> <p>Number of participants evaluated: overall 54 participants were included, with 33 assigned to the PTA group and 21 to the stent group</p> <p>Age (mean), years: 74.9 PTA, 68.9 stent</p> <p>Gender: 13/33 males PTA, 12/21 males stent</p> <p>Inclusion criteria: critical limb ischaemia, with Rutherford classification 4 to 6; lesion criteria characterised as the following: isolated stenoses > 70%, sequential stenoses up to cumulative length 12 cm, or total occlusion of crural arteries with maximum length 12 cm; target vessel must be a distal runoff vessel; written informed consent; life expectancy \geq 12 months</p> <p>Exclusion criteria: endovascular procedure at the target vessel within the last 3 months; refused informed consent; known allergy against clopidogrel or aspirin; indication for oral anticoagulation (atrial fibrillation); concomitant participation in another clinical trial. Lesions in the inflow arteries needing to be treated were submitted to standardised treatment of femoropopliteal arteries</p>
Interventions	For all patients eligible for the trial, antegrade access was chosen. After a 6 F sheath (Brite Tip, Cordis, Johnson & Johnson, New Brunswick, NJ, USA) was introduced, a diagnostic angiogram was obtained. 3000 units of unfractionated heparin was administered

Brodmann 2011 (Continued)

The target lesion in the infrapopliteal arteries was selected, and in case of successful passage of the target lesion with a hydrophilic-coated guidewire (Standard Glide Wire, 0.035 inch, Terumo Medical Corporation, Somerset, NJ, USA; V-18, Control™ Wire, Boston Scientific, Marlborough, MA, USA; or Hi-Torque Sparta Core 14 Guide Wire, Abbott Vascular, Abbott Park, IL, USA) and the help of a support catheter, the randomisation process was done as described above

If the lesion could not be passed with a guidewire, the patient was not included. To secure standardised documentation of the target lesion, a measuring tape was applied, leading down from the popliteal fossa to the foot of the patient. Before and after the procedure, angiography was performed in 2 planes, with a difference in angle of at least 30 degrees. In case of lesions in the inflow arteries, these were treated before the revascularisation procedure of the infrapopliteal arteries was performed

PTA group:

- The procedure was performed with the Amphirion Deep catheter (Invatec S.r.l., Roncadelli (Bs), Italy)

Stenting group:

- Primary stent placement was performed with a balloon expandable stent with a silicon-carbide coating - the Motion Explorer Stent (Biotronik, GmbH&Co. KG, Berlin, Germany). Stents with a diameter of 2.5 mm up to 3.5 mm and a length of 15 mm up to 25 mm were used. The lesion was exactly calculated using a programme for measurements. A 0.014-inch guidewire (HI Torque, Sparta Cor 14, Guidant Corporation, Santa Clara, CA, USA) was used for PTA and stenting procedures

Medication:

- The evening before the procedure, the participant received 300 mg clopidogrel; after the procedure, all participants were treated with low-molecular-weight heparin (enoxaparin 40 mg twice daily) for 48 hours
- Immediately after the procedure, the participant was put on a dual platelet aggregation therapy, with aspirin 100 mg a day and clopidogrel 75 mg a day for 3 months
- 3 months post procedure, participants were put on aspirin 100 mg a day as long-term prophylactic therapy

Outcomes

The main study endpoint was 1-year clinical benefit, defined by improvement of at least 1 Rutherford category compared to baseline

Quote: "Follow-up examinations for all patients in the trial were performed the day after the successful procedure, at month 3, 6 and 12 thereafter. At each date a clinical evaluation referring to the Rutherford classification was done. In case of Rutherford classification 5 – 6 the wound was measured geometrically and compared in size to the prior visits. For rest pain evaluation, a standardised pain scale (NRS, numeric rating scale) was used. Walking distance was evaluated by treadmill testing. Ankle brachial index (ABI) and colour coded duplex sonography of the target lesion were done at each visit. The target lesion was targeted by duplex sonography referring to the measurement during the intervention. A measuring tape was once again applied leading down from the popliteal fossa to the foot of the patient to re-find the formerly treated lesion. Colour coded duplex sonography was performed by two experienced study technicians and included an evaluation of the whole artery treated. The definition of 70% re-stenosis was based on a proximal PVR > 3,4 calculated on duplex ultrasound. PVR was defined as peak systolic flow velocity in the lesion divided by the peak systolic flow velocity ~ 1 cm proximal to the lesion. If a relevant re-obstruction was suspected digital subtraction angiography (DSA) was performed, and at month 12 all patients underwent magnetic angiography (MRA). In all patients at each time of evaluation concomitant medication and medical events (especially cardiovascular events) were taken"

Secondary endpoints were 3-month and 6-month primary patency rate; 3-, 6-, and 12-month secondary patency; and 12-month target lesion revascularisation rate

The second primary endpoint was 12-month primary patency, defined as freedom from re-stenosis > 70% detected with duplex ultrasound

Quote: "The definition of 70% restenosis was based on a proximal PVR > 3,4 calculated on duplex ultrasound. PVR was defined as peak systolic flow velocity in the lesion divided by the peak systolic flow velocity ~ 1 cm proximal the lesion"

Brodmann 2011 (Continued)

Major adverse events were any amputation, the need for acute surgical revascularisation, and death related to the procedure

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation process was conducted with a computer-generated list (blocked randomisation)"
Allocation concealment (selection bias)	Low risk	Quote: "The patients were listed for primary stent implantation or PTA alone with the usage of sequential numerated closed envelopes, which contained information about the planned procedure" Quote: "The blinding was warranted due to sealed envelopes and randomisation was done in the catheter lab immediately after successful passing of the target lesion with the guide wire. The randomisation was performed per patient"
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The whole follow up period of 12 months was completed by 44 patients. 9 patients (16.7%) had died, 8 due to cardiovascular death, one had developed lung cancer. One patient refused to show up for the follow up visits after 3 months" No ITT analysis was performed
Selective reporting (reporting bias)	Low risk	None
Other bias	High risk	Quote: "Originally the trial was planned as a multicenter trial with the appropriate randomisation therefore, but at the end it was performed as a monocentric study, because the other participating centers had difficulties including appropriate patients. They did not include any patient over the whole study period. This explains the different numbers of patients in the two treatment groups" Quote: "At baseline evaluation all cardiovascular risk factors were more pronounced in the stent group than in the PTA group, with the biggest and statistically significant difference in hyperlipidemia in spite of lipidemic treatment (n = 14 (66.7%) versus 6 (18.2%); P < 0.0001). For diabetes mellitus, concerning the fact of insulin therapy there was a difference between the stent and PTA group, too (47.6% versus 36.4%)"

Rand 2006

Methods

Country: Austria
Setting: hospital

Angioplasty versus stenting for infrapopliteal arterial lesions in chronic limb-threatening ischaemia (Review)

Rand 2006 (Continued)

Study design: RCT

Level of randomisation: participant

Participants

No. of participants randomised: The study population consisted of 51 patients who were treated for critical chronic limb ischaemia (Fontaine stages III and IV), defined as rest pain, ischaemic ulcer, and gangrene. Patients with only claudication were not included in this study

Exclusions post randomisation: none

Number of participants evaluated: 51 participants with 95 lesions: PTA group: 27 participants (53 lesions), stent group: 24 participants (42 lesions)

Shifted to another arm: none

Number of participants evaluated: 51; 44 were consecutively investigated and randomised at 1 centre to treatment of lesions by either PTA or stent application; 7 from 2 other centres were enrolled

Age (mean), years: 72; mean age for the individual group not specified

Gender: did not specify

Inclusion criteria: chronic critical limb ischaemia stages III and IV of the Fontaine classification; isolated stenosis > 70% or occlusion of the tibial arteries; up to 3 lesions; lesions that were up to 3 cm with cumulative lesion length ≤ 9 cm, including the tibiofibular trunk, anterior and posterior tibial arteries, and fibular artery. There was no further limitation regarding lesion position. Patients with a significant inflow obstruction at the pelvic or superficial femoral artery level were not included

Exclusion criteria: evidence of a systemic coagulopathy with anticoagulant and antiplatelet treatment contraindicated; previously implanted stents in the target lesion; total occlusion in the target vessel following the target lesion; without distal runoff; inflammatory vascular disease; peptic ulcer or gastric/intestinal bleeding in the previous 6 months; clinically assessed intolerance to contrast medium

Interventions

PTA group:

- Lesions were routinely treated with a 5 Fr conventional balloon angioplasty catheter and guidewire (Bijou 2.5–4 mm, Boston Scientific, Galway, Ireland; guidewire M 0.035-inch, Terumo, Tokyo, Japan)

Stenting group:

- Stent applications were performed with a 0.014-inch guidewire (HI Torque, Sparta Core 14, Guidant Corporation, Santa Clara, CA) and carbostents (Sorin, Biomedica, Italy) with diameter range of 2.0 to 4 mm and length of 15 to 25 mm

Medication:

- At the beginning of the procedure, 5000 units of heparin was administered intra-arterially
- Post-interventional anticoagulation therapy for the PTA group consisted of low-molecular-weight heparin (Enoxaparin 2 to 40 mg) for 3 days and acetylsalicylic acid (ASA; ThromboAss, 100 mg per day permanently)
- Adjunct therapy for the stent group consisted of clopidogrel (Plavix), administered as a bolus of 300 mg on the day of the procedure and 75 mg per day orally for 4 weeks, and ASA medication permanently
- Quote: "Due to its main effect on early restenosis clopidogrel is given only to patients who have received stents and not to patients who underwent PTA, as early restenosis is not regarded a major problem in this patient group"

