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Antiplatelet and anticoagulant drugs for prevention of restenosis/ reocclusion following peripheral endovascular treatment (Review)

Robertson L, Ghouri MA, Kovacs F

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[Intervention Review]

Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment

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Editorial note: This review has been superseded by Cochrane Reviews: 'Antithrombotics after infra-inguinal bypass grafting' (<https://doi.org/10.1002/14651858.CD015141>) and 'Antithrombotics after infra-inguinal peripheral endovascular treatment' (<https://doi.org/10.1002/14651858.CD015142>).

ABSTRACT

Background

Peripheral arterial disease (PAD) is frequently treated by balloon angioplasty. Restenosis/reocclusion of the dilated segments occurs often, depending on length of occlusion, lower leg outflow, stage of disease and presence of cardiovascular risk factors. To prevent reocclusion, patients are treated with antithrombotic agents. This is an update of a review first published in 2005.

Objectives

To determine whether any antithrombotic drug is more effective in preventing restenosis or reocclusion after peripheral endovascular treatment, compared to another antithrombotic drug, no treatment, placebo or other vasoactive drugs.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched 14 February 2012) and CENTRAL (2012, Issue 1).

Selection criteria

We selected randomised controlled trials (RCTs). Participants were patients with symptomatic PAD treated by endovascular revascularisation of the pelvic or femoropopliteal arteries. Interventions were anticoagulant, antiplatelet or other vasoactive drug therapy compared with no treatment, placebo or any other vasoactive drug. Clinical endpoints were reocclusion, restenosis, amputation, death, myocardial infarction, stroke, major bleeding and other side effects, such as minor bleeding, puncture site bleeding, gastrointestinal side effects and haematoma.

Data collection and analysis

We independently extracted and assessed details of the number of randomised patients, treatment, study design, patient characteristics and risk of bias. Analysis was based on intention-to-treat data. To examine the effects of outcomes such as reocclusion, restenosis, amputation and major bleeding, we computed odds ratios (OR) with 95% confidence intervals (CI) using a fixed-effect model.

Main results

Twenty-two trials with a total of 3529 patients are included (14 in the original review and a further eight in this update). For the majority of comparisons, only one trial was available so results were rarely combined in meta-analyses. Individual trials were generally small and risk of bias was often unclear due to limitations in reporting. Three trials reported on drug versus placebo/control; results were consistently available for a maximum follow-up of only six months. At six months post intervention, a statistically significant reduction in reocclusion was found for high-dose acetylsalicylic acid (ASA) combined with dipyridamole (DIP) (OR 0.40, 95% CI 0.19 to 0.84), but not for low-dose ASA combined with DIP (OR 0.69, 95% CI 0.44 to 1.10; $P = 0.12$) nor in major amputations for lipo-ecraprost (OR 0.89, 95% CI 0.44 to 1.80). The remaining trials compared different drugs; results were more consistently available for a longer period of 12 months. At 12 months post intervention, no statistically significant difference in reocclusion/restenosis was detected for any of the following comparisons: high-dose ASA versus low-dose ASA (OR 0.98, 95% CI 0.64 to 1.48; $P = 0.91$), ASA/DIP versus vitamin K antagonists (VKA) (OR 0.65, 95% CI 0.40 to 1.06; $P = 0.08$), clopidogrel and aspirin versus low molecular weight heparin (LMWH) plus warfarin (OR 0.31, 95% CI 0.06 to 1.68; $P = 0.18$), suloctidil versus VKA: reocclusion (OR 0.59, 95% CI 0.20 to 1.76; $P = 0.34$), restenosis (OR 1.87, 95% CI 0.66 to 5.31; $P = 0.24$) and ticlopidine versus VKA (OR 0.71, 95% CI 0.37 to 1.36; $P = 0.30$). Treatment with cilostazol resulted in statistically significantly fewer reocclusions than ticlopidine (OR 0.32, 95% CI 0.13 to 0.76; $P = 0.01$). Compared with aspirin alone, LMWH plus aspirin significantly decreased occlusion/restenosis (by up to 85%) in patients with critical limb ischaemia (OR 0.15, 95% CI 0.06 to 0.42; $P = 0.0003$) but not in patients with intermittent claudication (OR 1.73, 95% CI 0.97 to 3.08; $P = 0.06$) and batroxobin plus aspirin reduced restenosis in diabetic patients (OR 0.28, 95% CI 0.13 to 0.60). Data on bleeding and other potential gastrointestinal side effects were not consistently reported, although there was some evidence that high-dose ASA increased gastrointestinal side effects compared with low-dose ASA, that clopidogrel and aspirin resulted in fewer major bleeding episodes compared with LMWH plus warfarin, and that abciximab resulted in more severe bleeding episodes.

Authors' conclusions

There is limited evidence suggesting that restenosis/reocclusion at six months following peripheral endovascular treatment is reduced by use of antiplatelet drugs compared with placebo/control, but associated information on bleeding and gastrointestinal side effects is lacking. There is also some evidence of variation in effect according to different drugs with cilostazol reducing reocclusion/restenosis at 12 months compared with ticlopidine and both LMWH and batroxobin combined with aspirin appearing beneficial compared with aspirin alone. However, available trials are generally small and of variable quality and side effects of drugs are not consistently addressed. Further good quality, large-scale RCTs, stratified by severity of disease, are required.

PLAIN LANGUAGE SUMMARY

Drugs to prevent the re-occurrence of narrowing of blood vessels in peripheral arterial disease after the blood vessels have been surgically widened

Peripheral arterial disease of leg arteries can progressively cause leg pain on walking, pain at rest, ulcers and gangrene because of reduced blood flow. An inflatable balloon catheter inserted into the artery is used to widen and unblock the affected artery (termed angioplasty) yet reoccurrence of narrowing (restenosis) or obstruction (reocclusion) frequently occurs because of platelet clumping (aggregation) and activated blood clotting in the damaged blood vessel. This review of 22 randomised clinical trials, with a combined total of 3529 patients, set out to determine if any drug was more effective than another in preventing occlusion or restenosis of the artery after the blood vessels have been surgically widened. For the majority of comparisons, only one study was available. Evidence suggests that some drugs which reduce platelet aggregation, such as higher-dose aspirin, can reduce the rate of reocclusion six months after surgery, but evidence on associated side effects and for longer-term restenosis rates is scarce. There is also some evidence of variation in effect according to different drugs, with reocclusion/restenosis rates lower in people taking cilostazol compared with ticlopidine 12 months after surgery and, in patients with more severe disease, those taking low molecular weight heparin in addition to aspirin compared with aspirin alone. Batroxobin plus aspirin compared with aspirin alone may be an effective treatment in diabetic patients. However, available trials are generally small and of variable quality and side effects of drugs are not consistently addressed. Further good quality, large-scale randomised controlled trials, grouped by severity of disease, are required.

BACKGROUND

Description of the condition

Peripheral arterial disease (PAD) leads to ischaemic pain on walking (intermittent claudication, i.e. muscular pain due to a lack of blood supply) or, if more severe, to rest pain and gangrene (necrotic tissue, mostly at the toes). Based on the severity of symptoms the stages of the disease are defined as Fontaine stages I to IV ([Fontaine 1954](#)), where stage I is asymptomatic, stage IIa is the occurrence of intermittent claudication after a pain-free walking distance of more than 200 metres, stage IIb is intermittent claudication after less than 200 metres, stage III is rest pain and stage IV is the presence of ischaemic ulcers. An alternative classification of PAD ([Rutherford 2001](#)) is also used, with stages II and III representing moderate and severe claudication respectively, stage IV is ischaemic pain at rest and stages V and VI are minor tissue loss (non-healing ulcer, focal gangrene with diffuse pedal ischaemia) and major tissue loss (extending above transmetatarsal level, functional foot no longer salvageable) respectively.

Percutaneous transluminal angioplasty (PTA) is a well established endovascular procedure for lower limb atherosclerosis. First invented by Dotter and Judkins ([Dotter 1964](#)) and technically improved by Grüntzig ([Grüntzig 1974](#)), the method is used in the treatment of obstructed arteries of the lower limbs, and as a modified procedure of the upper limbs, coronary, carotid, mesenteric and renal arteries. In PTA, an arterial obstruction is treated either by dilatation of a stenosis (i.e. a narrowing of the vessel diameter) or recanalisation of a total vessel occlusion, using a wire-guided inflatable balloon catheter. For treatment of the lower limbs, usually the femoral artery in the groin is cannulated and a deflated balloon catheter is inserted and pushed forward along the guide-wire to the sites of obstruction. The method can be combined with local thrombolysis (LTL) and percutaneous transluminal thromboembolectomy (PTEE) ([Schneider 1989](#); [Zehnder 2000](#)) in cases of acute-on-chronic disease or embolic occlusions.

In cases complicated by major endothelial damage, so-called arterial dissection, or non-satisfactory dilatation with relevant residual stenosis, a wall stent may be implanted to reduce the risk of reocclusion. Stent walls are mainly applied at the aortic bifurcation or iliac segments, whereas the femoropopliteal level until recently was associated with a higher risk for reocclusion due to smaller vessel diameters in distal arteries ([Do 1992](#); [Mahler 1999](#); [Palmaz 1985](#); [Strecker 1988](#)). However, with the recent new generation of stents including nitinol and drug-eluting stents, outcomes at the femoropopliteal levels have clearly improved ([Duda 2001](#); [Mewissen 2004](#); [Sabeti 2004](#); [Vogel 2003](#)).

Peripheral catheter interventions are relatively minor procedures performed under local anaesthesia allowing early and full mobilisation, i.e. within 24 hours if continuous thrombolysis is not applied. However, as a result of this intervention, atherosclerotic plaques are ruptured and platelets aggregate at the site of injury ([Block 1981](#); [Ferns 1992](#); [Fuster 1995](#)). Extensive vessel wall damage coupled with low shear stress and poor infrapopliteal outflow are mostly responsible for the occurrence of reocclusion ([Schwartz 1998](#); [Ward 2001](#); [Wentzel 2003](#)). Additionally, in the initial phase after catheter intervention, a hypercoagulable state prevails, as parameters of activated coagulation, including thrombin-antithrombin complexes (TAT), D-Dimer and Fibrinopeptide A (Fa)

become elevated in the plasma ([Tschöpl 1997](#)). This activated coagulation system produces conditions favourable for early thrombotic occlusion, where 'early' is usually defined as a period covering the first four weeks after the intervention ([Tsakiris 1999](#)). Subsequently, a condition of the arterial wall called 'intimal hyperplasia' may follow which is responsible for intermediate and late-term restenosis and reocclusion. Intimal hyperplasia occurs as a result of denudation (tearing off of the inner lining) of the endothelium caused by manipulation of the vessel wall with the catheter. Media smooth muscle cells are stimulated to grow into the intimal layer followed by the inclusion of foam cells and calcium ([Haudenschild 1995](#); [Jorgensen 1990](#)). Reported rates of arterial reocclusion or symptomatic restenosis following femoropopliteal PTA are between 5% and 25% for early events and about 40% at one year ([Schillinger 2003](#)). The five-year patency rate was reported to be 83% for iliac and 58% for femoropopliteal PTA, whilst patients with stenoses or occlusions of less than 3 cm had a favourable long-term patency rate of 74% ([Gallino 1984](#)). Patients subjected to local thrombolysis show higher incidences ([Decrinis 1993](#); [Parent 1989](#)). The implantation of drug-eluting or nitinol stents ([Mewissen 2004](#)) following PTA is considered an intervention with the capacity to reduce the occurrence of intimal hyperplasia ([Duda 2002](#); [Minar 2000](#); [Vogel 2003](#)).

Why it is important to do this review

Drug interventions to prevent thrombosis and/or intimal hyperplasia leading to reocclusion and restenosis of the treated segments would make an important contribution to the sustained success of endovascular treatment. Current peri-interventional treatment strategies mostly include aspirin intake before and after PTA, initial administration of either unfractionated or low molecular weight heparin ([Ellis 1989](#)) followed mostly by antiplatelet drugs or anticoagulants on a long-term basis ([Do 1994](#); [Hess 1985](#); [Shammas 2003b](#); [Watson 2000](#)). However, reported recurrent event rates ought to be improved. This is an update of a Cochrane review first published in 2005.

OBJECTIVES

To determine whether anticoagulants, antiplatelets or any other vasoactive drug compared with each other, with placebo and to no treatment show any advantages in preventing early occlusion, or mid-term and long-term occlusions or restenosis after percutaneous transluminal angioplasty, local thrombolysis, percutaneous transluminal thromboembolectomy or angioplasty and stent implantation.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials comparing any antiplatelet or anticoagulant or vasoactive drug with placebo or with any other antiplatelet or anticoagulant or vasoactive drug were included. Randomised trials comparing a drug to no drug were also included, if they met the otherwise defined criteria for inclusion. All retrospective trials, or those without comparison group, were excluded.

Types of participants

Patients with symptomatic chronic or acute PAD, defined as stages II to IV on the Fontaine classification or stages II to VI on the Rutherford classification, due to obstructions of the aortic, iliac, femoral, popliteal or crural arterial segments were included if they had undergone any endovascular treatment. The latter comprises PTA alone, or combined with implantation of a stent and/or PTEE and/or LTL and/or laser-assisted PTA (i.e. recanalisation of a long occlusion by the use of laser energy applied from an intraluminally placed probe, e.g. a Nd-YAG laser). Diagnosis of PAD and stage, as well as definition of the obstructed segment, were to be based on the findings of clinical examination, ankle brachial index (ABI) measurement, duplex sonography and angiography.

Types of interventions

Trials were included that compared anticoagulant therapy, antiplatelet therapy or other pharmacological measures following angioplasty with no treatment, placebo or any other vasoactive drug.

Types of outcome measures

We analysed outcome measures for all time points reported, mainly at two to four weeks and three, six, 12, 24 and 36 months after the intervention. The variation depended on the length of each trial. Because of the risk of unit of analysis errors when using multiple time points for the purpose of this review, we chose 12 months as the primary time point for measuring reocclusion.

Primary outcomes

- Occlusion or restenosis > 50%, shown by duplex sonography or angiography, according to previously described diagnostic criteria (Moneta 1987; Ranke 1992)

Secondary outcomes

- Amputation
- Death
- Myocardial infarction
- Stroke
- Major bleeding (i.e. requiring blood replacement therapy or intensive care)
- Side effects (minor bleeding, puncture site bleeding, gastrointestinal side effects and haematoma)

Search methods for identification of studies

There was no restriction on publication language.

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched 14 February 2012) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 1, part of *The Cochrane Library*, www.thecochranelibrary.com. See [Appendix 1](#) for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL and AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are

described in the [Specialised Register](#) section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

We scrutinised reference lists of identified trials for further information.

Data collection and analysis

Selection of studies

For this update, one author (LR) used the selection criteria to identify trials for inclusion. Two authors (MG and FK) independently confirmed this selection and any disagreements were resolved by discussion.

Data extraction and management

All authors independently extracted the data for the new studies considered (Baumgartner 2007; Iida 2008; Koppensteiner 2006; Nehler 2007; Schindler 2008; Tan 2008; Wang 2011). We extracted the number of patients allocated to different treatment groups in each trial in order to allow an intention-to-treat analysis. We inserted data collected from each trial onto a computerised form, including columns for reference; study design (clinical trial, journal article, multicentre study); indication (PAD stage, segment obstructed); technique used (PTA, subintimal PTA, laser-assisted PTA, stent implantation, LTL, PTEE); type of anticoagulant, heparin, antiplatelet drug, vasoactive drug; time schedule including start and stop of drug therapy; dose; number of patients (age, sex); previous interventional or surgical treatment; episodes of cardiovascular disease before operation; number and time point of reocclusion; number of patencies; number controlled by angiography or duplex sonography; number of deaths, stroke, myocardial infarction, amputation, major bleedings; and special remarks (out-flow, in-flow, technical difficulties). The authors of the original review extracted the data for the previously included studies. We entered data into Review Manager (RevMan), the systematic review software from the Cochrane Collaboration (RevMan 2011).

Assessment of risk of bias in included studies

Three authors (LR, MG, FK) independently assessed the risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The 'Risk of bias' tool provides a strict protocol to assess allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential sources of bias. For each of the six domains, we assessed the risk of bias as 'low risk', 'high risk' or as 'unclear risk of bias', with unclear risk of bias indicating that there was insufficient information available to permit judgement of either low or high risk of bias. Disagreements were resolved by discussion between the three authors.

Measures of treatment effect

Analysis was based on intention-to-treat data from the individual clinical trials. To examine the effects of binary outcomes, such as primary occlusion after angioplasty, amputation and bleeding complications, we computed odds ratios (OR) using a fixed-effect model. We calculated the 95% confidence intervals (CI) of the effect sizes.

We performed the following comparisons:

1. antiplatelet treatment versus placebo;
2. one antiplatelet treatment versus another antiplatelet treatment;
3. high-dose antiplatelet treatment versus low-dose antiplatelet treatment;
4. antiplatelet versus anticoagulant treatment;
5. one vasoactive drug versus antiplatelet treatment;
6. one vasoactive drug versus anticoagulant treatment;
7. one anticoagulant treatment versus another anticoagulant treatment;
8. one anticoagulant treatment plus antiplatelet treatment versus antiplatelet treatment alone;
9. prostaglandin versus placebo;
10. angiotension-receptor blocker versus angiotension-converting enzyme inhibitor.

Unit of analysis issues

The unit of randomisation was the individual participant in the majority of included studies. Where studies included patients undergoing bilateral PTA, we gave consideration to whether the limbs had the same or different treatments. Only studies where both limbs received exactly the same treatment were included. For these studies, we evaluated data by limb rather than patient. All of the trials involved repeat observations on participants at different points in time ranging from 24 hours to 36 months post PTA and thus were prone to unit of analysis errors. Therefore, for the purpose of this review, we chose 12 months as the primary time point for measuring reocclusion. Where two or more studies with low methodological and statistical heterogeneity were included, we performed a meta-analysis.

Dealing with missing data

We sought information about drop outs, withdrawals and other missing data from the included studies. When not reported, we made attempts to obtain missing data by contacting authors.

Assessment of heterogeneity

We planned to assess the heterogeneity between pooled studies by using the χ^2 test regarding characteristics and quality of included studies.

Assessment of reporting biases

We planned to assess reporting biases using funnel plots. However, there were too few studies to make the results meaningful. Therefore, we assessed reporting biases by individual trials.

Data synthesis

The intention was to perform a fixed-effect meta-analysis of the included trials but since we anticipated that the trials might not be homogeneous, we intended to perform subgroup analyses of the included trials according to variables such as severity of disease, severity of occlusions and restenosis, and different interventions.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses by the following:

1. chronic versus acute disease;

2. occlusions > 10 cm versus occlusions < 10 cm;
3. stenosis > 50%;
4. separate intervention techniques;
5. separate obstruction segments.

However, data were not available in sufficient quantities to perform all the planned subgroup analyses.

RESULTS

Description of studies

Results of the search

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#) for details of included and excluded trials.

For this update there were an additional 26 reports of studies retrieved for consideration from the search of the Specialised Register. Two were additional publications for the previously included study by [Ranke 1994](#). There were nine reports relating to eight new included studies and one report to a new excluded study ([Ishii 2008](#)). One was an abstract of an ongoing study ([Mirror 2011](#)). We contacted the author but, at the time of this update, the results had not been published and therefore data from this study could not be used. The remaining reports were not relevant for this update.

Included studies

For this update there were an additional eight studies included ([Ansel 2006](#); [Baumgartner 2007](#); [Iida 2008](#); [Koppensteiner 2006](#); [Nehler 2007](#); [Schindler 2008](#); [Tan 2008](#); [Wang 2011](#)) making a total of 22 randomised clinical trials which we included in a formal analysis ([Ansel 2006](#); [Baumgartner 2007](#); [Do 1994](#); [Dörffler-Melly 2005](#); [Duda 2001](#); [Heinz 1996](#); [Heiss 1990](#); [Hess 1978](#); [Iida 2008](#); [Koppensteiner 2006](#); [Mahler 1987](#); [Minar 1995](#); [Nehler 2007](#); [Pilger 1991](#); [Ranke 1994](#); [Schindler 2008](#); [Schneider 1987](#); [Schweizer 2001](#); [Study group 1994](#); [Tan 2008](#); [Wang 2011](#); [Weichert 1994](#)). Fifteen studies were single-centre whilst the studies of [Mahler 1987](#) and [Weichert 1994](#) were performed in two centres, [Schneider 1987](#) in three centres, [Ansel 2006](#) in five centres, the [Study group 1994](#) in 12 hospital centres and [Nehler 2007](#) was conducted in 28 centres in the UK and USA. The RIO trial ([Baumgartner 2007](#)) was a multicentre study conducted across Europe but the authors did not specify the number of participating sites involved. The study of [Heiss 1990](#) appears in two comparison categories, i.e. in acetylsalicylic acid (ASA) versus placebo and in ASA high-dose versus ASA low-dose, because the study compared high-dose ASA/dipyridamole (DIP) versus low-dose ASA/DIP versus placebo.

Fifteen of the 22 included trials were performed in German speaking countries: eight in Germany, four in Switzerland and three in Austria. Of the remaining seven trials, two were conducted in China and one in Japan and Sweden and the USA. One multicentre trial was conducted across Europe while another trial was conducted in both the UK and the USA.

Participants

All study participants were treated for symptomatic PAD, the majority at a stage of intermittent claudication. Five studies included participants at a critically ischaemic stage ([Do 1994](#); [Koppensteiner 2006](#); [Nehler 2007](#); [Schweizer 2001](#); [Wang 2011](#)).

In the study by Wang 2011, 45% of participants had stage IV, V or VI disease according to the Rutherford classification for PAD. Furthermore, all participants in this study had diabetes. Nehler 2007 included only patients with critical limb ischaemia, 74% of whom had stage IV ischaemic ulceration as measured by the Fontaine classification.

Occlusions

The majority of studies included patients treated for femoropopliteal lesions (Ansel 2006; Baumgartner 2007; Do 1994; Dörffler-Melly 2005; Heinz 1996; Heiss 1990; Iida 2008; Koppensteiner 2006; Mahler 1987; Minar 1995; Pilger 1991; Ranke 1994; Schindler 2008; Schneider 1987; Tan 2008). Some studies examined occlusions in the iliac artery (Duda 2001; Study group 1994), the infrapopliteal artery (Nehler 2007; Wang 2011) or lesions at the pelvic level (Schweizer 2001). The studies by Hess 1978 and Weichert 1994 had a less specific inclusion criteria and included any patient with a chronic arterial stenosis or occlusion of the lower extremity.

Not all trials specified inclusion criteria for occlusion size. In the few studies that did report it, the length of occlusions varied from 1 to 20 cm (Tan 2008), < 3 to 10 cm (Ranke 1994), > 3 cm (Pilger 1991), > 5 cm (Dörffler-Melly 2005), ≥ 7 cm (Ansel 2006) and ≤ 10 cm (Do 1994; Mahler 1987; Schneider 1987). Duration of occlusion was reported in a few studies only. Duda 2001 only included patients who had an occlusion for six weeks or less while the inclusion criteria for entry into the Pilger 1991 study was a chronic occlusion for at least four months.

Endovascular procedures

PTA was performed either in the pelvic, femoral or popliteal regions. PTA alone was the technique used most frequently, while in some studies local thrombolysis and thromboembolectomy (Duda 2001; Dörffler-Melly 2005) or stent implantation was performed in some of the patients (Ansel 2006; Iida 2008; Schindler 2008; Tan 2008). In the study by Schindler 2008, patients who did not have a medical indication for stent implantation after PTA were excluded from the trial.

One study included patients treated by laser-assisted angioplasty (Pilger 1991). Randomisation occurred mostly after successful revascularisation but some studies randomised before PTA and then excluded patients in whom the revascularisation procedure was unsuccessful (Nehler 2007; Wang 2011). Where randomisation was performed before endovascular treatment, patients were excluded from the evaluation concerning antithrombotic treatment during follow-up. The trial by Weichert 1994 randomised patients to treatment 48 hours after the PTA procedure. Consequently any participant with an occlusion within 48 hours of the procedure was excluded from the study.

Patients were usually started on antiplatelet therapy the day before the endovascular treatment. Therapeutic standard was to administer 5000 IU heparin intra-arterially during the endovascular intervention and to start all patients on ASA at least one day before catheter interventions. Some studies used administered clopidogrel in addition to aspirin prior to the PTA procedure (Ansel 2006; Baumgartner 2007; Schindler 2008).

Pharmacological interventions

The comparisons of pharmacological interventions reported in the 22 included trials comprised:

1. ASA/DIP versus placebo (Heiss 1990; Study group 1994);
2. ASA versus ASA/DIP (Hess 1978);
3. high-dose ASA versus low-dose ASA (Heiss 1990; Minar 1995; Ranke 1994; Weichert 1994);
4. ASA/DIP versus VKA (Do 1994; Pilger 1991);
5. other antiplatelet agents or vasoactive drugs (clopidogrel plus aspirin versus low molecular weight heparin (LMWH) followed by warfarin (Tan 2008); suloctidil plus VKA versus VKA (Mahler 1987); ticlopidine versus VKA (Schneider 1987); cilostazol plus aspirin versus ticlopidine plus aspirin (Iida 2008); taprostene versus ASA/DIP (Heinz 1996); urokinase plus abciximab versus urokinase alone (Duda 2001); abciximab versus placebo (Ansel 2006; Baumgartner 2007; Dörffler-Melly 2005);
6. LMWH versus unfractionated heparin (UFH) (Schweizer 2001);
7. LMWH plus aspirin versus aspirin alone (Koppensteiner 2006);
8. lipo-ecraprost versus placebo (Nehler 2007);
9. batroxobin plus aspirin versus aspirin alone (Wang 2011);
10. candesartan versus quinapril (Schindler 2008).

Outcome measures

All investigators used pulse palpation, Doppler ultrasonographic pressure measurements, ABI (or systolic ankle pressure) and angiography where necessary to assess the patency of the treated arterial segments. Duplex sonography was not used in all trials. Primary patency assessment was the most frequently defined primary endpoint. Death was reported in 10 studies (Duda 2001; Iida 2008; Koppensteiner 2006; Nehler 2007; Pilger 1991; Ranke 1994; Study group 1994; Tan 2008; Wang 2011; Weichert 1994). Death from cardiovascular events including myocardial infarction was reported in six studies (Ansel 2006; Iida 2008; Koppensteiner 2006; Nehler 2007; Ranke 1994; Weichert 1994) while stroke was reported in four studies (Ansel 2006; Koppensteiner 2006; Ranke 1994; Weichert 1994). Amputations were reported in seven studies (Duda 2001; Iida 2008; Nehler 2007; Pilger 1991; Schweizer 2001; Study group 1994; Wang 2011). Seven studies assessed major bleeding episodes (Baumgartner 2007; Duda 2001; Dörffler-Melly 2005; Koppensteiner 2006; Study group 1994; Tan 2008; Wang 2011) and 12 studies measured adverse side effects or complications (Duda 2001; Heinz 1996; Iida 2008; Minar 1995; Nehler 2007; Pilger 1991; Ranke 1994; Schindler 2008; Schneider 1987; Tan 2008; Wang 2011; Weichert 1994).

Excluded studies

For this update one additional study was excluded (Ishii 2008) making a total of 10 studies (Allie 2003; Bulvas 1996; Horrocks 1997; Ishii 2008; Mueller 1997; Shammass 2003; Stavropoulos 2003; Strecker 2004; Tetteroo 1995; Zeitler 1973) which were excluded for various reasons such as lack of a control group (Allie 2003; Mueller 1997; Shammass 2003; Stavropoulos 2003) and lack of randomisation, selection or performance bias (Bulvas 1996; Horrocks 1997; Tetteroo 1995; Zeitler 1973). The studies by Ishii 2008 and Strecker 2004 were not randomised controlled trials.

Risk of bias in included studies

See Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Allocation concealment (selection bias)	Random sequence generation (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Ansel 2006	+	?	?	?	+	+	-
Baumgartner 2007	?	?	?	?	-	+	+
Do 1994	+	?	-	?	+	+	-
Dörffler-Melly 2005	+	?	+	+	+	+	-
Duda 2001	?	+	-	+	?	+	+
Heinz 1996	?	+	?	?	+	+	+
Heiss 1990	?	?	+	?	+	+	+
Hess 1978	?	?	+	?	+	+	+
Iida 2008	+	+	-	+	-	+	+
Koppensteiner 2006	?	+	-	+	?	+	-
Mahler 1987	+	?	+	?	?	+	+
Minar 1995	?	+	-	+	+	+	+
Nehler 2007	?	+	?	?	+	-	-
Pilger 1991	?	?	-	?	+	+	+
Ranke 1994	+	+	+	+	+	+	+
Schindler 2008	?	?	?	?	?	+	+
Schneider 1987	?	+	?	?	+	-	+

Figure 2. (Continued)

Schneider 1987	?	+	?	?	+	-	+
Schweizer 2001	?	?	-	+	+	+	+
Study group 1994	+	?	+	?	?	+	?
Tan 2008	?	?	?	?	?	-	?
Wang 2011	?	+	?	+	+	+	+
Weichert 1994	?	+	+	?	+	+	-

Allocation

All trials were described as randomised. Allocation concealment was by sealed envelopes in seven studies (Ansel 2006; Do 1994; Dörffler-Melly 2005; Iida 2008; Mahler 1987; Ranke 1994; Study group 1994), one of which specified that envelopes were opaque (Study group 1994). One study (Wang 2011) stated that the randomisation list was blocked until completion of the study. For the remaining 14 studies (Baumgartner 2007; Duda 2001; Heinz 1996; Heiss 1990; Hess 1978; Koppensteiner 2006; Minar 1995; Nehler 2007; Pilger 1991; Schindler 2008; Schneider 1987; Schweizer 2001; Tan 2008; Weichert 1994) the method of allocation concealment was not described and thus there was insufficient information available to permit judgement of either low or high risk of bias for these studies.

For random sequence generation, we deemed 10 studies (Duda 2001; Heinz 1996; Iida 2008; Koppensteiner 2006; Minar 1995; Nehler 2007; Ranke 1994; Schneider 1987; Wang 2011; Weichert 1994) as low risk of bias as authors had explicitly stated the method of random generation: computer-generated in six studies (Duda 2001; Heinz 1996; Iida 2008; Koppensteiner 2006; Wang 2011; Weichert 1994), random block permutations in one study (Ranke 1994), via a voice response system in one study (Nehler 2007), through adaptive randomisation in another study (Minar 1995) and by telephone randomisation in another (Schneider 1987). We deemed the remaining 12 studies (Ansel 2006; Baumgartner 2007; Do 1994; Dörffler-Melly 2005; Heiss 1990; Hess 1978; Mahler 1987; Pilger 1991; Schindler 2008; Schweizer 2001; Study group 1994; Tan 2008) to have an unclear risk of selection bias due to insufficient reporting of methods used for random sequence generation.

Blinding

In measuring performance bias, seven of the included studies (Dörffler-Melly 2005; Heiss 1990; Hess 1978; Mahler 1987; Ranke 1994; Study group 1994; Weichert 1994) were reported as 'double-blind' and were awarded a low risk of bias. In six (Dörffler-Melly 2005; Heiss 1990; Mahler 1987; Ranke 1994; Study group 1994; Weichert 1994) studies, authors reported that study drugs were identical in size, shape or colour and given in identical containers, thus ensuring blinding of both the study participants and personnel. We judged seven studies (Do 1994; Duda 2001; Iida 2008; Koppensteiner 2006; Minar 1995; Pilger 1991; Schweizer 2001) to be at a high risk of performance bias. In Do 1994, Iida 2008, Minar 1995 and Schweizer 2001, authors reported that neither participant nor study agents were blinded to treatment dose. Duda 2001 reported that study agents were not blinded to treatment to avoid delaying the start of the study. Finally, the study drugs in the trial of Koppensteiner 2006 were LMWH versus aspirin and

therefore neither study participant nor the staff administering the heparin could be blinded to treatment. Eight studies (Ansel 2006; Baumgartner 2007; Heinz 1996; Nehler 2007; Schindler 2008; Schneider 1987; Tan 2008; Wang 2011) did not provide enough information to permit a judgement and we deemed them to be at unclear risk of performance bias. Although Wang 2011 stated that the randomisation list was blocked so that radiologists and data collection staff were blinded to the treatment sequence, it was not stipulated that the trial was double-blind and, therefore, this trial was deemed to be at an unclear risk of performance bias.

For detection bias, that is blinding of outcome assessment, we classified eight studies (Duda 2001; Dörffler-Melly 2005; Iida 2008; Koppensteiner 2006; Minar 1995; Ranke 1994; Schweizer 2001; Wang 2011) as low risk as the authors had specified that those evaluating angiographic follow-up data were blinded to treatment. The remaining 14 studies (Ansel 2006; Baumgartner 2007; Do 1994; Heinz 1996; Heiss 1990; Hess 1978; Mahler 1987; Nehler 2007; Pilger 1991; Schindler 2008; Schneider 1987; Study group 1994; Tan 2008; Weichert 1994) did not provide information on blinding of outcome assessment and we thus classified them as unclear risk of detection bias.