Outcomes

Primary endpoint:

- 6-month angiographic patency rate of treated lesions, which was defined as re-stenosis < 70% (threshold 1: critical re-stenosis) or < 50% (threshold 2: subcritical re-stenosis), documented by CTA or DSA

Secondary endpoints:

- Minor and major amputations; major amputation referred to amputation above the metatarsal line
- Complications were classified according to recommended standards: major complications cause death, cause permanent disability, or necessitate revascularisation or other invasive treatment, or a prolonged hospital stay. Less significant complications were classified as minor complications
- Surgical revascularisation

Rand 2006 (Continued)

- Death

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random number generation not described
Allocation concealment (selection bias)	Low risk	Quote: "Numbered envelopes were prepared for one-to-one randomization to either PTA or primary stent placement. The randomization was performed per patient. Therefore, all lesions in a particular patient had to be treated by either PTA or primary stent placement" Type of envelope not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data evaluation performed by the 2 readers in a double-blinded fashion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 51 patients, 2 patients died, 3 patients underwent amputation, 1 patient underwent major heart surgery, which did not allow further follow-up, and 8 patients were lost to follow-up" Survival analysis performed
Selective reporting (reporting bias)	Low risk	None
Other bias	Unclear risk	Quote: "Due to its main effect on early restenosis clopidogrel is given only to patients who have received stents and not to patients who underwent PTA, as early restenosis is not regarded a major problem in this patient group" Quote: "We also observed a higher incidence of PTAs than stent applications per patient. This might be due to a certain degree of investigator bias, as potentially one balloon can be used for several lesions in contrast to the necessity of one stent per lesion" Quote: "The study was supported by the Ludwig Boltzmann Institute for Radiologic Tumor Diagnosis and the Ludwig Boltzmann Institute of Interdisciplinary Vascular Research"

Rand 2011

Methods

Country: InPeria II study at 6 centres in Europe (Austria, Italy, and Germany)
Setting: tertiary and university hospitals
Study design: RCT

Level of randomisation: limb

Participants

No. of participants: 88 consecutive patients: PTA group: 44 participants; stent group: 44 participants

Rand 2011 (Continued)

Age (mean), years: PTA group 62.2, stent group 68.2
Gender: PTA group 28 male/17 female, stent group 30 male/11 female
Exclusions post randomisation: none
Shifted to another arm: during the intervention in the PTA group, if residual stenosis (> 30%) and flow-limiting dissection were present, the participant was treated with stent; thus the participant crossed over into the stent group
Number of participants evaluated: 88; 44 in the PTA group (45 treated limbs) and 44 in the stent group (44 treated limbs). Total: 131 treated lesions (PTA group: 69 lesions; stent group: 62 lesions)

Losses to follow-up: 3 in the PTA group and 5 in the stent group died within the first 3 months after treatment. Two additional participants in the PTA group died between 3 and 6 months after treatment. Fifteen participants were not available for follow-up investigations at 3 months and an additional 20 participants were not available for investigations at 9 months owing to death or non-compliance

Inclusion criteria: symptomatic CLTI (stage 4 or 5 according to the Rutherford classification) due to a de novo lesion of an infrapopliteal artery. Lesions with stenosis \geq 50% of their diameter were considered for the trial. Patients with substantial inflow stenosis were eligible for inclusion if the stenosis had been successfully treated without complications. The target infrapopliteal artery was eligible provided that in-line circulation to the foot distal to the lesion was present

Exclusion criteria: previous treatment; total occlusion in the target vessel; no distal arterial runoff; underlying disease (e.g. renal failure, bleeding disorders)

Interventions	<p>PTA group (control):</p> <ul style="list-style-type: none"> Procedures were carried out with a Pegaso balloon (Sorin) when balloon length was suitable for lesion length (lesion length 30 mm) or with any other peripheral balloon when lesions were longer than 30 mm. Balloon diameter was selected to equal diameter of the artery <p>Stenting group:</p> <ul style="list-style-type: none"> Primary stenting was performed by using the InPeria Carbostent (Sorin), which is a balloon expandable stainless steel slotted tube device characterised by a permanent coating of a thin film of turbo-static carbon (Carbofi Im; Sorin) <p>Medication:</p> <ul style="list-style-type: none"> After arterial cannulation, 5000 units of intra-arterial heparin was administered in both study groups In the PTA group, participants were given 40 mg of enoxaparin twice daily for 3 days, and were put on 100 mg of aspirin daily indefinitely In the stent group, a loading dose of 300 mg of clopidogrel was given on the day of the procedure, followed by 75 mg of clopidogrel daily for 4 weeks and aspirin medication given permanently
Outcomes	<p>Primary endpoints assessed at 3 months and 9 months:</p> <ul style="list-style-type: none"> Assessment of clinical improvement after endovascular treatment based on American Heart Association Clinical Improvement Score after percutaneous interventions. Limb salvage rate (minor vs major amputation). <p>Secondary endpoints assessed at 9 months:</p> <ul style="list-style-type: none"> MLD before and after the revascularisation procedure Percentage of residual diameter stenosis (DS): defined as $100 [(RVD - 2 \text{ MLD})/RVD]$, where RVD is the reference vessel diameter Two binary re-stenosis rates (50% DS and 70% DS) Incidence of target lesion revascularisation at 9-month follow-up
Notes	Data analysis performed in this review used limbs as unit of measurement instead of treated lesion(s)
Risk of bias	
Bias	Authors' judgement Support for judgement

Rand 2011 (Continued)

Random sequence generation (selection bias)	High risk	Method of sequence generation not described
Allocation concealment (selection bias)	High risk	Quote: "Randomization (stent vs PTA) was performed in a 1:1 ratio, so that all patients enrolled in this study were randomized to undergo either stent placement or PTA alone for each leg separately. This means each leg in each patient was treated individually (stent vs PTA), but all lesions in the same leg would have been treated with the same procedure allocated to that leg" Method of allocation concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for; ITT analysis reported
Selective reporting (reporting bias)	Low risk	All outcomes reported; flow chart provided
Other bias	Low risk	Quote: "This study was pursued with support from Sorin Biomedica Cardio (Saluggia, Italy), which provided the investigational devices. The authors had complete control of the data and information submitted for publication, which was firmly in the hands of the Medical University of Vienna and the Karl Landsteiner Society, St Poelten, Austria, and was unbiased by industry"

Randon 2010

Methods	Country: Belgium Setting: Ghent University Hospital Study design: single-centre RCT Level of randomisation: participant
Participants	No. of participants randomised: total of 38 limbs in 35 participants with critical limb ischaemia were randomised to angioplasty (n = 22) or primary stenting (n = 16) Exclusions post randomisation: 1 participant in the PTA group did not receive intervention (n = 1); reason: stenosis < 70% Shifted to another arm: none Number of participants evaluated: 22 in the PTA group and 16 in the stenting group Age (mean), years: 72 years old in both groups Gender: PTA group: 14 male/8 female; stenting group: 6 male/10 female Inclusion criteria: All patients with CLTI (Rutherford 4 to 6, Fontaine III and IV) hospitalised at the Department of Vascular Surgery, Ghent University Hospital, for primary angioplasty of 1 or more crural vessels were randomised to primary stenting or angioplasty alone. For most patients, this was a last attempt before major amputation because of intractable pain or tissue loss. Some had no adequate venous conduit or no surgical target vessel, and the level of comorbidity was generally too high for general anaesthesia (ASA scores III and IV). All patients with stenosis of 70% or occlusions of the crural arteries were considered suitable for endovascular therapy. The length of the lesion was not an exclusion

Randon 2010 (Continued)

criterion, as even stenoses or occlusions > 10 cm were accepted (an exclusion criterion in most angioplasty studies and registries)

Exclusion criteria: acute limb ischaemia; multi-segmental inflow lesions (longer than 3 cm) above the knee; sepsis; myocardial infarction during previous 14 days; blue toe syndrome (microembolisation); inability to ambulate. Patients who needed bypass surgery for popliteal or superficial femoral occlusions and those who needed simultaneous angioplasty of the crural and more than one proximal vessel were excluded

Nine patients needed concomitant proximal angioplasty for stenosis: 6 patients at the level of the popliteal artery, 2 at the level of the superficial femoral artery, and 1 at the level of the common iliac artery. There were 20 men and 18 women. The mean age of all patients did not diverge statistically from the mean age of the subgroups (72 ± 9.8 years; range 50 to 88 years). In 15 limbs, 2 arteries were treated, and in 1 patient, all 3 crural arteries: only 1 of these vessels was included in the study

Interventions
Stenting group:

- The target lesion was pre-dilated. Both coronary balloon expandable stents (Jostent, Jomed Benelux Multi-link Vision Coronary Stent, Abbott, Abbott Park, IL, USA) and self-expandable stents (Astron Pulsar Stent, Biotronik, Berlin, Germany; Xpert Stent, Abbott) were used

PTA group (control):

- Bijou Dilatation Balloon (Boston Scientific, Natick, MA, USA), Fox SV Balloons (Abbott), or cutting balloons (Boston Scientific) were used

Additional intervention:

- Additional devices were used in 4 participants: 1 participant in the PTA group had a residual stenosis of 50%, which was treated during the same procedure with a cutting balloon (Boston Scientific), and in 3 participants, an Excimer laser was used to cross the lesion
- Quote: "In five patients we performed a subintimal instead of a transluminal recanalisation (two in the stent group and three in the PTA group). When it was impossible to cross the lesion, even with the use of an Excimer laser (used in three patients), the procedure was considered a technical failure and patients were treated conservatively, by bypass surgery, or with a major amputation, according to the runoff state of the vessels and patient condition"

Medication:

- Heparin was administered at a dose of 5000 IU at the beginning of the intervention
- All participants were discharged on antiplatelet drugs: low-molecular-weight heparin at a therapeutic dose for 1 week, 75 mg clopidogrel per day for 2 months, and low-dose aspirin (< 160 mg) indefinitely

Outcomes

- Primary patency at 6 months and 12 months, defined as clinical primary patency: this means freedom from re-stenosis; occlusion with recurrence of ischaemic rest pain or recurrence of ulceration, leading to redo angioplasty; bypass surgery; or major amputation
- Secondary patency at 6 months and 12 months, defined as freedom from redo angioplasty until recurrence of symptoms
- Limb salvage at 6 months and 12 months, defined as successful when a full-length limb was preserved; an above-the-ankle amputation was considered a failure
- Patient survival at 6 months and 12 months
- Technical success, defined as the ability to cross the lesion and perform an angioplasty with > 30% re-stenosis

Quote: "Patients were examined every 3 – 6 months after discharge till the end of the trial. Standard duplex scanning was performed every 6 months by one independent experienced investigator to exclude bias. The PSV was measured over the stent if possible. In the case of angioplasty alone the PSV was measured over the whole length of the treated artery. When the PSV was > 400 cm/s or when the treated artery was re-occluded, and the patients showed recurrence of rest pain, cessation of ulcer healing, or a new ulcer, a new angiography was performed. In most of the patients ABPI measurements were not possible or not reliable due to calcifications of the vessels. We preferred duplex over angiogra-

Randon 2010 (Continued)

phy for follow up because of the renal comorbidity of our patients and the fact that the most important outcome for these patients is not patency of the vessel but relief of rest pain and healing of their ulcers"

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by computer-generated randomization sequence"
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed by means of sealed, consecutively numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Standard duplex scanning was performed every 6 months by one independent experienced investigator to exclude bias"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	None
Other bias	Unclear risk	Declaration of conflict of interest not stated in the paper

Spreen 2016

Methods

Country: The Netherlands
Setting: 3 major vascular centres in the Netherlands
Study design: multi-centre RCT

Level of randomisation: participant

Participants

No. of participants randomised: A total of 144 limbs in 137 patients with critical limb ischaemia were randomised to angioplasty (69 limbs in 67 participants) or primary stenting (75 limbs in 74 participants) (4 participants included for 2 limbs, with 1 limb in each arm)

Exclusions post randomisation: 3 participants (3 limbs) in the PTA group did not receive intervention; reasons: intermittent claudication, renal failure without dialysis, and coagulation disorder. One participant (1 limb) in the stent group did not receive intervention; reason: vessel too small. Overall, 64 participants (66 limbs) received the allocated PTA intervention, and 73 participants (74 limbs) received the allocated stent treatment

Shifted to another arm: none

Age (mean), years: PTA group 73, stent group 74

Gender: PTA group 47 male/17 female, stent group 49 male/24 female

Gender: PTA group: 14 male/8 female, stent group 6 male/10 female

Inclusion criteria: age > 18 years; if female patient with child-bearing potential, may not be pregnant at study entry and must utilise reliable birth control for the duration of participation in the study; must be willing and able to comply with the specified follow-up evaluation; critical limb ischaemia, defined

Spreen 2016 (Continued)

as Rutherford category 4 (ischaemic rest pain), 5 (minor tissue loss), or 6 (major tissue loss); stenosis (> 50% luminal loss) or occlusion of an infrapopliteal artery, including the tibiofibular trunk, the anterior tibial artery, the posterior tibial artery, and the fibular artery; target lesion length \leq 90 mm; artery to be treated with diameter \geq 2 mm and \leq 6 mm; patent common iliac, external iliac, superficial femoral, and popliteal artery on the ipsilateral side before randomisation, possibly after treatment during the same session. At least 1 patent crural (anterior tibial, posterior tibial, or fibular) artery with expected unobstructed runoff to ankle level after treatment

Exclusion criteria: acute limb ischaemia; previous amputation of affected limb at or above ankle level; subacute limb ischaemia, which requires thrombolysis as first treatment modality; active bleeding or bleeding diathesis; recent (\leq 3 months) haemorrhagic stroke or any other CNS abnormality with increased risk of haemorrhage, such as intracranial neoplasm, arteriovenous malformation, intracranial aneurysm, or aneurysm repair; gastrointestinal or genitourinary bleeding of clinical significance within the previous 6 weeks before treatment; aneurysm in common femoral, superficial femoral, or popliteal artery on the ipsilateral side; surgical revascularisation involving the same limb within 30 days before the index procedure or planned surgical revascularisation of the same limb within 30 days of the index procedure; previous implanted stent at the index site; life expectancy < 6 months or other factors making clinical follow-up difficult; known allergy to acetylsalicylic acid (aspirin), clopidogrel, heparin, or paclitaxel; known allergy to contrast media; known heparin-induced thrombocytopenia (HIT type 2); unable or unwilling to tolerate anticoagulant, antiplatelet therapy, or contrast media; creatinine clearance 20 mL/min (as derived from Cockcroft-Gault formula); severely calcified lesions with expected resistance to stenting; poor inflow due to ipsilateral stenosis or occlusions of the iliac or femoropopliteal arteries that cannot be treated during the same session; significant vessel tortuosity or other parameters prohibiting access to the lesions and/or delivery of the stent; without (expected) distal runoff to the index site

Interventions

Stenting group:

- In the treatment arm, target lesions were treated with balloon expandable paclitaxel-eluting stainless steel stents (TAXUS Liberté; Boston Scientific, Natick, MA, USA). If necessary, according to the operator, mainly in cases of occlusion, lesions were pre-dilated. The full length of lesions was covered, and when necessary, overlapping stents were deployed (maximum 3 stents allowed)

PTA group (control):

- A balloon with diameter matching the target vessel was advanced over the guidewire and was inflated at the target lesion site. If bailout stenting was required (secondary to post-PTA occlusion or flow-limiting dissection), only non-drug-eluting bare-metal stents were allowed

Medication:

- During the procedure, 5000 international units of heparin was administered intra-arterially
- Post procedure, all participants were prescribed 100 mg carbasalate calcium daily indefinitely and 75 mg clopidogrel daily (with 300-mg loading dose) orally for \geq 6 months

Outcomes

Primary outcome:

- Patency per treated lesion at months, defined as \leq 50% loss of luminal diameter without re-intervention in the interim. If CTA was not available but digital subtraction angiography or duplex sonography was available, patency of treated sites was scored by those techniques

Secondary outcomes:

- Ischaemic categorisation of the treated leg by means of Rutherford classification (at 6 months and 12 months), minor and major amputation (at or below vs above ankle level, respectively) of the trial leg (at 6 months and 12 months), periprocedural (within 30 days) complications, serious adverse events, death

Notes

Risk of bias

Spreen 2016 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence on a 1:1 basis. Randomisation per limb and stratified in blocks per centre. Block size (n = 4) known only to the statistician
Allocation concealment (selection bias)	Low risk	Sealed and opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, operators, and investigators not blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for. ITT analysis reported
Selective reporting (reporting bias)	Low risk	None
Other bias	Unclear risk	One study author has received speakers' fees from Cordis Corporation, Fremont, CA, USA; Cook Medical, Bloomington, IN, USA; and AngioDynamics, Latham, NY, USA

Tepe 2010

Methods	Country: Germany Setting: hospital Study design: RCT Level of randomisation: participant
Participants	No. of participants randomised: 60 with current ulcers randomised Exclusions post randomisation: not mentioned Shifted to another arm: 3 participants received additional stent placement after primary endpoint: 2 in the PTA group and 1 in the stenting group Number of participants evaluated: 60 (63 limbs) Age (mean), years: stenting group 72.8, PTA group 72.2 Gender: 42 males, 21 females Inclusion criteria: Rutherford stage 5 or 6 with current ulcers on the basis of arterial disease; patent vessel to the distal lower leg; index lesion maximum 5 cm in length Exclusion criteria: not mentioned
Interventions	Sixty participants with current ulcers were randomly assigned to receive: <ul style="list-style-type: none"> • Sirolimus-coated stent with abciximab (n = 14) • Bare stent with abciximab (n = 16) • PTA with abciximab (n = 14) • PTA alone (n = 19) Medication:

Tepe 2010 (Continued)

- During the intervention, participants received 5000 IU heparin intra-arterially
- All participants received a clopidogrel and acetylsalicylic acid bolus before the intervention
- Abciximab (ReoPro) was administered as a bolus of 0.25 mg/kg BW (maximum 20 mg) and as a 12-hour intravenous infusion of 45 µg/kg BW diluted in 250 mL saline and injected with 21 mL/h
- Post-procedure medication consisted of clopidogrel 75 mg daily for 8 weeks and acetylsalicylic acid 100 mg daily as continuous medication

Concurrent stenoses of the inflow or outflow tract were treated in the same session by PTA

Outcomes	<p>Angiographic endpoints consisted of primary re-stenosis at 2 months and 6 months and overall patency. Re-stenosis was defined as re-narrowing of the index lesion by $\geq 50\%$</p> <p>Clinical endpoints were healing of ulceration, amputation rate, and overall survival</p> <p>Technical endpoints included technical success rate, subacute re-occlusions, and re-stenosis</p> <p>Technical success was defined as $< 30\%$ residual stenosis after the intervention</p>
Notes	<p>In the forest plot, the 4 groups were re-classified into 2 broad groups: stenting and PTA</p> <p>Stenting group: sirolimus-coated stent with abciximab (n = 14) and bare stent with abciximab (n = 16)</p> <p>PTA group: PTA with abciximab (n = 14) and PTA alone (n = 19)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random number generation not described
Allocation concealment (selection bias)	High risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Total of 63 limbs in 60 participants randomised</p> <p>Quote: "In total, 44 patients were available for follow up after two months and 37 patients after six months, respectively"</p>
Selective reporting (reporting bias)	Low risk	None
Other bias	High risk	Study supported by Eli Lilly; no explicit mention of the independence of the research team

ABI: ankle-brachial index.