Incomplete outcome data

We deemed 14 (Ansel 2006; Do 1994; Dörffler-Melly 2005; Heinz 1996; Heiss 1990; Hess 1978; Minar 1995; Nehler 2007; Pilger 1991; Ranke 1994; Schneider 1987; Schweizer 2001; Wang 2011; Weichert 1994) of the included studies to be at low risk of attrition bias. We deemed two studies (Baumgartner 2007; Iida 2008) to be at high risk. Baumgartner 2007 stated that 423 patients underwent revascularisation but only 392 were randomised to treatment. The reason for this loss of study participants is not specified and, therefore, we judged this study to be at a high risk of attrition bias. In the study by Iida 2008, there was an imbalance in the number of patients who withdrew due to side effects of the study drugs. The remaining six studies (Duda 2001; Koppensteiner 2006; Mahler 1987; Schindler 2008; Study group 1994; Tan 2008) did not provide sufficient information to permit judgement on risk of attrition bias.

Selective reporting

Nineteen (Ansel 2006; Baumgartner 2007; Do 1994; Duda 2001; Dörffler-Melly 2005; Heinz 1996; Heiss 1990; Hess 1978; Iida 2008; Koppensteiner 2006; Mahler 1987; Minar 1995; Pilger 1991; Ranke 1994; Schindler 2008; Schweizer 2001; Study group 1994; Wang 2011; Weichert 1994) of the 22 included studies reported data on all pre-specified primary and secondary outcomes as planned. The primary outcome of the Schneider 1987 study was restenosis > 50% in the dilated or recanalised segment as well as vascular

occlusion in other segments. However, data on the latter were not presented. In the study by [Nehler 2007](#), data on the 12-month follow-up visit are not presented. Finally [Tan 2008](#) did not report data on secondary outcomes including cardiovascular events and death. Consequently we deemed these three studies to be at high risk of reporting bias.

Other potential sources of bias

Fourteen studies ([Baumgartner 2007](#); [Duda 2001](#); [Heinz 1996](#); [Heiss 1990](#); [Hess 1978](#); [Iida 2008](#); [Mahler 1987](#); [Minar 1995](#); [Pilger 1991](#); [Ranke 1994](#); [Schindler 2008](#); [Schneider 1987](#); [Schweizer 2001](#); [Wang 2011](#)) appeared to be free from other sources of bias. In two studies ([Study group 1994](#); [Tan 2008](#)) there was insufficient information to permit a judgement. We judged six studies ([Ansel 2006](#); [Do 1994](#); [Dörffler-Melly 2005](#); [Koppensteiner 2006](#); [Nehler 2007](#); [Weichert 1994](#)) to be at a high risk of bias. Results in the trial by [Ansel 2006](#) were contradictory and the issue could not be resolved despite talks with the trialists to clarify the data. Additionally, this trial was halted early due to safety issues regarding nitinol stent fractures. In [Do 1994](#) there was an imbalance in the proportion of participants with femoropopliteal occlusions in the two treatment groups. In [Dörffler-Melly 2005](#) there was an imbalance in post interventional treatment between the study groups, with participants randomised to abciximab given VKA post PTA while those randomised to a placebo were given ASA post PTA. Furthermore, this study included five participants who underwent PTA on both limbs making it unclear how this would affect the study results. In [Koppensteiner 2006](#), the baseline characteristics of the study population were different: 73% of the intermittent claudication group were smokers compared to 53% of the critical limb ischaemia group. Such an imbalance in this important risk factor is likely to affect the results. The trial by [Nehler 2007](#) was terminated early after an interim analysis was completed after only 36% of the planned study participants had completed the six-month assessment. Furthermore, the authors also reported that this study was underpowered to detect a small possible effect size. [Weichert 1994](#) was also stopped earlier than planned, suggesting that the trialists were hoping for a particular result. Stopping the trial early is likely to have biased the estimate of treatment effect. Consequently, we deemed these two studies to be at a high risk of reporting bias.

Effects of interventions

Acetylsalicylic acid (ASA)/dipyridamole (DIP) versus placebo

[Heiss 1990](#); [Study group 1994](#): We performed a formal meta-analysis for reocclusion six months after percutaneous transluminal angioplasty (PTA), whereas at discharge one, three and 12 months after PTA only data from the Swedish study group ([Study group 1994](#)) were available. Results for the incidence of reocclusion at six months, as evaluated in 356 patients, show no statistically significant overall effect for the administration of ASA given at low doses (fixed-effect odds ratio (OR) 0.69, 95% confidence interval (CI) 0.44 to 1.10; $P = 0.12$). For the [Heiss 1990](#) trial the OR showed a stronger effect (OR = 0.51) than for the Swedish trial. [Heiss 1990](#) used 100 mg of ASA, whereas the Swedish trial group administered only 50 mg ASA daily. In addition, Heiss et al assigned 66 patients to receive 330 mg of ASA; when this group was compared to the placebo group six months after PTA, the positive effect on reduction of primary occlusion was even stronger

than with the lower dose (OR 0.40, 95% CI 0.19 to 0.84). This effect was statistically significant ($P = 0.02$).

In the Swedish study, amputation occurred in five patients in the placebo group (5.8%) and in one patient in the ASA group (1%). Death within 30 days of PTA occurred in two patients of each group (1.7% placebo, 2.2% ASA/DIP). Bleeding at the puncture site occurred in five patients in the placebo group (6%) and in seven patients in the ASA group (8%). Gastrointestinal side effects were not mentioned. The data on amputation and incidence of death could not be pooled as [Heiss 1990](#) did not report on these outcomes. However, the Swedish group's results showed no statistically significant reduction in amputation rate at one month (OR 0.21, 95% CI 0.02 to 1.79), death at one month (OR 1.07, 95% CI 0.15 to 7.70) as well as in bleeding at the puncture site in the placebo group (OR 1.52, 95% CI 0.47 to 4.96).

ASA versus ASA/DIP

[Hess 1978](#): This trial evaluated early patency at 14 days after mostly femoral and popliteal angioplasty. Only 101 of the original 110 patients were included, as successful revascularisation could not be achieved in nine patients, i.e. a failure rate of 10%. Primary patency rates at 14 days were 84% in the ASA/DIP and 70% in the ASA group. There was no statistically significant effect for the combined application of ASA/DIP regarding early occlusion at 14 days (OR 0.43, 95% CI 0.17 to 1.14). Data were not available for bleeding complications or other outcome parameters of this review.

High-dose ASA versus low-dose ASA

Four trials published between 1990 and 1995 were truly randomised, including 930 patients at the time point six months after PTA and 798 patients at one and three months after PTA. High-dose ASA included 900 or 1000 mg with the exception of 330 mg in the [Heiss 1990](#) trial, which combined ASA with DIP, whereas low doses ranged from 50 to 300 mg ASA. Only Heiss et al used a combination of ASA/DIP (Asasantin), while the other trials compared ASA alone. Early occlusion, i.e. within one month after intervention, could be assessed in three trials ([Minar 1995](#); [Ranke 1994](#); [Weichert 1994](#)), showing no advantage for the administration of high doses of ASA (OR 1.45, 95% CI 0.63 to 3.36). At six months after PTA the results were not much different, again showing no positive effect for high-dose ASA (OR 0.99, 95% CI 0.71 to 1.38). Among the four trials, two showed a slight advantage for higher doses ([Heiss 1990](#): OR 0.78 and [Minar 1995](#): OR 0.90). The trial with the lower of the high doses (330 mg, [Heiss 1990](#)) showed the most positive effect. At the time points three and 12 months there were 798 and 575 patients included with OR 1.38 (95% CI 0.85 to 2.23) and 0.98 (95% CI 0.64 to 1.48), respectively, for primary occlusion. Follow-up until two years after PTA was only performed in the trial of [Minar 1995](#), including 85 patients with similar results as described for the earlier time points (OR 1.07, 95% CI 0.62 to 1.85). It should be noted that [Ranke 1994](#) had very low reocclusion rates in both groups.

Two studies ([Minar 1995](#); [Ranke 1994](#)) reported on gastrointestinal side effects and we pooled them together in a meta-analysis. Overall, a higher dose of aspirin was associated with a significantly increased risk of experiencing gastrointestinal (GI) side effects (OR 1.85, 95% CI 1.15 to 2.98; $P = 0.01$) but the heterogeneity between the studies was high ($P = 0.01$). The difference in gastrointestinal side effects between high-dose and low-dose aspirin was no longer statistically significant when we performed a random-effects

analysis (OR 2.54, 95% CI 0.54 to 11.9; $P = 0.24$, analysis not shown). No information was available on bleeding and amputation.

ASA/DIP versus vitamin K antagonists (VKA)

Do 1994 and **Pilger 1991**: The two trials allowed pooled comparison of post interventional administration of ASA/DIP versus phenprocoumon, a VKA, in 289 patients at one, three, six and 12 months follow-up. Treatment effect was not significant for either of the two drug regimens at all time points (one month: OR 2.73, 95% CI 0.71 to 10.51; three months: OR 0.90, 95% CI 0.41 to 1.99; six months: OR 0.78, 95% CI 0.43 to 1.41; 12 months: OR 0.65, 95% CI 0.40 to 1.06). However, the two trials differed greatly in their basic preconditions: **Pilger 1991** included only patients that were not successfully treatable by standard catheter intervention; all these chronic occlusions were recanalised by laser-assisted PTA and were prone to more frequent reocclusion risk due to their characteristics.

In **Do 1994**, nine and 11 patients, respectively, did not complete the study in the anticoagulation and ASA/DIP groups due to reasons unrelated to treatment. These included pneumonia, pancreatitis, cerebrovascular insufficiency ($n = 2$), myocardial infarction ($n = 4$), gallstone operation, venous thromboembolism ($n = 2$), carotid stenosis, amputation of lower leg ($n = 2$), pulmonary oedema, pulmonary carcinoma, haemorrhoidal haemorrhage side effects of other drugs and non-compliance. Four patients in the anticoagulation group and five in the ASA/DIP group did not complete the study due to side effects related to treatment: cerebral haemorrhage (INR 3.5), anal bleeding, gastrointestinal bleeding ($n = 2$), headache ($n = 2$), nausea ($n = 2$), indigestion and fatigue.

In **Pilger 1991**, death (2%), amputation (1%) and side effects were reported for puncture site bleedings (14%). However, these outcomes were not reported according to the peri-interventional drug administration, but regarding the use of the YAG-laser during PTA. Therefore analysis of these outcomes could not be completed.

Clopidogrel plus aspirin versus low molecular weight heparin (LMWH) followed by warfarin

Tan 2008 conducted a randomised controlled trial in which patients received either clopidogrel plus aspirin or LMWH followed by warfarin. Clopidogrel plus aspirin showed no statistically significant improvement in immediate restenosis at 24 hours (OR 2.57, 95% CI 0.10 to 64.52), one month (OR 0.27, 95% CI 0.01 to 6.89), six months (OR 0.27, 95% CI 0.03 to 2.65), 12 months (OR 0.31, 95% CI 0.06 to 1.68) nor 18 months (OR 0.23, 95% CI 0.23 to 2.09). Overall, restenosis occurred in 11 out of 56 patients treated with clopidogrel plus aspirin compared to 17 out of 47 treated with LMWH (OR 0.43, 95% CI 0.18 to 1.05). However, patients treated with clopidogrel plus aspirin had significantly fewer major bleeding episodes than those treated with LMWH followed by warfarin (OR 0.08, 95% CI 0.01 to 0.63; $P = 0.02$). The authors state that there was no significant difference in cardiovascular event rate and mortality at 18 months between the two groups but do not present the data on these outcomes.

Suloctidil plus VKA versus VKA

Mahler 1987: Twelve months after treatment with either VKA alone or combined with suloctidil, the latter had no positive effect on either reocclusion (OR 0.59, 95% CI 0.20 to 1.76; $P = 0.34$) nor restenosis (OR 1.87, 95% CI 0.66 to 5.31; $P = 0.24$). Fourteen patients

in the treatment group and 10 in the placebo group dropped out of the study. Gastrointestinal side effects occurred in two patients of each group. No bleeding complications were reported. Drop outs were re-included for intention-to-treat analysis. Restenosis and reocclusion occurred significantly more frequently after one year in women compared to men (50% versus 23%). No information is available on the other outcomes of this review.

Ticlopidine versus VKA

Schneider 1987: In the 197 included patients, primary occlusion 12 months after PTA appeared to be diminished by 29% in the group receiving ticlopidine (OR 0.71, 95% CI 0.37 to 1.36) compared to those receiving VKA. However, this effect was statistically non-significant. Side effects occurred at a significantly higher rate in the ticlopidine group (OR 6.84, 95% CI 2.27 to 20.55; $P = 0.0006$), with 34% withdrawing from the study due to gastrointestinal side effects. No information is available on the other outcomes of this review.

Cilostazol plus aspirin versus ticlopidine plus aspirin

Iida 2008: In this randomised controlled trial of 127 patients with de novo femoropopliteal lesions, administration of cilostazol had a statistically significant effect on patency at 12, 24 and 36 months after endovascular recanalisation (OR 0.32, 95% CI 0.13 to 0.76 ($P = 0.01$); OR 0.39, 95% CI 0.17 to 0.88; OR 0.40, 95% CI 0.19 to 0.83, respectively).

Amputation during the 36-month follow-up occurred in four patients in the cilostazol group and in one patient in the ticlopidine group (OR 4.27, 95% CI 0.46 to 39.32). Four patients treated with cilostazol (6.3%) and six patients treated with ticlopidine (9.4%) died during follow-up (OR 0.66, 95% CI 0.18 to 2.44). The causes of death were myocardial infarction in two cilostazol and three ticlopidine patients, sudden death in one cilostazol and two ticlopidine patients, and renal failure in one patient from each treatment group. Six patients dropped out of the study due to adverse drug effects; five patients in the cilostazol group and one patient in the ticlopidine group (OR 5.43, 95% CI 0.62 to 47.87). The adverse effects in the cilostazol group were palpitations ($n = 3$), leg oedema ($n = 1$) and headache ($n = 1$), and one patient in the ticlopidine group withdrew because of an abnormal result on a liver function test. No acute, subacute or chronic thrombotic occlusions occurred. Bleeding complication rates were similar between the two groups but the data were not reported.

Taprostene versus ASA/DIP

Heinz 1996: In this small study, high-dose and low-dose taprostene had no superior effect, either on early occlusion within 72 hours, or on primary occlusion after three months (early occlusion for low-dose and early occlusion for high-dose: OR 8.33, 95% CI 0.32 to 215.68; after three months (low-dose and high-dose taprostene combined): OR 7.94, 95% CI 0.36 to 173.19).

Side effects were observed in eight patients treated with taprostene (four in the low-dose group and four in the high-dose group) such as flushing ($n = 8$), headache ($n = 5$), nausea/vomiting ($n = 8$), thrombophlebitis ($n = 1$), dysaesthesia (an abnormal unpleasant sensation) ($n = 1$) and dizziness ($n = 1$). Most side effects were described as moderate; only two as slight. No side effects were observed in the control group. No information is available on the other outcomes of this review.

Abciximab versus control

Four studies assessed the effects of abciximab; abciximab versus placebo was compared in three trials (Ansel 2006; Baumgartner 2007; Dörffler-Melly 2005) and one trial compared abciximab plus urokinase with urokinase alone (Duda 2001). Two studies (Duda 2001; Dörffler-Melly 2005) measured immediate occlusion within 24 hours and primary occlusions within three months of the PTA intervention. Results from the individual studies were conflicting. Duda 2001 determined that abciximab offered no improvement at either 24 hours nor three months. However, Dörffler-Melly 2005 concluded that abciximab had a statistically significant effect on patency at both 24 hours and three months. When we pooled the two studies together in a meta-analysis, abciximab offered no significant improvement in occlusion rate in the first 24 hours after PTA (OR 0.43, 95% CI 0.17 to 1.08) nor within three months of the PTA intervention (OR 0.58, 95% CI 0.25 to 1.34). We pooled a further two studies (Baumgartner 2007; Dörffler-Melly 2005) to compare primary occlusion six months after PTA. Results for the incidence of primary occlusion at six months, as evaluated in 490 patients, showed a statistically significant overall effect for the administration of abciximab (OR 0.44, 95% CI 0.30 to 0.64; $P < 0.0001$). Both trials showed similar effects with ORs of 0.44 and 0.43 for Baumgartner 2007 and Dörffler-Melly 2005 respectively. Dörffler-Melly 2005 measured minor bleeding at six months while Baumgartner 2007 measured severe bleeding at 30 days. Due to the differences in severity of bleeding and the time frame over which it was measured, this outcome could not be pooled into a meta-analysis.

Duda 2001 also measured amputations, major bleeding episodes and minor complications. The amputation rate at three months was positively influenced by abciximab (OR 0.17, 95% CI 0.03 to 1.00). Major bleeding events were not significantly influenced by the administration of abciximab, although a tendency towards increased bleeding rates was seen. There were four major bleeds (three arterial access site, one abdominal wall), all in the urokinase plus abciximab group; none in the urokinase group (OR 3.97, 95% CI 0.20 to 77.15). However, major bleeding was never fatal nor led to an invalidity state of the patients. Minor complications, including groin haematoma, gingival bleeding, distal embolus and macrohaematuria, did not differ significantly between the two treatment groups (OR 0.66, 95% CI 0.19 to 2.28). There were no procedure-related deaths, intracranial bleeds or infections. No patients were lost to follow-up in this trial.