ABPI: ankle-brachial pressure index.

AMS: absorbable metal stent.

ASA: acetylsalicylic acid.

ASA: American Society of Anesthesiologists.

BW: body weight.
 CFDU: colour flow Doppler ultrasound.
 CLTI: chronic limb-threatening ischaemia.
 CNS: central nervous system.
 CTA: computed tomography angiography.
 DS: diameter stenosis.
 DSA: digital subtraction angiography.
 HIT: heparin-induced thrombocytopenia.
 ITT: intention-to-treat.
 LLL: late lumen loss.
 MLD: minimal lumen diameter.
 MRA: magnetic resonance angiography.
 PSV: peak systolic velocity.
 PTA: percutaneous transluminal angioplasty.
 PVR: peak velocity ratio.
 QVA: quantitative vascular angiography.
 RCT: randomised controlled trial.
 RVD: reference vessel diameter.
 TLR: target lesion revascularisation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bosiers 2012	Comparison of 2 different stents
Bradbury 2010	Description of severity and extent of disease using the Bollinger angiogram scoring method and the TransAtlantic Inter-Society Consensus II classification in the BASIL trial
Rastan 2011	Comparison of 2 different stents
Scheinert 2012	ACHILLES trial: RCT of stent vs angioplasty for treatment of infrapopliteal arterial disease. Rutherford stages 3 to 5 were included. As outlined in our protocol, we intended to include in our analysis only patients with Rutherford stages 4 to 6. Further, the study did not provide subgroup data specific to stage 4 and 5 patients and thus is excluded from the review
Schulte 2015	EXPAND trial: RCT of stent vs angioplasty for treatment of infrapopliteal arterial disease. Rutherford stages 3 to 5 were included. As outlined in our protocol, we intended to include in our analysis only patients with Rutherford stages 4 to 6. Further, the study did not provide subgroup data specific to stage 4 and 5 patients and thus is excluded from the review
Siablis 2007	Prospective, non-randomised, single-centre, controlled, double-arm study. Stenting was performed as a bailout procedure for suboptimal angioplasty results (flow-limiting dissection, elastic recoil, or post-angioplasty residual stenosis > 30%). In the first 29 participants, infrapopliteal stenting was performed with bare-metal stents (group B), and in the other 29 participants, sirolimus-eluting stents were used (group S)
Siablis 2014	IDEA trial: RCT comparing paclitaxel-coated balloon angioplasty vs drug-eluting stents in long infrapopliteal lesions. Inclusion criteria were Rutherford classes 3 to 6 and angiographically documented infrapopliteal disease with minimum lesion length of 70 mm. As outlined in our protocol, we intended to include in our analysis only patients with Rutherford stages 4 to 6. Further, the study did not provide subgroup data specific to stage 4 and 5 patients and thus is excluded from the review

RCT: randomised controlled trial.

Characteristics of ongoing studies [ordered by study ID]

NCT01644487

Trial name or title	Self Expanding Nitinol Stent Versus Balloon Angioplasty Alone for the Below The Knee Arteries (SENSBTK)
Methods	Study type: interventional Allocation: randomised Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	Enrolment: 50 Age eligible for study: 20 to 80 years Genders eligible for study: both Accepts healthy volunteers: no Inclusion criteria: <ul style="list-style-type: none"> • Symptomatic critical limb ischaemia (Rutherford 4 to 6) • Signed informed consent • Target lesion length < 8 cm by angiographic estimation • Stenosis > 50% or occlusive atherosclerotic lesion of the ipsilateral infrapopliteal artery • Reference vessel diameter should be 2.0 to 4.5 mm Exclusion criteria: <ul style="list-style-type: none"> • Known allergy to heparin, aspirin, or other anticoagulant/antiplatelet therapies or bleeding diatheses, or unable, or unwilling, to tolerate such therapies • Taking warfarin • History of previous life-threatening contrast media reaction • Currently enrolled in another investigational device or drug trial • Currently breastfeeding, pregnant, or intending to become pregnant • Mentally ill or retarded • Acute critical limb ischaemia • Major bleeding history within prior 2 months • Severe hepatic dysfunction (> 3 times normal reference values) • Significant leucopenia, neutropenia, thrombocytopenia, anaemia, or known bleeding diathesis • Life expectancy < 1 year due to comorbidity • Reference segment diameter not suitable for available stent design • Previously implanted stent(s) or PTA at the same lesion site • Inflow-limiting arterial lesions left untreated
Interventions	Experimental group: a group of patients who will undergo subsequent primary stenting following successful conventional balloon angioplasty Active comparator: a group of patients who will undergo routine conventional balloon angioplasty alone without stenting
Outcomes	Primary outcome measures: angiographic binary re-stenosis rate (time frame: 12 months)
Starting date	Study start date: July 2012 Estimated study completion date: July 2018 Estimated primary completion date: July 2017 (final data collection date for primary outcome measure)
Contact information	Principal investigator contact: Seung Woon Rha, MD, PhD; 82226263020; swrha617@yahoo.co.kr

NCT01644487 (Continued)

Contact: Yun Hyeong Cho, MD, PhD; 82318106776; princette@hanmail.net

Notes

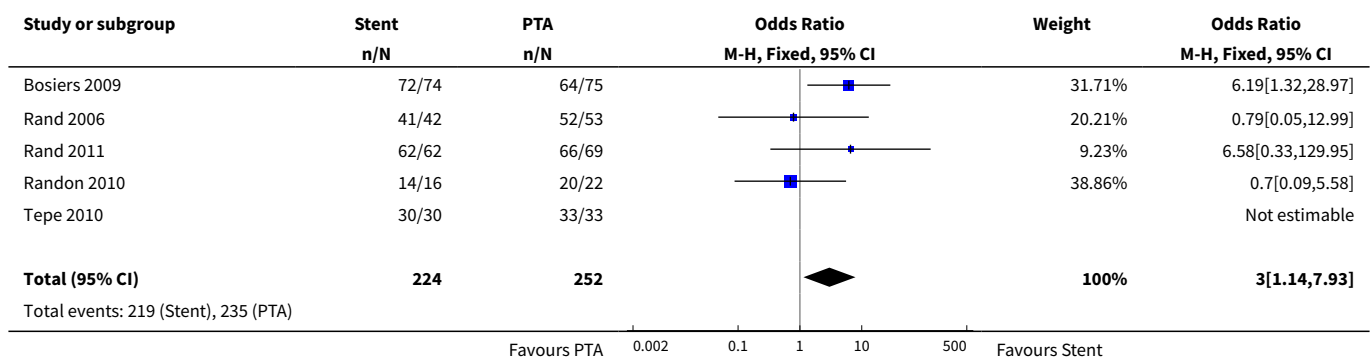
PTA: percutaneous transluminal angioplasty.