Dörffler-Melly 2005 determined that abciximab offered a significant improvement in occlusion rates at one month (OR 0.18, 95% CI 0.14 to 0.88). However, the effect was not significant three months after revascularisation (OR 0.56, 95% CI 0.23 to 1.36). There were no major bleeding complications in this study, but significantly more minor bleeding events, mostly access site bleeding, without requiring surgical intervention or erythrocyte transfusion (OR 2.64, 95% CI 1.04 to 6.73). No other side effects were observed. Post interventional treatment with VKA did not positively influence patency rates compared to ASA.

The RIO trial (Baumgartner 2007) results indicated a significantly increased risk of severe bleeding at 30 days (OR 5.16, 95% CI 1.12 to 23.87). Patients treated with abciximab were also over five times more likely to experience other bleeding, primarily at the access site in the groin (OR 5.66, 95% CI 1.62 to 19.74). No information is available on the other outcomes of this review.

The trial by Ansel 2006 was included in the review but data could not be extracted as the results reported in the paper were contradictory. Restenosis rates reported in the table were 12.0% in the abciximab group compared to 13.4% in the placebo group. However in the text within the results section, restenosis rates were reported the other way round: 13.4% in the abciximab group compared 12.0% in the placebo group. We contacted the author in an attempt to clarify the results. However, the correct restenosis rate remains unknown and therefore these data could not be included in the review due to concerns over their accuracy.

LMWH versus unfractionated heparin (UFH)

Schweizer 2001: In the 172 included patients, the overall effect of nadroparin was a significant reduction of restenosis of more than 50% or reocclusion at three weeks, three months and six months after angioplasty (OR 0.42, 95% CI 0.21 to 0.83; OR 0.43, 95% CI 0.22 to 0.82; OR 0.35, 95% CI 0.19 to 0.65, respectively). However, no significant treatment-related differences were found for the subgroup of patients ($n = 62$) who had undergone angioplasty in the pelvic region. In contrast, when angioplasty was performed in the superficial femoral artery ($n = 110$), the degree of restenosis was significantly lower among patients receiving nadroparin calcium compared to those given heparin at three weeks, three months and six months (OR 0.16, 95% CI 0.07 to 0.40; $P < 0.0001$). There were no significant differences in the rates of haematoma between the two treatment groups (OR 1.50, 95% CI 0.73 to 3.11) nor in the number of amputations at six months (OR 1.00, 95% CI 0.20 to 5.10). No information is available on the other outcomes of this review.

LMWH plus aspirin versus aspirin alone

Koppensteiner 2006: This study included 275 patients: 196 with intermittent claudication and 79 with critical limb ischaemia. Overall, no significant difference was found in the rate of reocclusion at 12 months between the two treatment groups (OR 0.89, 95% CI 0.56 to 1.42). However, when reocclusion was analysed by severity of disease, the addition of LMWH to ASA was significantly more effective in reducing restenosis in patients with critical limb ischaemia than ASA alone (OR 0.15, 95% CI 0.06 to 0.42; $P = 0.0003$). In patients with intermittent claudication, combining LMWH with ASA offered no significant effect over ASA alone (OR 1.73, 95% CI 0.97 to 3.08; $P = 0.06$). There were no cases of heparin-induced thrombocytopenia in the treatment group nor major bleeding events in either group. Injection-site bruising occurred in seven patients in the LMWH group, one of whom discontinued the medication. During follow-up, 13 patients died from myocardial infarction ($n = 10$), stroke ($n = 1$), malignant disease ($n = 1$) and venous thromboembolism ($n = 1$). However, data on deaths were not presented according to treatment type so further analysis could not be conducted.

Lipo-ecraprost versus placebo

Nehler 2007: In this randomised controlled trial of 284 patients with critical limb ischaemia, lipo-ecraprost offered no significant benefit on amputation at six months (OR 0.89, 95% CI 0.44 to 1.80). Mortality rates were also similar in both treatment arms at six months (OR 0.66, 95% CI 0.31 to 1.40), with 62% and 63% of deaths in the lipo-ecraprost and placebo groups respectively, due to cardiovascular causes. Non-fatal cardiovascular adverse events including myocardial infarction, congestive heart failure and stroke, occurred at a similar rate in both groups (OR 1.18, 95% CI 0.55 to 2.52). Of the 141 patients randomised to lipo-

ecraprost, there were 2650 reported adverse events compared to 947 in the 143 patients who received a placebo. However, only 8% of adverse events in the lipo-ecraprost group were classified as serious compared to 23% in the placebo group (OR 0.29, 95% CI 0.24 to 0.36). Non-serious adverse events including headache, pain, hypotension, tachycardia, vasodilation, diarrhoea, nausea and vomiting, occurred at a significantly higher rate in the lipo-ecraprost group (OR 3.42, 95% CI 2.78 to 4.20; $P < 0.00001$). No information is available on the other outcomes of this review.

Batroxobin plus aspirin versus aspirin alone

Wang 2011 performed a randomised controlled trial on 111 diabetic patients with critical limb ischaemia, defined as Rutherford classification III or worse, and concluded that batroxobin plus aspirin reduced the rate of restenosis after arterial angioplasty (OR 0.28, 95% CI 0.13 to 0.60). Authors presented detailed data according to the number, site and length of lesions. Fifty-one patients treated with batroxobin had a total of 246 lesions compared to 267 lesions in the 60 control patients. The majority of lesions were in the infrapopliteal segment (70.3% versus 77.2%) and the remainder were in the femoropopliteal artery (29.7% versus 22.8% in the batroxobin and control groups respectively). Batroxobin was particularly effective in reducing restenosis in the infrapopliteal artery (OR 0.51, 95% CI 0.33 to 0.79; $P = 0.003$) but did not significantly reduce the rate of restenosis in the femoropopliteal artery (OR 0.66, 95% CI 0.33 to 1.32). Results also indicated that batroxobin was superior to aspirin alone in the treatment of lesions greater than 10 cm (OR 0.46, 95% CI 0.28 to 0.74; $P = 0.002$) but not in lesions less than 10 cm (OR 0.68, 95% CI 0.38 to 1.22). There were no significant differences in the number of deaths (OR 0.58, 95% CI 0.05 to 6.59) nor amputations (OR 0.28, 95% CI 0.07 to 1.00) between the treatment and control groups.

Candesartan versus quinapril

Schindler 2008 compared the AT1-receptor blocker candesartan against the angiotensin converting enzyme (ACE) inhibitor quinapril on restenosis after stent angioplasty in the superficial femoral artery. Eleven patients were randomised into each treatment group. The authors reported that candesartan was of benefit in reducing restenosis but this did not reach statistical significance (OR 0.21, 95% CI 0.04 to 1.31). The authors reported the number of adverse events but did not state their nature. The rate did not differ significantly by treatment group (OR 3.75, 95% CI 0.32 to 43.31). No information is available on the other outcomes of this review.

DISCUSSION

Summary of main results

In this update, eight new trials were added to trials included in the original review, in order to evaluate the efficacy and safety of antiplatelet, anticoagulant or other vasoactive agents administered in patients with peripheral arterial disease (PAD) treated by catheter intervention in the pelvic or femoropopliteal arteries.

At six months following endovascular treatment, a statistically non-significant positive effect on patency was shown with 50 to 100 mg acetylsalicylic acid (ASA) combined with dipyridamole (DIP), evaluated in only a small group of 356 patients. When looking at fixed-effect odds ratios (OR) of the single trials, it was striking that Heiss 1990 et al reported a considerably stronger

effect than the Swedish group (Study group 1994) (OR 0.51 versus 0.83, respectively). This difference might be due to the fact that in the Heiss study, 96% of the patients presented with intermittent claudication and only 4% of patients suffered from critical limb ischaemia, whereas in the Swedish trial only 59% of patients included were claudicants but 41% had critical limb ischaemia, the latter being a stronger risk factor for a poor outcome. The incidences of death and amputation, as recorded in the Swedish group, were only different regarding amputation for patients receiving aspirin. Possible reasons for this lack of effect might be the small number of patients (only one trial including 223 patients), short follow-up and endpoint not being evaluated systematically in all patients.

The question of whether combined therapy with ASA/DIP would be superior to ASA alone in terms of early occlusion was investigated in one early trial (Hess 1978). Results could not significantly prove superiority of the addition of DIP to ASA. Moreover, it should be pointed out that all the placebo-controlled comparisons looked at ASA and DIP and there were no unconfounded randomised comparisons of ASA alone versus placebo. Thus, it cannot be concluded that aspirin is indicated. Indeed, the meta-analysis of ASA/DIP versus placebo did not show evidence of efficacy of ASA/DIP, implying that any form of prophylaxis might not be indicated here. However, this may reflect a lack of evidence rather than a lack of efficacy.

We pooled data extracted from four further trials comparing high-dose to low-dose ASA to evaluate the efficacy and safety in patients treated with angioplasty presenting with the same characteristics described above. Analysis of these data revealed that higher doses of ASA (300 to 1000 mg) did not significantly improve patency rates following angioplasty compared with low doses of ASA (50 to 300 mg) at any time point of follow-up. This indicates that neither early nor late reocclusion rates are reduced with higher doses of ASA. In contrast, side effects, mainly gastrointestinal, were clearly more frequent in the high-dose groups.

Two studies comparing ASA/DIP with vitamin K antagonists (VKA) in 289 patients (Do 1994; Pilger 1991) found that antiplatelet therapy had a tendency to improve patency after femoropopliteal angioplasty at three, six and 12 months but this did not reach statistical significance. However, the trials differed by the fact that patients in the Pilger 1991 trial all had long chronic femoropopliteal occlusions that were recanalised by laser-assisted angioplasty. This population has a much higher risk for reocclusion than the population evaluated in the Do 1994 trial. This might be the reason why VKA showed a tendency to improve patency at one month. At later time points, results suggest that platelet activation may play a more important role in the mechanism of arterial reocclusion of catheter-treated artery segments than the local coagulation system does. This hypothesis is emphasised by the results of one trial (Schneider 1987), comparing ticlopidine, a thienopyridine derivative, with a VKA.

Iida 2008 offered evidence on the effectiveness of the antiplatelets cilostazol versus ticlopidine. The trial showed that cilostazol was more effective than ticlopidine in preventing reocclusion at 12, 24 and 36 months after percutaneous transluminal angioplasty (PTA). However, this study was open label and thus at high risk of performance bias. Schneider 1987 had previously measured the effectiveness of ticlopidine compared with the anticoagulant VKA, showing no difference in restenosis rates at 12 months.

The efficacy of low molecular weight heparin (LMWH) was assessed in two studies. [Tan 2008](#) determined that clopidogrel plus aspirin offered no favourable effect over LMWH followed by warfarin but those treated with LMWH were at increased risk of major bleeding. The other study by [Koppensteiner 2006](#) showed that LMWH, when combined with aspirin, had a positive effect on restenosis rates in patients with critical limb ischaemia but in patients with intermittent claudication, LMWH offered no advantage over aspirin alone.

Two of the studies included in the review measured the efficacy of abciximab. The [Baumgartner 2007](#) trial was completed on 392 participants while the study by [Dörffler-Melly 2005](#) was only on 98 participants. This difference in study size is reflected in the confidence intervals around the risk, with [Baumgartner 2007](#) showing narrower confidence intervals reflecting the larger sample size. Both trials administered the same dosage of abciximab (0.25 mg/kg bolus then maintenance of 0.125 mcg/kg/min for 12 hours). However, pre- and post PTA treatments differed slightly. [Baumgartner 2007](#) administered ASA 100 mg/day and also clopidogrel 65 mg/day for 28 days while [Dörffler-Melly 2005](#) administered heparin during the introduction and after the removal of the arterial sheath.

Overall, batroxobin was associated with a significant improvement in restenosis rates in patients with diabetes ([Wang 2011](#)). Analysis by lesion location and length showed that it was most effective in treating lesions greater than 10 cm and also in those located below the knee. However this evidence is based on only one study and all participants were diabetic. Further studies examining different lesion sizes and locations in non-diabetic patients are required before substantial conclusions can be drawn about the efficacy of batroxobin.

A number of trials evaluated the efficacy of antithrombotic drugs on early patency, especially in high-risk long-segment femoropopliteal occlusions. [Table 1](#) gives an overview of the reported early patency rates in the respective treatment and control groups. The range is between 70% and 99%, with a tendency towards improved rates occurring within recent years. Reasons for this improvement might be the availability of more sophisticated interventional devices as well as standard therapy with pre-interventional administration of ASA and intra-interventional of heparin. One trial gave evidence that intra- and post interventional administration of LMWH is significantly more effective on early as well as mid-term patency rates after femoropopliteal angioplasty without increased bleeding risks ([Schweizer 2001](#)). It seems that otherwise reported inhibition of intimal hyperplasia by LMWH might be an interesting hypothesis ([Schwartz 1998](#)). Reported data of non-controlled trials using direct thrombin inhibitors as, for example, bivalirudin in the same situation suggest an even more potent effect with less bleeding complications ([Allie 2003](#); [Shammas 2003](#)). Randomised controlled trials, however, are still not available. Another drug that has been used as an adjunctive treatment in long-segment femoropopliteal occlusions is the GPIIb/IIIa inhibitor abciximab which must be administered intravenously. This potent platelet inhibitor seems to be effective at avoiding early thrombotic occlusions caused by extended endothelial lesion and dissections caused by manipulation with the angioplasty catheter ([Dörffler-Melly 2005](#)). A 90% and 80% reduction of occlusion risk was found at 24 hours and one month following recanalisation and an almost 60% reduction was seen after six months.

In conclusion, there is limited evidence suggesting that restenosis/reocclusion at six months following peripheral endovascular treatment is reduced by use of antiplatelet drugs compared with placebo/control, but associated information on bleeding and gastrointestinal side effects is lacking. There is also some evidence of variation in effect according to different drugs with cilostazol reducing reocclusion/restenosis at 12 months compared with ticlopidine and both LMWH and batroxobin combined with aspirin appearing beneficial compared with aspirin alone. However, available trials are generally small and of variable quality and side effects of drugs are not consistently addressed. Further good quality, large-scale RCTs, stratified by severity of disease, are required.

Overall completeness and applicability of evidence

It has to be noted that in the present systematic review, the individual trials are heterogeneous and pooled data should be considered cautiously. In particular, the location of the stenosis or occlusion to be treated was sometimes in the pelvic region and in a majority of people in the femoropopliteal segment, a fact that is associated with a difference in endovascular results. Therefore, patency rates of interventions above the inguinal ligament (pelvic) are basically higher compared with those below the inguinal ligament (femoropopliteal or below). The same is true for short versus long segment obstructions. Due to the relatively small number of available trials and patients per comparison, a subgroup analysis of the outcome in iliac or femoropopliteal obstructions could not be performed. Furthermore, few of the included studies presented data according to severity of PAD. Therefore treatment was often administered to an overall study sample which included participants with intermittent claudication or critical limb ischaemia. Grouping these patients together with no regard for stage of disease could influence the results observed as critical limb ischaemia is associated with a higher reocclusion rate. Where possible, we performed subgroup analysis by severity of venous disease.

Quality of the evidence

For the majority of the included studies the risk of bias was low or unclear. Selection bias could not be determined in the majority of studies as authors failed to report the methods used in concealing allocation and random number generation. Not all randomised controlled trials (RCTs) were blinded and therefore we deemed the risk of performance bias high or unclear in over half of the studies. The majority of studies accounted for all participants and reported data on all pre-specified study outcomes, thus contributing to the low risk of attrition and reporting bias observed. The majority of studies were free from other sources of bias.

Potential biases in the review process

In this systematic review we identified all the RCTs that compared antithrombotic drugs with other drugs, placebo or no treatment in the prevention of reocclusion after peripheral endovascular treatment. We believe our search for RCTs has been inclusive and it is unlikely that our standardised methods of study selection and data extraction could have introduced bias. Due to the variable presentation of the outcomes by the trialists we could not always pool the data.

Agreements and disagreements with other studies or reviews

It has been suggested that clopidogrel combined with aspirin provides a more potent inhibition of platelet aggregation. This was supported by the CURE trial ([CURE 2003](#)) of patients with acute coronary syndromes, where the number of vascular events such as cardiovascular death, myocardial infarction and stroke was significantly reduced with clopidogrel. However, the trial also determined that clopidogrel increased the risk of major bleeding. The only study ([Tan 2008](#)) included in our review which measured the effectiveness of clopidogrel plus aspirin compared to LMWH followed by warfarin, found no significant treatment effect for either of the two drug regimens. Furthermore, the rate of major bleeding was significantly lower in the clopidogrel group than in those treated with LMWH.

Another clinical trial evaluated clopidogrel combined with ASA versus ASA after femoropopliteal angioplasty (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularisation) ([CAMPER](#)). Unfortunately, this study had to be stopped due to insufficient randomisation numbers after one year. It seems that too many patients treated for femoropopliteal angioplasty in the USA already receive off-label combined clopidogrel/aspirin therapy. Thus, whether or not this combination therapy is useful for improving femoropopliteal patency and other clinical endpoints in PAD patients might never be elucidated.

AUTHORS' CONCLUSIONS

Implications for practice

There is limited evidence suggesting that restenosis/reocclusion at six months following peripheral endovascular treatment is reduced by use of antiplatelet drugs compared with placebo/control, but associated information on bleeding and gastrointestinal side

effects is lacking. There is also some evidence of variation in effect according to different drugs with cilostazol reducing reocclusion/restenosis at 12 months compared with ticlopidine and both low molecular weight heparin (LMWH) and batroxobin combined with aspirin appearing beneficial compared with aspirin alone. However, available trials are generally small and of variable quality and side effects of drugs are not consistently addressed. Further good quality, large-scale randomised controlled trials (RCTs), stratified by severity of disease, are required.

Implications for research

There is a lack of randomised clinical trials showing the effect of specific duration of antiplatelet or anticoagulant therapy in patients with peripheral arterial disease (PAD) treated with peripheral angioplasty. Trials are required with sample sizes large enough to be able to detect clinically relevant treatment benefits, to show whether any form of prophylaxis is needed in this area. In addition, all trialists studying the effect of any preventive drug for early or late reocclusion after PTA should present most of their data detailed not only for therapy groups, but also stratified according to severity of disease with subgroups for participants with intermittent claudication and critical limb ischaemia and diabetes. Where possible, trials should present data according to regions above or below the inguinal ligament as suggested by the TransAtlantic Inter-Society Consensus ([TASC 2000](#)). Clinical trials evaluating the usefulness of thienopyridines, clopidogrel, LMWHs, direct thrombin inhibitors or other new antithrombotic agents might contribute to a sustained treatment effect of peripheral endovascular treatment in patients with PAD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ansel 2006

Study characteristics

Methods	<p>Design: randomised placebo-controlled multicentre trial</p> <p>Method of randomisation: 1:1 ratio in a blinded fashion assigned by sealed envelopes distributed to the participating sites</p> <p>Exclusions after randomisation: none</p>
Participants	<p>Country: USA</p> <p>Setting: 5 hospitals</p> <p>Participants: 51 patients assigned to treatment with abciximab (n = 27) or placebo (n = 24)</p> <p>Mean age: 69.1 years, 70.1 years abciximab group, 68.0 years placebo group</p> <p>Sex: 35 (68.6%) men, 17 (63%) men abciximab group, 18 (75%) men placebo group</p> <p>Inclusion criteria: ≥ 20 years, intermittent claudication requiring percutaneous revascularisation of a single lower extremity, angiographic stenosis of SFA $\geq 60\%$ length (≥ 7 cm), occlusions (≤ 22 cm), with at least one patent tibial artery</p> <p>Exclusion criteria: contraindication to antiplatelet medications, anticoagulants, contrast media or to any other medication used in the study protocol due to allergic reactions, bleeding diatheses, coagulopathy or other disorder, allergic to nitinol, concomitant hepatic insufficiency, thrombophlebitis, uremia or deep vein thrombus and/or receiving dialysis or immunosuppressant therapy, recent haemorrhagic stroke (< 6 months), contraindication to abciximab, septicaemia at time of procedure, severe co-existing illness that may prove life threatening within 12 months or life expectancy < 1 year, occluded popliteal artery making stent thrombosis likely, aneurysm in the SFA or popliteal artery, poor aortoiliac or common femoral "inflow" which would not be adequate to support a femoropopliteal bypass graft, significant vessel tortuosity, prior revascularisation of the same limb within 30 days of study procedure, reference vessel diameter < 4 mm</p>
Interventions	<p>Treatment: abciximab 0.25 mg/kg bolus followed by 10 μg/min infusion for 12 hours</p> <p>Control: placebo bolus and infusion (saline provided in vials that matched abciximab)</p> <p>All patients received intravenous heparin therapy, 325 mg orally once daily and clopidogrel 75 mg daily at least 24 hours prior to the procedure. Patients remained on aspirin (325 mg daily) for the duration of the follow-up time period and clopidogrel (75 mg daily) for 2 months post procedure</p>
Outcomes	<p>Primary: cumulative restenosis defined as a decrease in ankle brachial index of > 0.15 and in-stent duplex scan systolic velocity ratio of ≥ 2.5</p> <p>Primary: adverse clinical event defined as death (30-day) or repeat revascularisation within 9 months</p>

Ansel 2006 (Continued)

Secondary: acute angiographic success, absence of procedural-related complications (i.e. death, stroke, bleeding requiring > 2 units blood transfusion), any complication that required hospital admission or surgical procedure, change in walking time to claudication at 9 months, change in Rutherford category at 9 months, maintenance of primary patency at 9 months

Notes	<p>Results reported in the paper are conflicting. Table V shows the restenosis rate of 12.0% in the abciximab group and 13.4% in the placebo group at 9 months. However, in the text of the results section, the restenosis rates are reported as the opposite way round: 13.4% in the abciximab group and 12.0% in the placebo group. Contact was made with the author to clarify the results but we were unsuccessful in resolving this issue.</p> <p>The trial was halted early, at approximately 50% of the planned enrolment, due to data from a European trial which demonstrated an association between nitinol and stent fractures.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	<p>Quote: "Randomisations were assigned by sealed envelopes distributed to the participating sites"</p> <p>Comment: adequate allocation concealment</p>
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "Randomly assigned in a 1:1 fashion"</p> <p>Comment: method of random sequence generation not explicitly stated</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Quote: "Placebo (saline provided in vials that matched abciximab)"</p> <p>Comment: likely that blinding did occur but cannot determine if both study participants and personnel were blinded to treatment</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors do not report on blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of withdrawals, deaths and losses to follow-up are reported by authors
Selective reporting (reporting bias)	Low risk	Data on primary and secondary outcomes are reported
Other bias	High risk	Results in table and text of the paper are contradictory and this issue remains unresolved despite contact with the trialists to clarify. Trial was halted early due to a safety issue regarding nitinol stent fractures. Halting the trial likely to bias the true estimate of the treatment effect.

Baumgartner 2007

Study characteristics

Methods	<p>Design: randomised, placebo-controlled, multicentre trial</p> <p>Method of randomisation: not stated</p> <p>Exclusions post randomisation: not stated</p>
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Baumgartner 2007 (Continued)

Participants	Country: Europe Setting: not stated Participants: n = 392; 197 allocated to abciximab, 195 to placebo Median age: not stated Sex: not stated Inclusion criteria: patients with dual anti-platelet therapy undergoing endovascular revascularisation of chronic, long-segment femoro-popliteal occlusions Exclusion criteria: not stated
Interventions	Treatment: abciximab 0.25 mg/kg bolus plus maintenance at 0.125 µg/kg per minute for 12 hours Control: placebo All patients were given ASA 100 mg/day. Clopidogrel was initiated at 65 mg/day for 28 days.
Outcomes	1. Composite of all-cause mortality, amputation at any level, repeat target-vessel intervention and target-vessel re-occlusion at 30 days 2. Severe bleeding 3. Target vessel re-occlusion at 6 months 4. Restenosis (> 50% lesions) at 6 months

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not stated
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized" Comment: methods of random sequence generation not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors do not report on blinding of study participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors do not report on blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors state that 423 patients underwent revascularisation for occlusions but only 392 patients received abciximab or placebo Comment: potential withdrawals or losses to follow-up not reported by authors
Selective reporting (reporting bias)	Low risk	Data on primary and secondary endpoints are reported

Baumgartner 2007 (Continued)

Other bias	Low risk	Study appears to be free from other sources of bias
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Do 1994

Study characteristics

Methods	Design: an open, single-centre randomised clinical trial Method of randomisation: sealed envelopes, allocation of patients to the study groups concealed. Randomisation was on the day following successful revascularisation. Exclusions post randomisation: all randomised patients were included in primary patency analysis, including those not completing the study for various reasons and those lost to follow-up Drop outs: 20 No power calculation
Participants	Country: Switzerland Setting: hospital Participants: n = 160; 81 allocated to oral anticoagulants (phenprocoumon), 79 to ASA/DIP Mean age: 67 ± 7 years in the phenprocoumon group, 69 ± 8 years in the ASA/DIP group (overall 68 ± 8 years) Sex: 62% men (phenprocoumon) versus 58% (ASA/DIP) Inclusion criteria: PAD stage II to IV, angiographically proven successful PTA of stenoses or occlusions < 10 cm at the femoropopliteal level, no residual stenosis > 50%. Written informed consent. Exclusion criteria: age more than 80 years, other platelet inhibitors taken, if contraindication for ASA/DIP was known, manifest presence of other disease limiting the prospective 12 month follow-up
Interventions	Treatment: phenprocoumon Control: ASA 75 mg and DIP 200 mg twice daily ASA/DIP started 24 to 48 hours for all patients Duration of study therapy: 1 year
Outcomes	Primary patency (for reocclusion or restenosis > 50%) Follow-up: 1 year
Notes	Details on randomisation method and concealment of allocation were not reported in the article but could be completed after direct contact with the trialists

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal allocation of patients to study groups. This was not reported in the paper but the information was obtained directly from the trialists.
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed" Comment: methods not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "As it is not possible to conduct a blind study involving anticoagulant agents because of the necessary monitoring, this study was conducted in an open fashion" Comment: participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: authors do not state if outcome assessors were blinded to treatment allocation

Do 1994 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for failure to complete the study, including withdrawals due to adverse drug effects, are explicitly stated and are similar between both treatment groups
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary study outcome were reported
Other bias	High risk	Comment: baseline characteristics of the study population differed between the 2 treatment groups. Of the patients receiving anticoagulation, 47% had femoropopliteal occlusions compared to 32% of those receiving aspirin and dipyridamole.

Dörffler-Melly 2005

Study characteristics

Methods	Design: a single-centre, investigator-initiated, randomised, double-blinded clinical trial Method of randomisation: sealed envelopes from an independent person. Treatment type remained concealed until the end of the study. Exclusions post randomisation: none Drop outs: 4
Participants	Country: Switzerland Setting: hospital Participants: 98 patients (103 limbs) assigned to either abciximab (n = 47, 50 limbs) or placebo (n = 51, 53 limbs) Mean age: 71 ± 11 and 71 ± 10 years Sex: 45% and 47% men, respectively No significant differences in patient characteristics Inclusion criteria: > 18 years old, > 5 cm occlusion of the native femoropopliteal artery including the trifurcation (TASC type D lesion). Written consent. Exclusion criteria: peripheral revascularisation within the previous month, cerebrovascular event within the previous 2 years, intracranial neoplasm, aneurysm, arteriovenous malformation, vasculitis, uncontrolled arterial hypertension with a systolic pressure of more than 200 mmHg or a diastolic blood pressure of more than 110 mmHg despite antihypertensive treatment, known haemorrhagic diathesis, active bleeding, major surgery, gastrointestinal bleeding or genitourinary bleeding within the previous 6 weeks, absence of written consent
Interventions	Treatment: abciximab bolus of 0.25 mg per kilogram body weight after wire passage of the occlusion, followed by an infusion of 0.125 µg/kg per minute up to a maximum dose of 10 mg per minute for 12 hours Control: placebo in a preparation indistinguishable from the active study drug 100 mg aspirin one day before PTA for all patients. A standard dose of 5000 IU heparin was given with introduction of the arterial sheath and repeated with a half standard dose of 2500 IU heparin after 2 hours. After completion of the procedure intravenous heparin therapy (up to a maximum dose of 10 IU per kilogram body weight per hour) was allowed to start 1 hour after removal of the sheath.
Outcomes	1. 30 days primary occlusion 2. In-hospital reocclusion (within 24 hours), 3 and 6 months primary occlusion 3. 6 months bleeding events

Notes

Risk of bias

Dörffler-Melly 2005 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned by means of closed envelopes" Comment: allocation was probably concealed
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned" Comment: probably done but exact randomisation method was not explicitly stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind. The control group received a placebo in a preparation that was indistinguishable from the active study drug" Comment: blinding of the participants and personnel was achieved
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Duplex sonographic assessment was performed by two blinded technicians" Comment: blinding of outcome assessment was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient in the abciximab group and three patients in the placebo group dropped out of the study" Comment: number of drop outs stated but reasons for drop outs are not given. It is unlikely that the 3 drop outs were due to an adverse effect of the drug as all the drop outs occurred in the placebo group.
Selective reporting (reporting bias)	Low risk	Data on all pre-specified primary and secondary outcomes are reported
Other bias	High risk	Quote: "Postinterventional medication with VKA was prescribed significantly more often in the abciximab group, whereas ASA was prescribed more often in the placebo group" Comment: baseline imbalance in post interventional treatment between the study group likely to affect results. Included 5 patients undergoing surgery on both limbs. It is unclear how this will have affected the results.

Duda 2001
Study characteristics

Methods	Design: a single-centre, single-blinded, investigator-initiated clinical trial Method of randomisation: by independent computer-generated randomisation list. Concealment of allocation guaranteed. Randomisation of the patients was performed in a 5:2 ratio in favour of the urokinase plus abciximab group to optimise the assessment of safety of the combination therapy. Exclusions after randomisation: none Intention-to-treat analysis, no power calculation
Participants	Country: Germany Setting: hospital Participants: 70 patients assigned to treatment with urokinase and abciximab (n = 50), or urokinase alone (n = 20) in a 5:2 ratio Median age: 68 years (28 to 86 years) Sex: 56% men

Duda 2001 (Continued)

Inclusion criteria: age 18 to 90 years, PAD with an occlusion of either the iliac or femoropopliteal segment for 6 weeks or less, written consent

Exclusion criteria: acute limb-threatening ischaemia requiring immediate action and restoration of flow within 1 hour, female patient with childbearing potential, recent major trauma, or resuscitation or active internal bleeding, severe hepatic or renal disorder, platelet count less than $10 \times 10^9/\text{litre}$, autoimmune disease, recent thrombolysis, inclusion in another clinical trial, prior inclusion in the current trial, known allergic reactions to abciximab or urokinase, heparin or aspirin

Interventions	<p>Treatment: abciximab administered at the start of urokinase infusion as an intravenous bolus injection of 0.25 mg per kilogram of body weight, followed by an intravenous maintenance infusion of 0.125 µg/kg per minute for 12 hours</p> <p>Control: urokinase alone</p> <p>In both groups, urokinase was administered through a 5 to 30 cm long multislide slit catheter passed through the entire thrombus with an initial bolus of 25,000 IU per 10 cm of thrombus for the first two hours and 2000 IU per minute for 2 more hours if necessary. Urokinase was increased to 4000 IU if the thrombus mass or antegrade flow were insufficient after 4 hours. If no degree of recanalisation was observed after 4 hours, urokinase was stopped and thrombo-aspiration or PTA performed.</p>
Outcomes	<p>Primary combined safety endpoint at 30 days after randomisation, defined as procedure-related death, major bleeding, prolonged hospitalisation</p> <p>Primary effectiveness endpoints were amputation-free survival without open surgery or major amputation at 90 days</p> <p>Secondary endpoints were angiographic patency and time required for thrombolytic therapy to restore blood flow</p>
Notes	The administration of abciximab in patients included in this study was mainly thought of as an adjunctive agents to support lytic recanalisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: methods not stated
Random sequence generation (selection bias)	Low risk	<p>Quote: "Patients were randomly assigned to one of two treatment groups. Randomization was performed in a 5:2 ratio. The study medication allocation schedule was computer generated"</p> <p>Comment: adequate random generation</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "Study-agent blinding would have delayed the start of the study"</p> <p>Comment: authors state that trial was single-blinded. It is clear that personnel were not blinded but insufficient information to determine if participants were blinded to treatment.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "After locking the database, two readers who were unaware of the patients' group assignments analysed the digital subtraction angiograms"</p> <p>Comment: blinding of outcome assessment done</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Quote: "Five patients refused to undergo follow-up duplex ultrasound"</p> <p>Comment: it is not clear when ultrasound was performed as follow-up ranged from 3 to 14 months for both treatment groups. Reocclusion 30 days after randomisation is presented but it is not clear if this excludes the 5 participants who refused to undergo a follow-up ultrasound to check for reocclusion.</p>

Duda 2001 (Continued)

Selective reporting (reporting bias)	Low risk	Data on all pre-specified primary and secondary outcomes were presented
Other bias	Low risk	Study appears to be free from other sources of bias