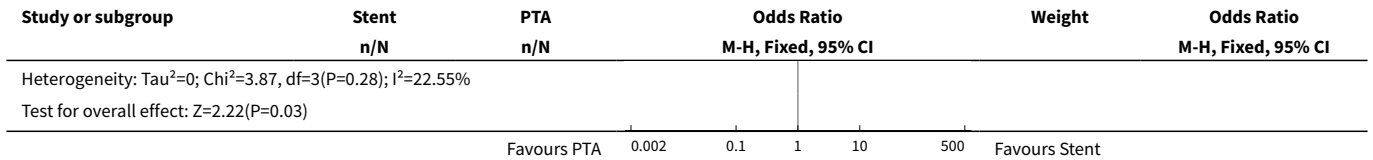
DATA AND ANALYSES

Comparison 1. PTA versus stent

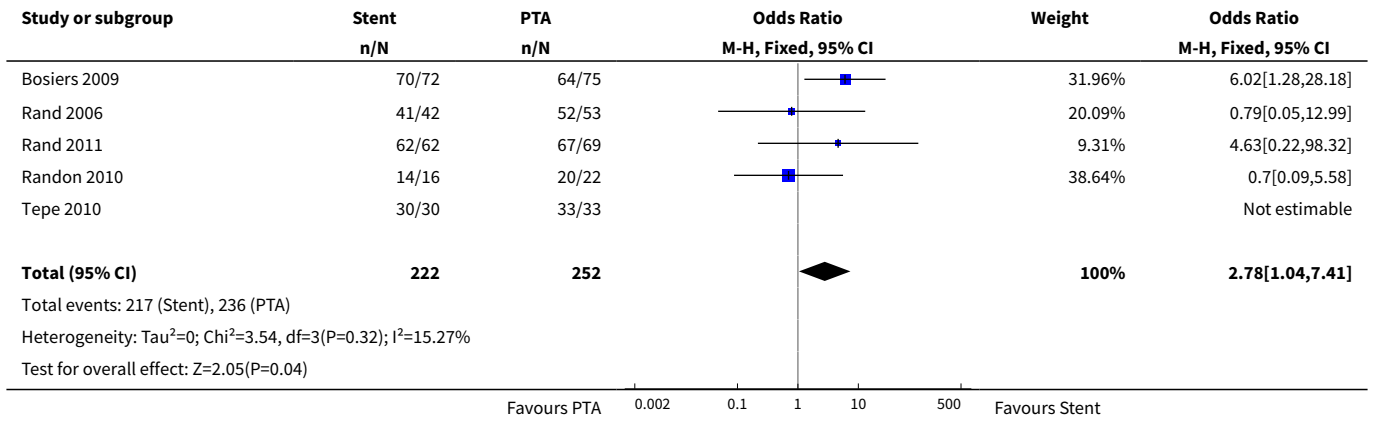
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Technical success ITT	5	476	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [1.14, 7.93]
2 Technical success TA	5	474	Odds Ratio (M-H, Fixed, 95% CI)	2.78 [1.04, 7.41]
3 Procedural complications ITT	5	360	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.01, 53.60]
4 Procedural complications TA	5	359	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.01, 47.70]
5 Primary patency < 6 months ITT	3	456	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.37, 2.11]
6 Primary patency < 6 months TA	3	309	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.32, 3.00]
7 Amputation ITT	4	306	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.56, 3.22]
8 Amputation TA	4	252	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.59, 3.40]
9 Mortality ITT	6	497	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.43, 1.17]
10 Mortality TA	6	487	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.42, 1.15]

Analysis 1.1. Comparison 1 PTA versus stent, Outcome 1 Technical success ITT.

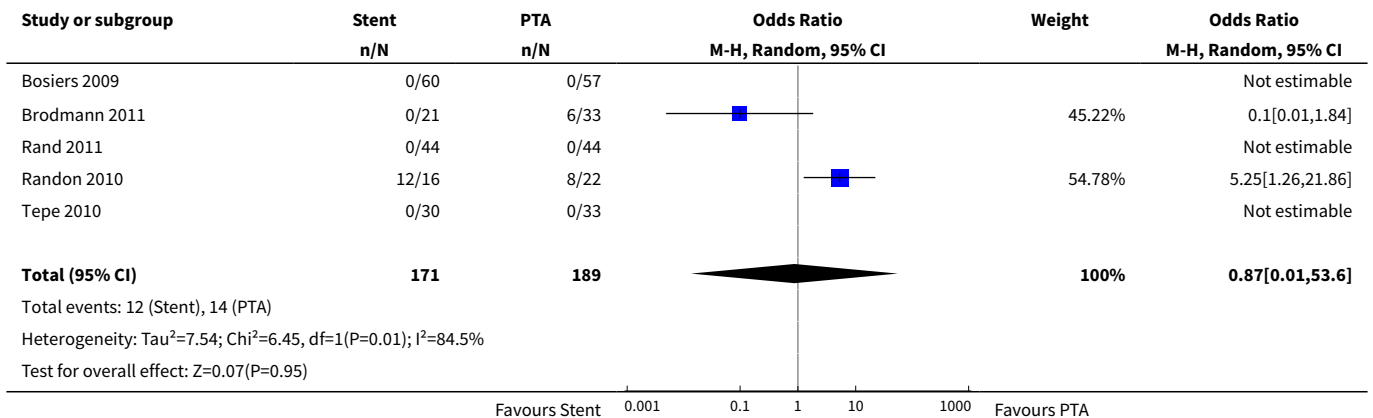




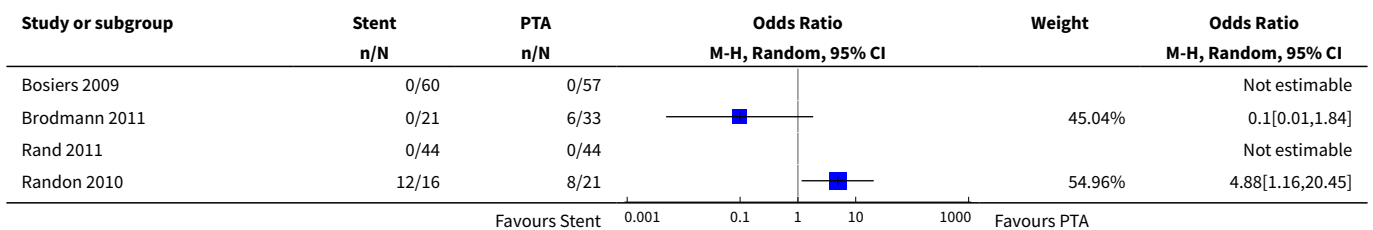
Analysis 1.2. Comparison 1 PTA versus stent, Outcome 2 Technical success TA.

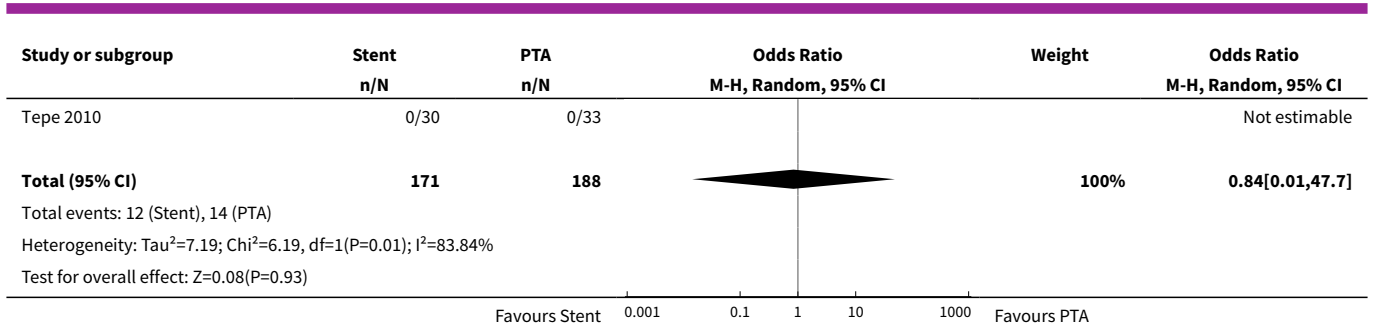


Analysis 1.3. Comparison 1 PTA versus stent, Outcome 3 Procedural complications ITT.

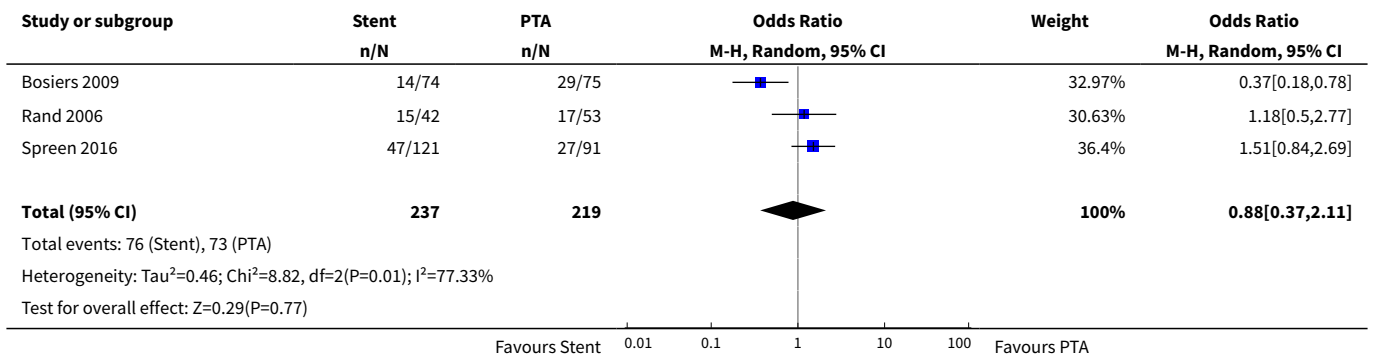


Analysis 1.4. Comparison 1 PTA versus stent, Outcome 4 Procedural complications TA.

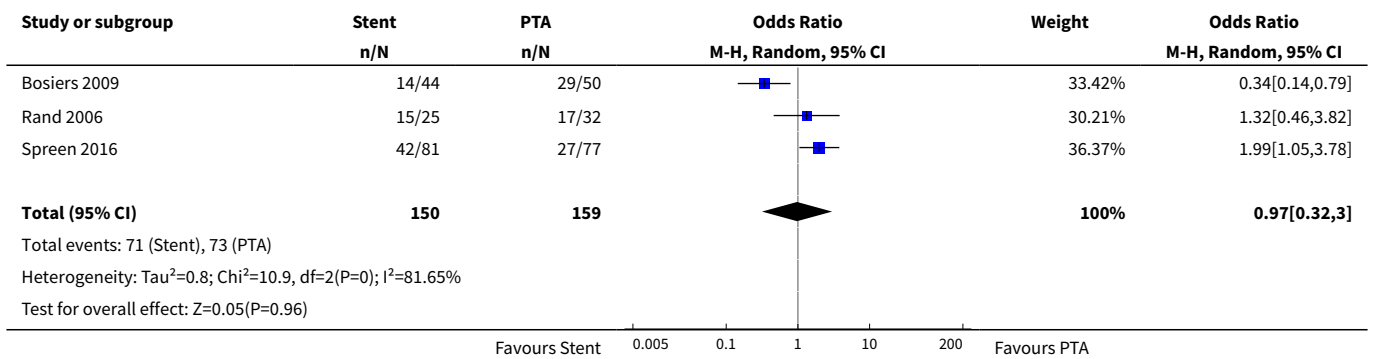




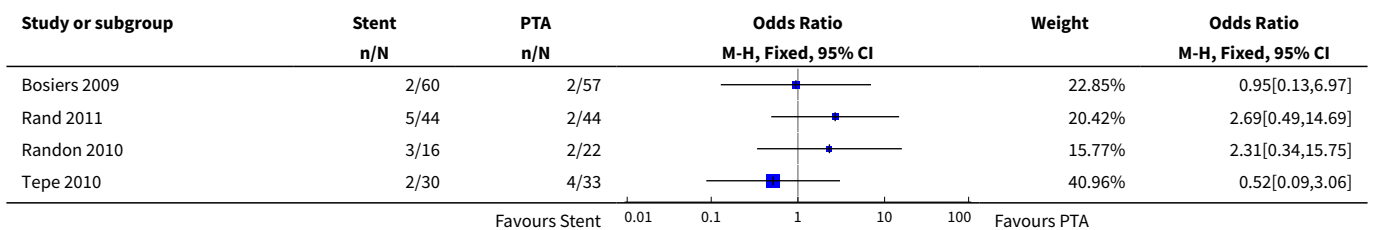
Analysis 1.5. Comparison 1 PTA versus stent, Outcome 5 Primary patency < 6 months ITT.