Heinz 1996

Study characteristics

Methods	Design: single-centre, randomised, double-blinded clinical pilot trial Method of randomisation: randomisation was prior to PTA Exclusions post randomisation: 1 No power calculation
Participants	Country: Germany Setting: hospital Participants: n = 19; 6 receiving Taprosten low-dose (group I), 6 Taprosten high-dose (group II) and 7 placebo (group III) Mean age in groups I, II and III: 56 ± 4 years, 59 ± 11 years and 66 ± 7 years, respectively Sex: 4 men and 2 women in groups I and II, 3 men and 3 women in group III Inclusion criteria: stenosis or occlusion in the superficial femoral artery, written informed consent Exclusion criteria: other platelet inhibitors taken, contraindication for ASA or Taprosten, recent surgery or bleeding events
Interventions	Treatment group I: low-dose Taprosten, 2 hours before PTA (50 ng/kg/min), followed by 12.5 ng/kg/min for 8 hours, followed by placebo for 16 hours; a total of 12,000 ng/kg Taprosten was administered. Treatment group II: high-dose Taprosten, a total of 24,000 ng/kg Taprosten in the same modality as group I. All patients of group I and II received simultaneously placebo capsules for ASA/DIP 4 times Control (group III): intravenous placebo infusion with identical modality as groups I and II but treated with capsules containing a combination of ASA/DIP (330 /75 mg) Duration: infusion continued for 24 hours after PTA. Afterwards either aspirin or vitamin K antagonist.
Outcomes	1. Thrombocyte deposition before, 3 and 24 hours after PTA 2. Primary patency within 72 hours and 3 months following PTA 3. Side effects
Notes	Details on randomisation procedure and patient characteristics that were not reported in the published article could be completed upon personal contact with the investigators (Prof. W. Theiss, Munich, Germany)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Method not reported
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list of triple blocks Comment: adequate random sequence generation

Heinz 1996 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors state that study was double-blind but do not provide any more information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported Comment: insufficient information to permit the judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data are accounted for
Selective reporting (reporting bias)	Low risk	Data on pre-specified study outcomes are reported as planned
Other bias	Low risk	Study appears to be free from other sources of bias

Heiss 1990
Study characteristics

Methods	Design: a single-centre, randomised, double-blinded clinical trial Method of randomisation: not reported Exclusions post randomisation: not reported Losses to follow-up: 43
Participants	Country: Germany Setting: hospital Participants: 199 patients Age: 35 to 85 years (mean age equal in all 3 treatment groups); mean age not reported Sex: 134 men, 65 women Patient characteristics did not significantly differ between groups Inclusion criteria: arteriosclerotic lesions with > 50% narrowing of the lumen in the femoropopliteal artery segment. Angiographical evaluation was performed 4 to 6 weeks before intervention. Only patients with primary successful PTA were included. Informed consent. Exclusion criteria: patients with impaired inflow were excluded, i.e. with stenosis > 50% in pelvic region, disturbed blood or platelet function, severe concomitant diseases, long-term immobilisation
Interventions	Treatment group I: ASA 330 mg and DIP 75 mg Treatment group II: ASA 100 mg and DIP 75 mg Control: placebo Treatment was started 1 to 2 hours after successful PTA and continued for 6 months
Outcomes	1. Deterioration (restenosis or reocclusion) of the treated artery segments 2. Side effects were not assessed and concurrent events not defined Secondary outcomes (myocardial infarction, stroke and death) were not evaluated
Notes	It was not specified whether patients were all initially heparinised. All patients originally included in the study were also included in the present analysis (including drop outs). Those who did not complete the study for any reason were considered as failures. This accounts for the differences in the results reported by the trialists and those presented in our analysis.

Risk of bias

Heiss 1990 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not stated
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised into treatment groups" Comment: methods not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind. The capsules were identical and given in a double-blind way" Comment: blinding of participants and personnel probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: authors do not state if sonographers were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal are stated for all participants and are also presented by treatment group
Selective reporting (reporting bias)	Low risk	Data on pre-specified study outcomes are presented
Other bias	Low risk	The study appears to be free from other sources of bias

Hess 1978
Study characteristics

Methods	Design: randomised, single-centre trial Method of randomisation: not reported, only 'randomly allocated' was mentioned Concealment of allocation: double-blind Exclusions post randomisation: 9 due to unsuccessful recanalisation Losses to follow-up: none at 14 days follow-up
Participants	Country: Germany Setting: hospital Participants: n = 101, 50 receiving ASA, 51 ASA/DIP Specific data on baseline characteristics was not reported, only mentioned, that distribution of sex, age, body weight and size, ABPI, smoking habits, hyperlipidaemia and arterial hypertension were not significantly different in both groups. Patients were not stratified according to baseline characteristics. Inclusion criteria: patients with a symptomatic chronic arterial stenosis or occlusion of the lower extremities Exclusion criteria: not explicitly described; due to the defined inclusion criteria, patients with acute occlusions were excluded. Unsuccessful revascularisation was recognised as a reason for exclusion. Details on patient characteristics and randomisation procedure were not reported. Data showing the proportion of claudicants were not given, instead, the numbers of patients with stenoses or occlusions < 2 cm in length were given for both groups: 25 versus 23 in the ASA group and 29 versus 18 in the ASA/DIP group.
Interventions	Treatment 1: ASA 330 mg x 3 times per day Treatment 2: ASA 330 mg + DIP 75 mg x 3 times per day. Both started 24 hours before endovascular treatment and were continued for 14 days. The drug preparations were administered in identically looking and tasting capsules, indistinguishable to patients and investigators.

Hess 1978 (Continued)

Outcomes	Patency was assessed 14 days after revascularisation by measurement of systolic ankle pressure and pulse palpation or angiography	
Notes	First 70 patients were treated by the use of the Dotter catheter, while the following 41 patients were treated by the Grüntzig catheter. The Dotter device was replaced in favour for the Grüntzig device due to increased bleeding complications.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Methods not reported
Random sequence generation (selection bias)	Unclear risk	Method not reported but states "randomly allocated"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported that study was double-blind. The drug preparations were administered in identically looking and tasting capsules, indistinguishable to patients and investigators.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinded outcome assessment Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for
Selective reporting (reporting bias)	Low risk	Data on pre-specified study outcome were reported as planned
Other bias	Low risk	Study appears to be free of other sources of bias

Iida 2008

Study characteristics	
Methods	Design: randomised, open-label, blinded study in patients treated with EVT for de novo femoropopliteal lesions Method of randomisation: computer-generated random digits Concealment of allocation: random assignments in sealed envelopes Losses to follow-up: 16 (6 adverse effects: 5 cilostazol, 1 ticlopidine and 10 deaths: 4 cilostazol, 6 ticlopidine)
Participants	Country: Japan Setting: hospital Participants: n = 127, 63 cilostazol, 64 ticlopidine Age: mean 70 ± 9 years and 70 ± 8 years

Ida 2008 (Continued)

Sex: cilostazol: 19 M, 44 F. Ticlopidine: 16 M, 48 F

Inclusion criteria: patients with de novo lesions of > 50% diameter stenosis, occlusion without inflow lesions

Exclusion criteria: acute onset CLI, previous bypass surgery or angioplasty for FP lesions, presence of untreated pelvic lesions, known intolerance to the medication or contrast agents

Interventions	<p>Treatment: oral cilostazol 200 mg daily</p> <p>Control: ticlopidine 200 mg daily</p> <p>Pre-PTA: aspirin 100 mg daily at least 1 week before EVT plus UFH 5000 IU. Both groups also received aspirin 100 mg daily.</p> <p>Follow-up: 1, 3 and 6 to 12 months, every 3 months afterwards</p>
Outcomes	<p>Primary outcome: patency defined as peak systolic velocity ratio > 2.4</p> <p>Secondary outcomes: adverse events, restenosis, TLR, amputation, death</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	<p>Quote: "Assignments were placed in sealed envelopes"</p> <p>Comment: concealment methods adequately stated</p>
Random sequence generation (selection bias)	Low risk	<p>Quote: "Randomization was performed with the use of computer generated random digits"</p> <p>Comment: adequate random generation</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "Open label"</p> <p>Comment: study participants and personnel were not blinded to treatment allocated</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Two independent observers blinded to the medication evaluated all follow-up data"</p> <p>Comment: probably done</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	Slight imbalance in the number of patients who withdrew due to side effects of the study drugs. Five (7.9%) participants treated with cilostazol withdrew due to adverse effects compared to one (1.5%) participant treated with ticlopidine.
Selective reporting (reporting bias)	Low risk	Data on all pre-specified primary and secondary outcomes are presented
Other bias	Low risk	Study appeared to be free from other sources of bias

Koppensteiner 2006
Study characteristics

Koppensteiner 2006 (Continued)

Methods	<p>Design: randomised controlled trial in patients undergoing PTA of femoropopliteal arteries</p> <p>Method of randomisation: block randomisation using a computer random-number generator to select random permuted blocks</p> <p>Concealment of allocation: not stated</p> <p>Losses to follow-up: 20 (15 aspirin group, 5 dalteparin plus aspirin group)</p>
Participants	<p>Country: Austria</p> <p>Setting: hospital</p> <p>Participants: n = 275, 137 dalteparin, 138 aspirin</p> <p>Age: mean 69.9 ± 10 years and 7.20 ± 11 years</p> <p>Sex: dalteparin 56 males, aspirin 60 males</p> <p>Inclusion criteria: symptomatic patients with angiographically or sonographically documented femoropopliteal > 50% de novo or recurrent lesions if femoropopliteal angioplasty was primarily successful</p> <p>Exclusion criteria: nonatherosclerotic vascular disease, lesions in femoropopliteal bypass grafts, stent implantation, heparin or aspirin intolerance, anticoagulant treatment before PTA, pregnancy, life expectancy < 12 months, stroke, surgery of the eye or of the central nervous system ≤ 6 months, proliferative diabetic retinopathy, active bleeding, haemorrhagic diathesis, renal failure, uncontrolled arterial hypertension</p>
Interventions	<p>Treatment: LMWH dalteparin 2500 IU subcutaneously once daily + 100 mg aspirin orally</p> <p>Control: 100 mg aspirin orally</p> <p>Pre-PTA: 100 mg aspirin</p> <p>Follow-up: 1, 3, 6 and 12 months</p>
Outcomes	<p>Primary outcome: occurrence of restenosis > 50% or reclusion as documented by duplex ultrasonography at 12 months</p> <p>Secondary outcomes: recurrence or worsening of clinical symptoms, defined as deterioration by at least 1 Rutherford category and deterioration of ABI defined as decrease > 0.1</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: methods not stated
Random sequence generation (selection bias)	Low risk	<p>Quote: "Patients were block randomised to one of two treatment arms. The randomisation code was developed using a computer random-number generator to select random permuted blocks"</p> <p>Comment: exact randomisation method explicitly stated</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients randomised to received LMWH were instructed by a nurse in the method of self-injection"

Koppensteiner 2006 (Continued)

		<p>Comment: given that the treatments were LMWH + ASA versus ASA alone, blinding of study participants and personnel could not be done as one treatment group were required to self-inject while the other group did not</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "All sonographers were blinded to the group assessment"</p> <p>Comment: single-blind only</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Fifteen (10.9%) participants randomised to aspirin and 5 (3.6%) participants randomised to LMWH plus aspirin were lost to follow-up. The cause of death is given for all participants but authors do not state whether is related to treatment and it cannot be separated by treatment group. Potential for attrition bias due to withdrawals.</p>
Selective reporting (reporting bias)	Low risk	<p>Data on pre-specified primary and secondary outcomes are presented</p>
Other bias	High risk	<p>Quote: "These two patient subgroups, according to severity of PAD, were different with respect to female gender and diabetes, which were more frequent in the CLI group. Smokers were more frequent in patients with claudication. Lesion length was longer in patients with CLI"</p> <p>Comment: baseline characteristics of all participants regardless of severity of disease, were similar. Yet when split by severity of disease, the rates of smoking were statistically different between the IC group (73%) and the CLI group (53%). Such an imbalance in this important risk factor could affect the results.</p>

Mahler 1987
Study characteristics

Methods	<p>Design: randomised, placebo-controlled, 2-centre study</p> <p>Method of randomisation: sealed envelope (not reported, but completed upon contacting the trialists); randomisation 24 to 48 hours after PTA</p> <p>Concealment of allocation: double-blind</p> <p>Exclusions post randomisation: 24</p> <p>Losses to follow-up: 24</p>
Participants	<p>Country: Switzerland</p> <p>Setting: hospital</p> <p>Participants: 123 patients, 99 analysed; 48 suloctidil, 51 placebo</p> <p>Age: mean 66 years (range 35 to 82) and 65 years (range 39 to 81)</p> <p>Sex: 71 men, 52 women</p> <p>Inclusion criteria: chronic PAD with stenosis or occlusions < 10 cm, written consent, successful PTA</p> <p>Exclusion criteria: concomitant liver or renal disease, known tumour, expected survival less than 1 year (not reported but completed upon direct contact with the trialists)</p>
Interventions	<p>Treatment: oral anticoagulation + suloctidil 600 mg daily dose</p> <p>Control: oral anticoagulation + placebo</p> <p>All patients received 5000 IU heparin during intervention. Aspirin was given twice (500 mg each) 24 hours before intervention started. Phenprocoumon or acenocoumarol was started within 48 hours after PTA.</p> <p>Duration: 12 months</p>
Outcomes	<p>Reocclusion during the first year after PTA</p>

Mahler 1987 (Continued)

Endpoint definitions were improvement of clinical symptoms, palpable pulses, improvement of pulse waves distal to PTA site, reduction of ABPI difference by at least 20 mmHg. Remaining drug capsules were counted each time.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Sealed envelope (not reported but stated by trialists when contacted for further information)
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly allocated to either one of the two groups" Comment: probably done but the method of sequence generation is not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind. Identical capsules" Comment: blinding of study participants and personnel probably achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors do not state if sonographers were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 24 patients excluded from the study (drop outs) 10 cases belonged to the placebo-group and 14 to the group under suloctidil" Comment: reasons for dropping out of the study stated but are not presented by treatment group. Cannot determine if rate of adverse drug effects was higher with one treatment
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary study outcomes are presented
Other bias	Low risk	Study appears to be free from other sources of bias

Minar 1995

Study characteristics

Methods	Design: randomised, open, single-centre clinical trial Method of randomisation: by adaptive randomisation based on Pocock and Simon 1975, based on sequential treatment assignment with balancing for prognostic factors Concealment of allocation: non-blinded Exclusions post randomisation: none Losses to follow-up: 9
Participants	Country: Austria Setting: hospital Participants: n = 216, 107 received 1000 mg ASA, 109 received 100 mg Age: mean 65 ± 10 and 66 ± 10 years Sex: 121 men, 95 women Inclusion criteria: symptomatic PAD, written consent Exclusion criteria: impaired inflow, anticoagulation, anti-inflammatory drugs

Minar 1995 (Continued)

Patient characteristics including cardiovascular risk factors in the 2 treatment groups were well matched

Interventions	Treatment: 1000 mg/d aspirin Control: 100 mg/d aspirin Before PTA and on the 2 following days, all patients were administered 500 mg ASA IV. In addition, 5000 IU heparin administered during PTA, followed by IV heparin 1000 IU/hour until aPTT reached 3 times its normal value for the first 3 days after PTA. Follow-up: 24 months
Outcomes	Primary: angiographically confirmed stenosis > 50% at 1, 5 days and at 1, 6, 12 and 24 months following PTA Secondary: side effects
Notes	Randomisation was started 2 days after PTA. Thus, patients in whom early reocclusion occurred within 2 days after PTA, were excluded from the study and not re-included in our analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not stated
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to either group through adaptive randomization" Comment: random generation adequately described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients and the main investigators were not blinded to dose assignment" Comment: study participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Noninvasive laboratory testing, duplex ultrasound investigations, and angiographic follow-up investigations were performed and analysed by investigators without knowledge of group randomization" Comment: blinding of outcome assessment achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: loss to follow-up adequately described by treatment group and is equally balanced
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary outcomes are reported
Other bias	Low risk	Study appears to be free from other sources of bias

Nehler 2007

Study characteristics

Methods	Design: randomised, multicentre, double-blind, placebo-controlled trial Method of randomisation: stratification by diabetic status within each study site (conducted at a single randomisation centre via a voice response system) using a Zelen's approach
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Nehler 2007 (Continued)

Exclusions post randomisation: 38 were randomised before revascularisation but were not treated, most commonly due to a change in medical status

Participants	<p>Country: United Kingdom and United States</p> <p>Setting: 28 hospitals, 9 UK, 19 USA</p> <p>Participants: 284 patients assigned to lipo-ecraprost (n = 141) or placebo (n = 143)</p> <p>Mean age: 71 years (47 to 90) and 73 years (40 to 93)</p> <p>Sex: lipo-ecraprost 95 men, 46 women; placebo 104 men, 39 women</p> <p>Inclusion criteria: > 40 years age, CLI clinically defined by the presence of distal extremity pain at rest requiring use of analgesics for at least 2 weeks or the presence of peripheral ischaemic ulcers or areas of gangrene and haemodynamic evidence of CLI</p> <p>Exclusion criteria: previous major contralateral amputation at or above the ankle, area of individual ulcer/gangrene on index limb > 20 cm², antihypertensive therapy changed within previous 4 weeks or persistent or recurrent systolic blood pressure measurements < 90 mmHg, clinical evidence of sepsis, end stage renal disease, symptomatic arrhythmias, advanced atrioventricular block, severe heart failure, myocardial infarction ≤ 12 weeks of treatment initiation, serum aspartate aminotransferase or alanine aminotransferase exceeded 3 times upper limit of normal or serum bilirubin concentration exceeded 1.5 times the upper limit of normal, prostanoid therapy for PAD or another investigational drug ≤ 90 days of randomisation, women surgically sterilised, ≥ 1 year postmenopausal, practicing adequate contraception for ≥ 12 weeks before entering the study</p>
Interventions	<p>Treatment: 60 µg ecraprost administered intravenously ≤ 72 hours of revascularisation and then on each of 5 days per week for a total of 8 weeks</p> <p>Control: placebo</p>
Outcomes	<ol style="list-style-type: none"> 1. Major amputation above or below the ankle 2. Death within 180 days of the initial study treatment 3. Cardiovascular adverse events 4. Primary patency
Notes	<p>Study was stopped earlier than planned to expedite analysis of the primary endpoint and secondary endpoint using the 6-month data and also to minimise study costs and research subject inconvenience. As a result, although 6-month data were obtained for all available patients, excluding those lost to follow-up, only 146 of the patients completed a 12-month visit.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Random sequence generation (selection bias)	Low risk	<p>Quote: "Patients were randomised within each study site (conducted at a single randomization centre via a voice response system) and using a modified Zelen's approach"</p> <p>Comment: adequate random sequence generation</p>
Blinding of participants and personnel (performance bias)	Unclear risk	Authors state that study was double-blind but do not provide any more information

Nehler 2007 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Revascularization patency was determined by the site investigator" Comment: unclear as to whether the site investigator who performed the duplex ultrasound was blind to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients excluded post randomisation and lost to follow-up are all accounted for
Selective reporting (reporting bias)	High risk	Results from the 12-month follow-up examination are not reported
Other bias	High risk	Quote: "The Data and Safety Monitoring Board conducted a protocol-specified interim analysis after 36% of the planned number of patients had completed the 6-month assessment.... A protocol amendment resulted in the study being terminated after the final patient completed the 6-month assessment. This was done to expedite analysis of the primary endpoint and secondary endpoint using the 6 month data, as well as to minimize study costs and research subject inconvenience" Comment: study was terminated when an interim analysis showed that lipoeicraprost provided no additional benefit in the reduction of major amputation or death, yet only 36% of the intended study population had completed the 6-month assessment. High risk of reporting bias. Quote: "The protocol predicted an overall event rate of the primary endpoint of 30% major amputation or death, however, the major amputation rate in the placebo arm was only 13% (compared with the predicted 20%). As a result, the trial may have been underpowered and a numerically small benefit of lipoeicraprost on amputation cannot be excluded. Further, the study was powered to detect a 75% reduction in amputations and thus was underpowered to detect smaller possible effect sizes" Comment: high risk of bias due to the trial being underpowered

Pilger 1991

Study characteristics

Methods	Design: randomised, single-centre, open trial Method of randomisation: not reported Concealment of allocation: open Exclusions post randomisation: 3 Losses to follow-up: none
Participants	Country: Austria Setting: hospital Participants: n = 129, 66 randomised to ASA/DIP, 63 to VKA Age: not reported Sex: 125 men, 42 women Inclusion criteria: chronic occlusion of the femoropopliteal artery > 3 cm for at least 4 months, written consent. Adequate inflow documented. Exclusion criteria: successful standard guide wire passage (Teflon 0.035 in.) through the occlusion. Unsuccessful recanalisation by Nd-YAG laser treatment. 30% with CLI, 72% smoking, 31% diabetes mellitus

Pilger 1991 (Continued)

Interventions	<p>All patients received 3 x 330 mg ASA/75 mg DIP on the day prior to the endovascular procedure. During angioplasty, 5000 IU of UFH were administered intra-arterially, followed by heparin 1000 IU per hour IV for 48 hours. After successful endovascular treatment, patients were randomised to either treatment: 3 x 330 mg ASA/75 mg DIP daily</p> <p>Control: phenprocoumon (target INR not reported)</p>
Outcomes	<p>Primary: patency at discharge, 1, 3, 6, 12, 18, 24, 30 and 36 months after endovascular treatment</p> <p>Secondary: death, amputation, side effects</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not stated
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "Patients were randomised"</p> <p>Comment: methods not stated</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "Open trial"</p> <p>Comment: blinding not completed</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants and reasons for withdrawal in each treatment group are explicitly stated
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary outcomes are presented
Other bias	Low risk	The study appears to be free from other sources of bias

Ranke 1994
Study characteristics

Methods	<p>Design: single-centre, randomised clinical trial in patients treated by PTA in the femoropopliteal and iliac segment</p> <p>Method of randomisation: blocked randomisation with block size of 4 patients using random permuted blocks, central randomisation. Randomisation code was kept sealed in opaque envelopes and unknown to any of the study participants.</p> <p>Concealment of allocation: double-blinded (coded aspirin prepared by pharmacy)</p> <p>Exclusions post randomisation: 57</p> <p>Losses to follow-up: 44</p>
Participants	<p>Country: Germany</p> <p>Setting: hospital</p>

Ranke 1994 (Continued)

Participants: n = 216; 175 allocated to 900 mg ASA, 184 allocated to 50 mg ASA
 Patients were randomised after successful PTA and stratified into 3 groups: iliac artery stenosis (A), femoral artery stenosis < 3 cm (B) and femoral artery stenosis 3 to 10 cm (C)
 Age: mean 61 ± 12 years and 62 ± 12 years
 Sex: 75% and 72% men
 Cardiovascular risk factors did not differ significantly between groups
 Inclusion criteria: symptomatic PAD, PTA treatment in abdominal or femoropopliteal segments (but not both simultaneously), written consent
 Exclusion criteria: if a stent was implanted, coagulation disorders, gastroduodenal ulcer, allergic reactions to aspirin, haemodialysis, active malignoma, progressed coronary heart disease

Interventions	Treatment: 1000 mg ASA capsules Control: 50 mg ASA capsules Pre-PTA all patients received 1000 mg ASA Follow-up: 12 months
Outcomes	Primary outcome: angiographically confirmed occurrence of restenosis more than 50% diameter reduction Secondary outcomes: intolerable adverse side effects, death, stroke, myocardial infarction Follow-up was at 1 day and 1, 3, 6, 9 and 12 months
Notes	Men had better outcome (patency rates) than women in the 50 mg aspirin group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Blinded treatment allocation was obtained by central randomization. The randomization code was kept sealed in numbered opaque envelopes and was unknown to any of the participants in the study" Comment: methods of allocation concealment adequately described
Random sequence generation (selection bias)	Low risk	Quote: "Blocked randomization was performed separately in each stratum with a block size of four patients using random permuted blocks" Comment: method of random generation explicitly stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind. Coded aspirin was prepared by the pharmacy. The tablets of the two treatment regimens were identical in size, shape and colour. The randomization code was unknown to any of the participants in the study" Comment: blinding of study participants and personnel achieved
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All angiograms were read blindly" Comment: blinding of outcome assessment achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: reasons for failure to complete the study stated explicitly by treatment group
Selective reporting (reporting bias)	Low risk	Data on all pre-specified primary and secondary outcomes are presented
Other bias	Low risk	The study appears to be free from other sources of bias

Schindler 2008

Study characteristics

Methods	Design: double-blind, randomised, controlled, single-centre, proof-of-concept study
Participants	Country: Germany Setting: hospital Participants: 22 patients randomly assigned to receive candesartan (n = 11) or quinapril (n = 11) Age: candesartan 63 years, quinapril 68 years Sex: 16 men (8 in each group), 6 women (3 in each group) Inclusion criteria: mild to moderate hypertension ($RR_{sys} > 140$ mmHg and/or $RR_{dia} > 90$ mmHg) and Fontaine stage IIb peripheral arterial occlusive disease. Occlusion or stenosis $\geq 70\%$ of the SFA. Exclusion criteria: no medical indication for stent implantation after PTA, former revascularisation procedures in the same vessel segment, early restenosis within 14 days of the intervention, NYHA III or IV heart failure, resting blood pressure $> 180/100$ mm Hg, inability to perform treadmill ergometry, concomitant treatment with ACE inhibitors, β blockers, calcium antagonists or other AT_1 -receptor blockers, and serum creatinine level $> 180\mu\text{mol/L}$
Interventions	Treatment 1: 32 mg candesartan (16 mg in the morning and 16 mg in the evening) Treatment 2: 20 mg quinapril (10 mg in the morning and 10 mg in the evening) All patients received LMWH 6000 IE 3 times per day for 24 hours after the intervention, ASA 100 mg/day and clopidogrel 75 mg/day during follow-up
Outcomes	1. Restenosis in the treated segment 6 months after intervention as determined by angiography defined as a reduction in the luminal diameter of more than 69% according to the worst angiographic view at the narrowest site within the treated segment 2. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Random sequence generation (selection bias)	Unclear risk	Authors state that trial was "randomised" but do not specify methods used to generate random sequence
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors state that study was double-blind but do not provide any more information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors do not specify if sonographers conducting the duplex scan at week 6 and months 3 and 6 were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors do not present data on exclusions post randomisation, losses to follow-up or withdrawals

Schindler 2008 (Continued)

		Comment: insufficient information to permit judgement on risk of attrition bias
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary endpoints are presented
Other bias	Low risk	Study appears to be free from other sources of bias

Schneider 1987

Study characteristics

Methods	Design: randomised clinical trial of patients treated by PTA, 3 centres Method of randomisation: telephone randomisation by a blinded person of the drug company Concealment of allocation: open Exclusions post randomisation: 21, due to failed PTA or wrong indication Losses to follow-up: premature drug discontinuation: 10 and 6 patients in the VKA and ticlopidine groups, respectively, for poor compliance
Participants	Country: Switzerland Setting: hospital Participants: n = 197; 103 ticlopidine, 94 VKA Age: not reported Sex: not reported Inclusion criteria: femoropopliteal obstructions (maximum 10 cm length) due to chronic PAD Exclusion criteria: technical failure in PTA, need or contraindication for anticoagulants or antiplatelet agents for other medical reasons Gender, age, risk factors and concomitant diseases were matched and did not differ between comparison groups (figures not shown). There were 98% claudicants in the VKA group and 86% in the ticlopidine group.
Interventions	Treatment: ticlopidine 2 x 500 mg/day Control: VKA post PTA Pre-PTA: either 2 x 500 mg aspirin or 2 x 500 mg ticlopidine (blinded) for 3 days before angioplasty Follow-up: 12 months
Outcomes	Primary outcome: restenosis (> 50%) or reocclusion in the dilated or recanalised segment, as well as vascular occlusion in other segments Secondary outcomes: side effects and patient compliance Clinical evaluation including segmental pulse wave analysis, and ABPI measurement was performed directly before and after PTA, 3, 6 and 12 months after PTA. Angiography 1 year after PTA.
Notes	The study was stopped after 1 year because too many patients suffered from side effects in the ticlopidine study. Raw data retrieved from follow-up appointments at 3 and 6 months were not available from the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not stated
Random sequence generation (selection bias)	Low risk	Quote: "Telephone randomisation by a blinded person of the drug company" Comment: adequate generation of random sequence

Schneider 1987 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was double-blind at the start but the code was broken after PTA
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors do not state if outcome assessors were blinded to treatment Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All losses to follow-up are reported
Selective reporting (reporting bias)	High risk	Authors stated vascular occlusion in other segments as a pre-specified study outcome but data on this outcome are not presented
Other bias	Low risk	Study appears to be free of other sources of bias

Schweizer 2001

Study characteristics

Methods	Design: single-centre, open randomised clinical trial Method of randomisation: not reported Concealment of allocation: open Exclusions post randomisation: none Losses to follow-up: 4 (3 in nadroparin, 1 in heparin group)
Participants	Country: Germany Setting: hospital Participants: n = 172, 86 patients allocated to each study group Age: mean 66 ± 12.3 years (heparin group) and 67 ± 11.8 years (nadroparin group) Sex: 92 men, 80 women (50% and 57% men in the heparin and nadroparin group, respectively) No differences in demographic data between groups Inclusion criteria: angioplasty with remaining dissections at the pelvic or femoropopliteal level, PAD stages IIb, III, IV, unilateral claudication pain, ability to undergo treadmill testing, written consent Exclusion criteria: malignant or heart disease with life expectancy less than 1 year, prothrombin time < 60%, decompensated liver cirrhosis, renal insufficiency (creatinine > 200 µmol/litre), gastrointestinal disease, allergy to heparin or aspirin, heparin induced thrombopenia, < 6 months claudication symptoms, extensive dissection on the dilated vessel area with < 30% lumen restriction and no restricted flow-off of contrast medium
Interventions	Treatment: weight adjusted subcutaneous nadroparin calcium (LMWH, Fraxiparine) therapeutic dose followed by adjunctive oral aspirin 200 mg/day for 6 months Control: intravenous treatment with full heparinisation (UFH, Liquemin) followed by adjunctive oral aspirin for 6 months Duration: 7 days post PTA for (UFH and LMWH), 6 months aspirin
Outcomes	Primary outcome: degree of stenosis (normal findings; stenosis < 50%, > 50%, > 80%, occlusion) before and after angioplasty, 3 weeks, 3 months and 6 months after dilation Secondary outcomes: changes in the Fontaine stage, changes of ABPI
Notes	

Risk of bias

Schweizer 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method not stated
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned" Comment: probably done but method used to generate random sequence not explicitly stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open trial" Comment: blinding of participants and personnel not completed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Follow up sonography was performed by a blinded investigator with no knowledge as to the treatments that had been administered" Comment: blinding of outcome assessment achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary outcomes presented
Other bias	Low risk	The study appears to be free from other sources of bias

Study group 1994

Study characteristics

Methods	Design: multicentre randomised clinical trial (12 centres) Method of randomisation: computer-generated blocks of 10, concealed by a sealed envelope system Concealment of allocation: double-blind Exclusions post randomisation: 8 (5 in placebo and 3 in treatment group) Losses to follow-up: not reported
Participants	Country: Sweden Setting: hospital Participants: n = 223, 108 ASA/DIP group, 115 placebo group Age: mean age 65 and 66 years in the treatment and control group respectively Sex: 67% and 60% men Inclusion criteria: PAD in patients treated by PTA in the iliac, superficial femoral or popliteal artery, written consent Exclusion criteria: contraindications to ASA or already on continuous medication with ASA, other non-steroidal antiinflammatory drugs or oral anticoagulants
Interventions	Treatment: ASA 25 mg and dipyridamole 200 mg given twice daily as a combination tablet (Asasantin) Control: placebo Treatment was started 1 day before PTA and continued for 3 months. Usually 5000 IU of heparin were administered during PTA. Follow-up: 3 months

Study group 1994 (Continued)

Outcomes	Recurrence of stenoses or reocclusion evaluated at discharge and 1, 3, 6 and 12 months after PTA. Recurrence was defined as occurrence of predilatatory symptoms, ABPI in combination with ultrasonographic or angiographic findings.
Notes	Some patients were dilated in more than one segment, 6 in the ASA/DIP group and 4 in the placebo group. This small number was neglected in the analysis. The 5 patients of the placebo group and 3 of the treatment group that had been excluded by the trialists for different reasons (unsuccessful or partially successful PTA, early occlusion) were re-included in our analysis because randomisation and treatment start was before PTA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomized by a sealed envelope system" Comment: method of allocation concealment adequately described
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed in blocks of 10" Comment: exact method of random sequence generation was not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind. Identical placebo tablets" Comment: blinding of participants and personnel probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Vascular surgeons made an overall statement whether the angioplasty site was patent, restenosed or occluded. They based their conclusion on available information: clinical, ultrasonographic and/or angiographic" Comment: cannot determine if outcome assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors do not state drop outs or losses to follow-up so insufficient information to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary outcomes presented
Other bias	Unclear risk	Quote: "There were significantly more patients with cerebrovascular disease among placebo patients"

Tan 2008

Study characteristics

Methods	Study design: randomised controlled trial Method of randomisation: not stated Concealment of allocation: not stated Losses to follow-up: 4 (all control group)
Participants	Country: China Setting: hospital

Tan 2008 (Continued)