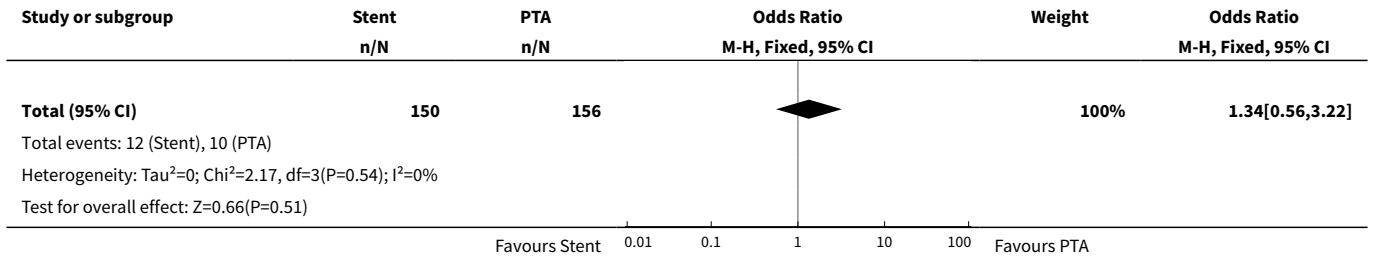


Analysis 1.6. Comparison 1 PTA versus stent, Outcome 6 Primary patency < 6 months TA.

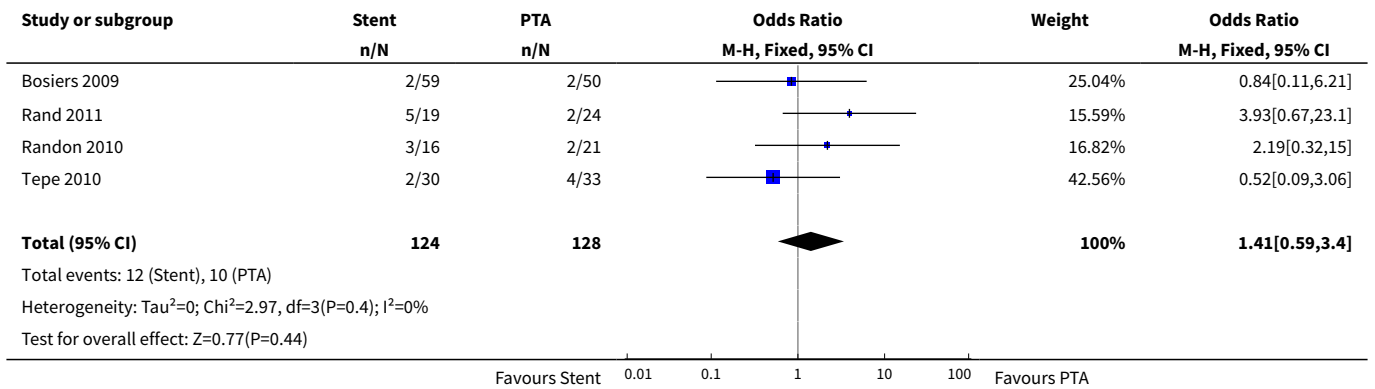


Analysis 1.7. Comparison 1 PTA versus stent, Outcome 7 Amputation ITT.

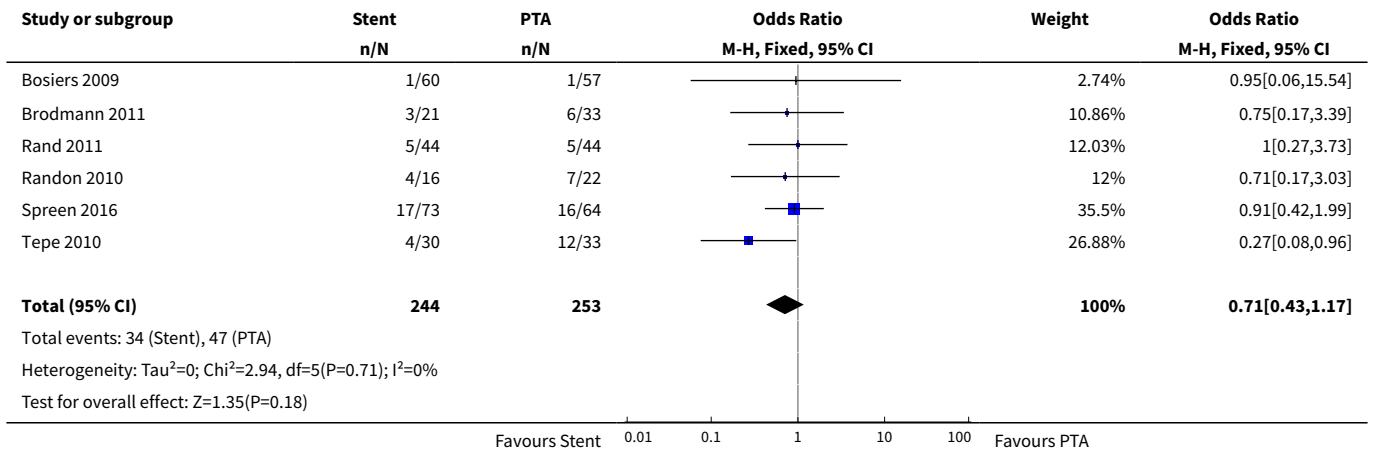




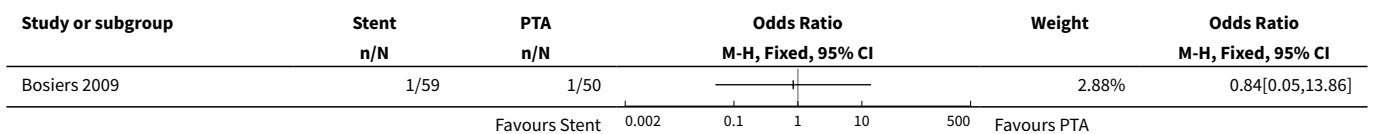
Analysis 1.8. Comparison 1 PTA versus stent, Outcome 8 Amputation TA.

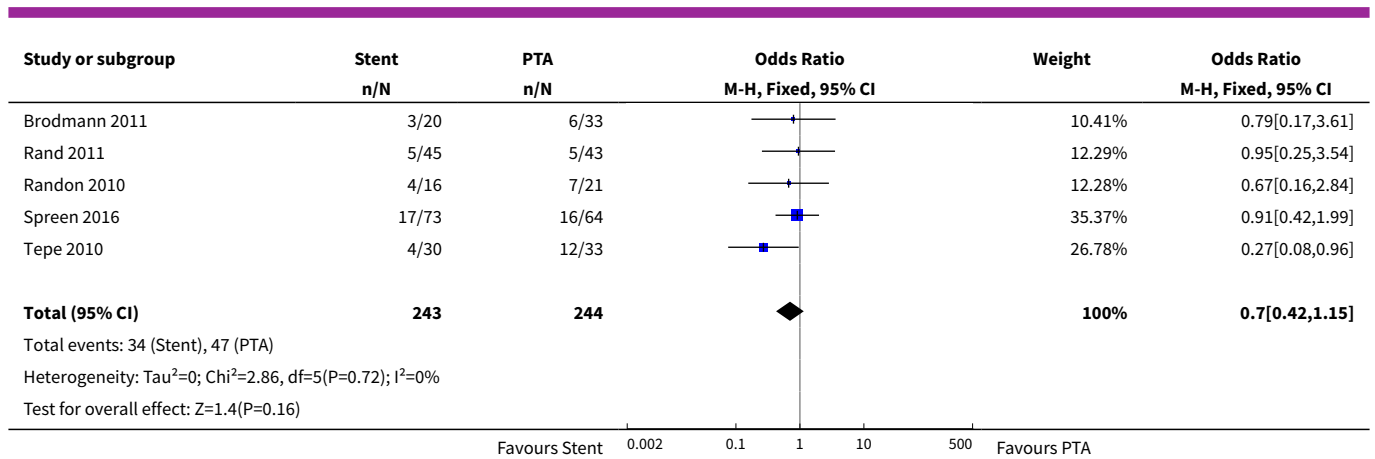


Analysis 1.9. Comparison 1 PTA versus stent, Outcome 9 Mortality ITT.



Analysis 1.10. Comparison 1 PTA versus stent, Outcome 10 Mortality TA.





ADDITIONAL TABLES

Table 1. Classification of peripheral arterial disease: Fontaine stages and Rutherford categories

Fontaine		Rutherford (adapted from table from Norgren 2007)		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
		II	2	Moderate claudication
IIb	Moderate to severe claudication	I	3	Severe claudication
		II	4	Ischaemic pain at rest
III	Ischaemic rest pain	III	5	Minor tissue loss
IV	Ulceration or gangrene	III	6	Major tissue loss

Table 2. A proposed classification of stents by individual parameters

A proposed classification of stents by individual parameters (table from Nelken 2004)	
Deployment method	Balloon expandable/angioplasty or self-expanding
Geometry	Closed cell, open cell, modified connectors; weave-braided, knitted; spiral coil, helix
Construction materials	Stainless steel, 316L, full hard stainless; tantalum; platinum; nitinol; cobalt alloys; bio-absorbable
Treated stents	Coated stents and drug-eluting stents: metals, bound drugs (passivation), ceramics, polymers, drug-eluting stents

APPENDICES

Appendix 1. CENTRAL search strategy, 22 March 2017

Search run on Wed Mar 22 2017		
#1	MESH DESCRIPTOR Arteriosclerosis	869
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	72
#4	MESH DESCRIPTOR Atherosclerosis	645
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	737
#6	MESH DESCRIPTOR Intermittent Claudication	726
#7	MESH DESCRIPTOR Ischemia	803
#8	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2236
#9	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	9508
#10	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	8384
#11	(peripheral near3 dis*):TI,AB,KY	3533
#12	(claudic* or IC):TI,AB,KY	3229
#13	(isch* or CLI):TI,AB,KY	24787
#14	arteriopathic:TI,AB,KY	7
#15	dysvascular*:TI,AB,KY	11
#16	(leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	99
#17	(limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	158
#18	((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	82
#19	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1113
#20	MESH DESCRIPTOR Popliteal Artery	282
#21	MESH DESCRIPTOR Tibial Arteries	33

(Continued)

#22	((poplite* or fempop* or infrapopliteal or tibial or tibiofibular or peroneal) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	244
#23	(below knee):TI,AB,KY	253
#24	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	45012
#25	MESH DESCRIPTOR Angioplasty EXPLODE ALL TREES	4177
#26	(angioplas* or percutan* or PTA or venoplasty):TI,AB,KY	14283
#27	(recanali* or revascular*):TI,AB,KY	7840
#28	dilat*:TI,AB,KY	7797
#29	(balloon or baloon):TI,AB,KY	7197
#30	MESH DESCRIPTOR Endovascular Procedures EXPLODE ALL TREES	6721
#31	endovascular:TI,AB,KY	1653
#32	MESH DESCRIPTOR Blood Vessel Prosthesis EXPLODE ALL TREES	412
#33	MESH DESCRIPTOR Blood Vessel Prosthesis Implantation EXPLODE ALL TREES	408
#34	MESH DESCRIPTOR Stents EXPLODE ALL TREES	3323
#35	(stent* or graft* or endograft* or endopros*):TI,AB,KY	25857
#36	powerlink or talent or excluder or aorfix or zenith or endologix or anaconda or Triascular or Cordis or Endurant or Quantum or Aneurx or Ancure or Advanta or Intracoil or Zilver or Luminex	591
#37	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	48585
#38	#24 AND #37	10184
#39	coronary:TI	17747
#40	renal:TI	12744
#41	myocardial:TI	11080
#42	heart:TI	16995
#43	(carotid OR cerebral OR stroke):TI	26794
#44	#39 OR #40 OR #41 OR #42 OR #43	79250
#45	#38 NOT #44	4490

Appendix 2. Database searches, 25 June 2018

Source	Search strategy	Hits retrieved
CENTRAL via CRSO	#1 MESH DESCRIPTOR Arteriosclerosis 946 #2 MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES 0 #3 MESH DESCRIPTOR Arteriosclerosis Obliterans 78 #4 MESH DESCRIPTOR Atherosclerosis 1057 #5 MESH DESCRIPTOR Arterial Occlusive Diseases 818 #6 MESH DESCRIPTOR Intermittent Claudication 823 #7 MESH DESCRIPTOR Ischemia 1529 #8 MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES 2772 #9 (atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY 12059 #10 ((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or re-occlus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 10524 #11 (peripheral near3 dis*):TI,AB,KY 4805 #12 (claudic* or IC):TI,AB,KY 4059 #13 (isch* or CLI):TI,AB,KY 31792 #14 arteriopathic:TI,AB,KY 7 #15 dysvascular*:TI,AB,KY 20 #16 (leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 130 #17 (limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 218 #18 ((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 106 #19 MESH DESCRIPTOR Leg EXPLODE ALL TREES 2795 #20 MESH DESCRIPTOR Popliteal Artery 301 #21 MESH DESCRIPTOR Tibial Arteries 37 #22 ((poplite* or fempop* or infrapopliteal or tibial or tibiofibular or peroneal) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY 340 #23 (below knee):TI,AB,KY 299 #24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 58387 #25 MESH DESCRIPTOR Angioplasty EXPLODE ALL TREES 4285 #26 (angioplas* or percutan* or PTA or venoplasty):TI,AB,KY 17853	1911

(Continued)

- #27 (recanali* or revascular*):TI,AB,KY 9723
- #28 dilat*:TI,AB,KY 9421
- #29 (balloon or baloon):TI,AB,KY 8392
- #30 MESH DESCRIPTOR Endovascular Procedures EXPLODE ALL TREES 7420
- #31 endovascular:TI,AB,KY 2483
- #32 MESH DESCRIPTOR Blood Vessel Prosthesis EXPLODE ALL TREES 430
- #33 MESH DESCRIPTOR Blood Vessel Prosthesis Implantation EXPLODE ALL TREES 432
- #34 MESH DESCRIPTOR Stents EXPLODE ALL TREES 3725
- #35 (stent* or graft* or endograft* or endoprosthe*):TI,AB,KY 32859
- #36 (powerlink or talent or excluder or aorfix or zenith or endologix or anaconda or Triascular or Cordis or Endurant or Quantum or Aneurx or Ancure or Advanta or Intracoil or Zilver or Luminex):TI,AB,KY 791
- #37 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 61169
- #38 #24 AND #37 13389
- #39 coronary:TI 20963
- #40 renal:TI 15210
- #41 myocardial:TI 12539
- #42 heart:TI 20907
- #43 (carotid OR cerebral OR stroke):TI 32775
- #44 #39 OR #40 OR #41 OR #42 OR #43 95337
- #45 #38 NOT #44 6176
- #46 01/01/2017 TO 25/06/2018:CD 292648
- #47 #45 AND #46 1911

Clinicaltrials.gov	peripheral artery disease OR pvd Angioplasty OR stent OR stenting OR Endovascular Procedures Start date on or after 01/01/2017 Last update posted on or before 06/26/2018	42
ICTRP Search Portal	peripheral artery disease OR pvd Angioplasty OR stent OR stenting OR Endovascular Procedures	16
MEDLINE	1 ARTERIOSCLEROSIS/ 56443 2 exp ARTERIOLOSCLEROSIS/ 149 3 Arteriosclerosis Obliterans/ 3974 4 ATHEROSCLEROSIS/ 30942 5 Arterial Occlusive Diseases/ 26481 6 Intermittent Claudication/ 7594 7 ISCHEMIA/ 47483	931

(Continued)

- 8 exp Peripheral Vascular Diseases/ 50011
- 9 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 170972
- 10 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 142839
- 11 (peripheral adj3 dis*).ti,ab. 37713
- 12 (claudic* or IC).ti,ab. 61912
- 13 (isch* or CLI).ti,ab. 345304
- 14 arteriopathic.ti,ab. 162
- 15 dysvascular*.ti,ab. 216
- 16 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 707
- 17 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 1808
- 18 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 1478
- 19 exp LEG/bs [Blood Supply] 25021
- 20 Popliteal Artery/ 8971
- 21 Tibial Arteries/ 1482
- 22 ((poplite* or fempop* or infrapopliteal or tibial or tibiofibular or peroneal) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 2222
- 23 below knee.ti,ab. 2705
- 24 or/1-23 771207
- 25 exp ANGIOPLASTY/ 59069
- 26 (angioplas* or percutan* or PTA or venoplasty).ti,ab. 158270
- 27 (recanali* or revascular*).ti,ab. 63853
- 28 dilat*.ti,ab. 132027
- 29 (balloon or baloon).ti,ab. 58152
- 30 exp Endovascular Procedures/ 106227
- 31 endovascular.ti,ab. 41162
- 32 exp Blood Vessel Prosthesis/ 27389
- 33 exp Blood Vessel Prosthesis Implantation/ 20589
- 34 exp STENTS/ 68512
- 35 (stent* or graft* or endograft* or endoprosthe*).ti,ab. 379475
- 36 (powerlink or talent or excluder or aorfix or zenith or endologix or anaconda or Triascular or Cordis or Endurant or Quantum or Aneurx or Ancure or Advanta or Intracoil or Zilver or Luminex).ti,ab. 118081

(Continued)

37 or/25-36 858143
 38 24 and 37 118933
 39 coronary.ti. 187093
 40 renal.ti. 255164
 41 myocardial.ti. 143393
 42 heart.ti. 279300
 43 (carotid or cerebral or stroke).ti,ab. 565188
 44 or/39-43 1350042
 45 38 not 44 65413
 46 randomized controlled trial.pt. 462606
 47 controlled clinical trial.pt. 92454
 48 randomized.ab. 414104
 49 placebo.ab. 189646
 50 drug therapy.fs. 2024675
 51 randomly.ab. 292381
 52 trial.ab. 430649
 53 groups.ab. 1805468
 54 or/46-53 4223684
 55 exp animals/ not humans.sh. 4466015
 56 54 not 55 3651071
 57 45 and 56 12116
 58 (2017* or 2018*).ed. 1396008
 59 57 and 58 931

 Embase

1 arteriosclerosis/ 33965 2 exp arteriosclerosis/ 598 3 peripheral occlusive artery disease/ 33214 4 atherosclerosis/ 136080 5 peripheral occlusive artery disease/ 33214 6 intermittent claudication/ 9762 7 ischemia/ 76632 8 exp peripheral vascular disease/ 1659635 9 (atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab. 236192 10 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 197030	6301
---	------

(Continued)

- 11 (peripheral adj3 dis*).ti,ab. 54293
- 12 (claudic* or IC).ti,ab. 62619
- 13 (isch* or CLI).ti,ab. 501091
- 14 arteriopathic.ti,ab. 206
- 15 dysvascular*.ti,ab. 239
- 16 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 987
- 17 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 2663
- 18 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 2085
- 19 popliteal artery/ 8511
- 20 tibial artery/ 2626
- 21 ((poplite* or fempop* or infrapopliteal or tibial or tibiofibular or peroneal) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 3292
- 22 below knee.ti,ab. 3440
- 23 or/1-22 2005601
- 24 exp angioplasty/ 82655
- 25 angioplas*.ti,ab. 56519
- 26 (recanal* or revascular*).ti,ab. 98197
- 27 (balloon or baloon).ti,ab. 89610
- 28 exp endovascular surgery/ 30698
- 29 endovascular.ti,ab. 60580
- 30 exp blood vessel prosthesis/ 13367
- 31 exp stent/ 152155
- 32 (stent* or graft* or endograft* or endopros*he*).ti,ab. 525915
- 33 (powerlink or talent or excluder or aorfix or zenith or endologix or anaconda or Triascular or Cordis or Endurant or Quantum or Aneurx or Ancure or Advanta or Intracoil or Zilver or Luminex).ti,ab. 77069
- 34 or/24-33 819330
- 35 23 and 34 268004
- 36 coronary.ti. 248958
- 37 renal.ti. 321018
- 38 myocardial.ti. 187858
- 39 heart.ti. 353011
- 40 (carotid or cerebral or stroke).ti. 355251

(Continued)

41 or/36-40 1382539
 42 35 not 41 155933
 43 randomized controlled trial/ 506719
 44 controlled clinical trial/ 460124
 45 random\$.ti,ab. 1312412
 46 randomization/ 78443
 47 intermethod comparison/ 236277
 48 placebo.ti,ab. 273953
 49 (compare or compared or comparison).ti. 470472
 50 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1757754
 51 (open adj label).ti,ab. 64655
 52 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 209368
 53 double blind procedure/ 151022
 54 parallel group\$1.ti,ab. 21843
 55 (crossover or cross over).ti,ab. 93145
 56 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. 283623
 57 (assigned or allocated).ti,ab. 332735
 58 (controlled adj7 (study or design or trial)).ti,ab. 295615
 59 (volunteer or volunteers).ti,ab. 224740
 60 trial.ti. 251607
 61 or/43-60 4046836
 62 42 and 61 33396
 63 (2017* or 2018*).em. 3617606
 64 62 and 63 6301

 CINAHL

S55 S53 AND S54 416
 S54 EM 2017 OR EM 2018 367,971
 S53 S40 AND S52 3,559
 S52 S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 341,911
 S51 MH "Random Assignment" 38,635
 S50 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies" 32,720
 S49 MH "Crossover Design" 11,198

416

(Continued)

S48 MH "Factorial Design" 919

S47 MH "Placebos" 8,351

S46 TX "multi-centre study" OR "multi-center study" OR "multicentre study"
OR "multicenter study" OR "multi-site study" 4,480

S45 TX crossover OR "cross-over" 14,551

S44 AB placebo* 28,287

S43 TX random* 218,886

S42 TX trial* 250,284

S41 TX "latin square" 142

S40 33 NOT 39 15,078

S39 S34 OR S35 OR S36 OR S37 OR S38 136,026

S38 TI carotid OR cerebral OR stroke 50,135

S37 TI heart 45,069

S36 TI myocardial 15,858

S35 TI coronary 27,524

S34 S23 AND S33 12,767

S33 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 72,689

S32 TX powerlink or talent or excluder or aorfix or zenith or endologix or ana-
conda or Triascular or Cordis or Endurant or Quantum or Aneurx or Ancure or
Advanta or Intracoil or Zilver or Luminex 4,750

S31 TX stent* or graft* or endograft* or endoprosthe* 34,651

S30 (MH "Stents+") 10,010

S29 (MH "Blood Vessel Prosthesis") 1,016

S28 TX balloon or baloon 6,736

S27 TX dilat* 10,252

S26 TX recanali* or revascular* 8,067

S25 TX angioplas* or percutan* or PTA or venoplasty 23,625

S24 (MH "Angioplasty+") 8,925

S23 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR
S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR
S22 90,560

S22 TX below knee 1,665

S21 TX (poplite* or fempop* or infrapopliteal or tibial or tibiofibular or per-
oneal) n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct*
or lesio* or block* or harden* or stiffen* or obliter*) 303

S20 (MH "Tibial Arteries") 146

S19 (MH "Popliteal Artery") 363

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S18 (MH "Leg/SU") 258

S17 TX (lower n3 extrem*) n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*) 122

S16 TX limb n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*) 278

S15 TX (leg n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*) 124

S14 TX dysvascular* 172

S13 TX arteriopathic 10

S12 TX isch* or CLI 39,424

S11 TX claudic* or IC 5,857

S10 TX peripheral n3 dis* 9,254

S9 TX (arter* or vascular or vein* or veno* or peripher*) n3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*) 12,664

S8 TX atherosclero* or arteriosclero* or PVD or PAOD or PAD 26,395

S7 (MH "Peripheral Vascular Diseases+") 10,402

S6 (MH "Ischemia") 3,371

S5 (MH "Intermittent Claudication") 852

S4 (MH "Arterial Occlusive Diseases") 1,608

S3 (MH "Atherosclerosis") 3,336

S2 (MH "Arteriosclerosis") 4,829

S1 (MH "Arteriosclerosis") 4,829

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	2 ATHEROSCLEROSIS/ 221	
	3 Intermittent Claudication/ 73	
	4 ISCHEMIA/ 263	
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	7 (peripheral adj3 dis*).ti,ab. 435	
	8 (claudic* or IC).ti,ab. 1024	
	9 (isch* or CLI).ti,ab. 1666	
	10 arteriopathic.ti,ab. 1	
	11 dysvascular*.ti,ab. 57	
	12 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*).ti,ab. 21	

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13 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 32

14 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 25

15 ((poplite* or fempop* or infrapopliteal or tibial or tibiofibular or peroneal) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab. 87

16 below knee.ti,ab. 359

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18 (angioplas* or percutan* or PTA or venoplasty).mp. [mp=abstract, heading words, title] 792

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20 dilat*.ti,ab. 220

21 (balloon or baloon).ti,ab. 90

22 endovascular.ti,ab. 28

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CONTRIBUTIONS OF AUTHORS

CC-TH: selected studies, extracted data, assessed risk of bias, wrote the review.

DS: commented on the review.

GNCK: selected studies, extracted data, assessed risk of bias, wrote the review.

JAR: commented on the review.

CA: commented on the review.

MLvD: acted as arbiter for study selection and data extraction, assessed risk of bias, wrote the review. provided support with methodological aspects of the review.

DECLARATIONS OF INTEREST

CC-TH: none known.

DS: none known.

GNCK: none known.

JAR: none known.

CA: none known.

MLvD: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added a paragraph to the methods section to explain how we addressed unit of analysis issues regarding participant or limb randomisation in this review.

We have added 'technical success' as a primary outcome and have upgraded the outcome 'procedural complication' to a primary outcome.

We have removed target lesion revascularisation (TLR) and minor amputation as outcome measures. TLR, defined as repeat percutaneous or surgical revascularisation of a lesion anywhere within the stent or within the 5-mm borders proximal or distal to the stent, is dependent on the willingness of the operator to intervene, regardless of the patency of the treated target. We therefore decided that this was not an appropriate outcome. Minor amputation of devascularised tissue/gangrene is considered part of the treatment for CLTI, and although revascularisation is aimed at preventing further tissue loss, it does not affect the outcome of tissue that is not viable and hence is considered not relevant as an outcome measure.

INDEX TERMS

Medical Subject Headings (MeSH)

*Stents [adverse effects]; Amputation [statistics & numerical data]; Angioplasty [adverse effects] [*methods] [mortality]; Endovascular Procedures [methods]; Ischemia [etiology] [*therapy]; Leg [*blood supply]; Leg Ulcer [etiology] [therapy]; Peripheral Arterial Disease [*complications]; Popliteal Artery; Quality of Life; Randomized Controlled Trials as Topic; Tibial Arteries; Vascular Patency

MeSH check words

Humans