Participants: 103 patients; 56 treatment group, 47 control group

Age: mean age 70 ± 8 years treatment group, 60 ± 9 years control group

Sex: 66 men, 37 women

Inclusion criteria: clinical diagnosis of PAOD, Fontaine stages IIb or III, ABI < 0.9, final stenosis > 50%, length of stenosis 1 to 20 cm

Exclusion criteria: underlying severe disease < 1 year life expectancy, contraindications to anticoagulant, gastrointestinal bleed < 3 months or other bleeding disorders, claudication symptoms

Interventions	Treatment: clopidogrel 75 mg and aspirin 100 mg daily Control: LMWH 5000 IU daily for 1 week then warfarin 2.5 mg daily Pre-PTA: not stated
Outcomes	Primary: restenosis, reocclusion and major bleeding Secondary: cardiovascular events, death and adverse drug reaction

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: no allocation concealment described
Random sequence generation (selection bias)	Unclear risk	Comment: methods not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: methods of blinding participants and personnel not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: methods of blinding outcome assessment not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the number of patients who were lost to follow-up was reported but they were not similar between groups. In the treatment group there were no drop outs but in the control group there were 4 drop outs. Reasons for withdrawal from the study are stated
Selective reporting (reporting bias)	High risk	Data on secondary outcomes, including cardiovascular events and death, are not reported
Other bias	Unclear risk	Insufficient information to permit this judgement as 'low risk' or 'high risk'

Wang 2011

Study characteristics

Methods	Design: randomised, double-blind, controlled clinical trial
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Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment (Review)

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Wang 2011 (Continued)

Method of randomisation: block randomisation

Exclusions post randomisation: angioplasty failure (n = 10)

Drop outs: loss to follow-up (n = 7) and withdrawal of consent (n = 1)

Participants	<p>Country: China</p> <p>Setting: hospital</p> <p>Participants: 129 patients randomly assigned to aspirin plus batroxobin (n = 58) or aspirin alone (n = 71)</p> <p>Age: batroxobin: 69.5 ± 6.9 years, control: 70.7 years ± 7.4 years</p> <p>Sex: 47 men (20 batroxobin, 27 aspirin), 82 women (38 batroxobin, 44 aspirin)</p> <p>Inclusion criteria: diabetes and symptomatic limb ischaemia (Rutherford classification ≥ III) who needed to undergo intraluminal and/or subintimal angioplasty for occlusive disease in the lower-limb vessels</p> <p>Exclusion criteria: active bleeding, haemorrhagic diathesis, haematocrit count < 33%, high or low systolic pressure (≥ 180 mmHg or ≤ 90 mmHg) and/or diastolic pressure ≥ 110 mmHg, severe impairment of liver function or renal failure, psychopathic conditions, pregnancy or lactation, fibrinogen < 0.5 g/L, life expectancy < 12 months, stroke or cardiac infarction < 6 months</p>
Interventions	<p>Treatment: batroxobin 5 IU/0.5 mL by IV drip: 2 doses before and 4 doses after arterial angioplasty procedure</p> <p>Control: same dose of placebo (normal saline solution)</p> <p>100 mg aspirin per day started on day after admission and continued for at least 12 months</p> <p>All patients received 6 doses of LMWH 5000 U by subcutaneous injection at 12-hour intervals after angioplasty procedure</p>
Outcomes	<ol style="list-style-type: none"> 1. Restenosis of > 50% of the diameter of the arterial vessel or reocclusion as documented by MR angiography or duplex imaging at 12 months 2. Amputation above the ankle 3. Death from any cause

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not stated
Random sequence generation (selection bias)	Low risk	<p>Quote: "The randomization code was developed by using a computer random-number generator to select random permuted blocks"</p> <p>Comment: adequate random sequence generation</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Randomization list was blocked so that the interventional radiologists, data collection and assessment staff were blinded to the treatment sequence"

Wang 2011 (Continued)

		Comment: study personnel were blinded to the treatment but it is unclear whether the study participants were blinded. Authors do not stipulate that trial was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Interventional radiologists, data collection and assessment staff were blinded to the treatment sequence" Comment: adequate blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: number of participants excluded post randomisation, lost to follow-up and withdrawals stated for each treatment group
Selective reporting (reporting bias)	Low risk	Data on all pre-specified primary and secondary outcomes are reported
Other bias	Low risk	Study appears to be free from other sources of bias

Weichert 1994
Study characteristics

Methods	Design: 2-centre randomised clinical trial Method of randomisation: computer-generated, according to blocks of 6 patients per predefined stratum (segment of treated arteries) with 3 patients to each dose Concealment of allocation: double-blind Exclusions post randomisation: 38 (17 and 21 patients in lower and higher dose group, respectively) Losses to follow-up: 6
Participants	Country: Germany Setting: hospital Participants: n = 223, 112 received 300 mg ASA, 111 received 1000 mg ASA Age: mean not reported* (see Notes) Sex: not reported* (see Notes) Inclusion criteria: chronic PAD, successful PTA of the lower leg arteries Exclusion criteria: patients with early occlusions within 24 hours were excluded because they were considered to have technical failure. Contraindication for ASA or need for treatment with anticoagulants were also exclusion criteria.
Interventions	Treatment: ASA 300 mg daily for 6 months Control: ASA 1000 mg daily for 6 months Follow-up visits were at 3 and 6 months or when a restenosis or reocclusion was suspected by the patient
Outcomes	1. Primary reocclusion in the treated leg 2. Occlusion on the contralateral leg 3. Myocardial infarction (MI), stroke 4. Death due to MI or stroke 5. Secondary outcome: discontinuation of drug therapy due to side effects
Notes	* Figures not shown, but age and sex were reported not to be different in both randomisation groups Patients with early occlusion (i.e. within 24 hours) were excluded because randomisation and therapy start was only 48 hours after PTA

Risk of bias

Weichert 1994 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Methods not stated
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in strata. Computer-generated, according to blocks of six patients per predefined stratum (segment of treated arteries) with three patients to each dose" Comment: method of random generation adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind. Both medications were of identical shape. They were assigned in identical containers" Comment: blinding of study participants and personnel achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of study terminators reported
Selective reporting (reporting bias)	Low risk	Data on pre-specified primary and secondary study outcomes are presented
Other bias	High risk	Quote: "After the inclusion of 218 patients no difference between the two dosages concerning reocclusion rate and side effects was detected. Since it was not expected, that the results with the intended 600 patients would relevantly change these results, the trial was stopped" Comment: authors stopped the trial when the treatment was shown to be more or less effective than hoped. Stopping the trial early is likely to bias the estimate of treatment effect.

ABPI: ankle brachial pressure index
 ACE: angiotensin converting enzyme
 ASA: acetylsalicylic acid (aspirin)
 aPTTT: activated partial thromboplastin time
 CLI: critical limb ischaemia
 DIP: dipyridamole
 EVT: endovascular therapy
 FP: femoropopliteal
 IC: intermittent claudication
 INR: international normalised ratio
 IU: international units
 IV: intravenous
 LMWH: low molecular weight heparin
 NYHA: New York Heart Association
 PAD: peripheral arterial disease
 PAOD: peripheral arterial occlusive disease
 PTA: percutaneous transluminal angioplasty
 SFA: superficial femoral artery
 TASC: TransAtlantic Inter-Society Consensus
 TLR: target lesion revascularisation
 UFH: unfractionated heparin
 VKA: vitamin K antagonist

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Allie 2003	Non-controlled clinical trial comparing peri-interventional bivalirudin versus historical data of UFH in patients undergoing iliac and renal angioplasty
Bulvas 1996	<p>Inappropriate randomisation. Performance bias. Only indirect rather than direct outcome measure for patency. Authors contacted for allocation to the specific comparison groups of those patients reported to have suffered from reocclusion; detailed information on randomisation procedure. Seemingly, patients were randomised consecutively with alternating allocation.</p> <p>Six patients did not receive aspirin and thus were treated differently causing a performance bias. They should have been excluded from the study to avoid such bias. A total of 115 patients were included and randomised one day before PTA. They were assigned to 4 different groups: Group A consisted of 25 patients (10 women, 15 men), mean age was 64 years, 22 had femoropopliteal occlusions (mean length 5.5 cm), and three had aorto-iliacal occlusions, 24 with successful PTA. 24/25 had PAOD stage IIb, one was stage III. Group B included 24 patients (18 men, 6 women), mean age 63 years, 20 femoropopliteal occlusions, four aorto-iliacal occlusion (mean length 5 cm), 19 had stage IIb, 1 stage IIa, 4 stage III; 24 had successful PTA. Group C included 27 patients (22 men, 5 women) with stenoses (mean length 1.7 cm), 19 on the femoropopliteal level, 8 aorto-iliacal; 19 patients presented with stage IIa, 7 with stage IIa, 1 with stage III. Mean age was 60 years, all patients underwent successful PTA. Group D consisted of 26 patients (23 men, 3 women), mean age was 59 years, 15 stenoses were on the femoropopliteal segment, 11 on the aorto-iliacal level (mean length 1.4 cm). 19 patients had stage IIb, 7 had stage IIa. All patients received ASA 250 mg daily except for 6 patients of whom it was not reported to which group they belonged (4 stopped for side effects and 2 patients with known allergies). Patients in group A and C received peroral heparan sulfate 100 mg daily in addition. Drug medication was started on the day of the intervention and continued for 3 to 4 months.</p>
Horrocks 1997	Performance bias noted since 7 of the 11 patients in the iloprost-group also received ASA, whereas the remaining 4 did not
Ishii 2008	Not a randomised controlled trial
Mueller 1997	Only the 100 patients treated with 100 mg ASA were followed up. No control group.
Shammas 2003	Non-controlled observation of bivalirudin administration during peripheral catheter interventions
Stavropoulos 2003	Non-controlled observations on the feasibility of abciximab treatment in femoropopliteal catheter interventions
Strecker 2004	Consecutive follow-up of patients treated by femoropopliteal stenting and combined therapy with clopidogrel and aspirin (The CLAFS-project). Not a randomised controlled trial.
Tetteroo 1995	Not a randomised trial. Performance bias found in the patient group receiving coumarin: some of the patients were started on anticoagulants before PTA and others afterwards
Zeitler 1973	There was a selection bias for those patients who were included without pre-interventional angiography and without pretreatment with ASA

ASA: acetyl salicylic acid (aspirin)

PAOD: peripheral arterial occlusive disease

PTA: percutaneous transluminal angioplasty

UFH: unfractionated heparin

Characteristics of ongoing studies [ordered by study ID]

Mirror 2011

Study name	Mirror trial: follow-up management of peripheral arterial intervention with clopidogrel
Methods	Randomised, double-blind study
Participants	Patients with chronic peripheral arterial disease which requires intervention receive placebo or clopidogrel before the intervention (best endovascular treatment) and for 6 months in follow-up
Interventions	Placebo or clopidogrel
Outcomes	Platelet activation, the effect on macro- and microcirculation will be assessed as well as clinical endpoints
Starting date	September 2005
Contact information	Principal investigator: Gunnar Tepe, University Hospital Tuebingen, Germany
Notes	Abstract presented at ESC Congress, Paris, France, 27-31 August 2011

DATA AND ANALYSES

Comparison 1. ASA/DIP versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Immediate occlusion, at discharge	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Primary occlusion, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Primary occlusion, 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Primary occlusion, 6 months	2	356	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.44, 1.10]
1.5 Primary occlusion, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 Primary occlusion, 6 months (ASA 330 mg)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7 Amputation, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8 Death, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Bleeding puncture site, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: ASA/DIP versus placebo, Outcome 1: Immediate occlusion, at discharge

Study or Subgroup	ASA/DIP		Placebo		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Study group 1994	2	108	1	115	2.15 [0.19 , 24.07]	

Analysis 1.2. Comparison 1: ASA/DIP versus placebo, Outcome 2: Primary occlusion, 1 month

Study or Subgroup	ASA/DIP		Placebo		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Study group 1994	14	108	23	115	0.60 [0.29 , 1.23]	

Analysis 1.3. Comparison 1: ASA/DIP versus placebo, Outcome 3: Primary occlusion, 3 months

Study or Subgroup	ASA/DIP		Placebo		Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Study group 1994	20	108	26	115	0.78 [0.40 , 1.49]	

Analysis 1.4. Comparison 1: ASA/DIP versus placebo, Outcome 4: Primary occlusion, 6 months

Analysis 1.5. Comparison 1: ASA/DIP versus placebo, Outcome 5: Primary occlusion, 12 months

Analysis 1.6. Comparison 1: ASA/DIP versus placebo, Outcome 6: Primary occlusion, 6 months (ASA 330 mg)

Analysis 1.7. Comparison 1: ASA/DIP versus placebo, Outcome 7: Amputation, 1 month

Analysis 1.8. Comparison 1: ASA/DIP versus placebo, Outcome 8: Death, 1 month

Analysis 1.9. Comparison 1: ASA/DIP versus placebo, Outcome 9: Bleeding puncture site, 1 month

Comparison 2. ASA versus ASA/DIP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Early occlusion 14 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: ASA versus ASA/DIP, Outcome 1: Early occlusion 14 days

Comparison 3. High-dose ASA versus low-dose ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Primary occlusion, 1 month	3	798	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.63, 3.36]
3.2 Primary occlusion, 3 months	3	798	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.85, 2.23]
3.3 Primary occlusion, 6 months	4	930	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Primary occlusion, 12 months	2	575	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.64, 1.48]
3.5 Primary occlusion, 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6 Gastrointestinal side effects	2	575	Odds Ratio (M-H, Fixed, 95% CI)	1.85 [1.15, 2.98]

Analysis 3.1. Comparison 3: High-dose ASA versus low-dose ASA, Outcome 1: Primary occlusion, 1 month

Analysis 3.2. Comparison 3: High-dose ASA versus low-dose ASA, Outcome 2: Primary occlusion, 3 months

Analysis 3.3. Comparison 3: High-dose ASA versus low-dose ASA, Outcome 3: Primary occlusion, 6 months **Analysis 3.4. Comparison 3: High-dose ASA versus low-dose ASA, Outcome 4: Primary occlusion, 12 months** **Analysis 3.5. Comparison 3: High-dose ASA versus low-dose ASA, Outcome 5: Primary occlusion, 24 months** **Analysis 3.6. Comparison 3: High-dose ASA versus low-dose ASA, Outcome 6: Gastrointestinal side effects**

Comparison 4. ASA/DIP versus VKA (phenprocoumon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Primary occlusion, 1 month	2	289	Odds Ratio (M-H, Fixed, 95% CI)	2.73 [0.71, 10.51]
4.2 Primary occlusion, 3 months	2	289	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.41, 1.99]
4.3 Primary occlusion, 6 month	2	289	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.43, 1.41]
4.4 Primary occlusion, 12 months	2	289	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.40, 1.06]
4.5 Primary occlusion, 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6 Primary occlusion, 36 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: ASA/DIP versus VKA (phenprocoumon), Outcome 1: Primary occlusion, 1 month

Analysis 4.2. Comparison 4: ASA/DIP versus VKA (phenprocoumon), Outcome 2: Primary occlusion, 3 months

Analysis 4.3. Comparison 4: ASA/DIP versus VKA (phenprocoumon), Outcome 3: Primary occlusion, 6 month

Analysis 4.4. Comparison 4: ASA/DIP versus VKA (phenprocoumon), Outcome 4: Primary occlusion, 12 months

Analysis 4.5. Comparison 4: ASA/DIP versus VKA (phenprocoumon), Outcome 5: Primary occlusion, 24 months

Analysis 4.6. Comparison 4: ASA/DIP versus VKA (phenprocoumon), Outcome 6: Primary occlusion, 36 months

Comparison 5. Clopidogrel plus aspirin versus LMWH followed by warfarin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Reocclusion/restenosis, 24 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.2 Reocclusion/restenosis, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.3 Reocclusion/restenosis, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.4 Reocclusion/restenosis, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.5 Reocclusion/restenosis, 18 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.6 Reocclusion/restenosis, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.7 Major bleeding	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 1: Reocclusion/restenosis, 24 hours **Analysis 5.2. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 2: Reocclusion/restenosis, 1 month**

Analysis 5.3. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 3: Reocclusion/restenosis, 6 months

Analysis 5.4. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 4: Reocclusion/restenosis, 12 months

Analysis 5.5. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 5: Reocclusion/restenosis, 18 months

Analysis 5.6. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 6: Reocclusion/restenosis, all

Analysis 5.7. Comparison 5: Clopidogrel plus aspirin versus LMWH followed by warfarin, Outcome 7: Major bleeding

Comparison 6. Suloctidil plus VKA (phenprocoumon) versus VKA (phenprocoumon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Primary occlusion/restenosis, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Primary restenosis, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.3 Primary occlusion, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Suloctidil plus VKA (phenprocoumon) versus VKA (phenprocoumon), Outcome 1: Primary occlusion/restenosis, 12 months

Analysis 6.2. Comparison 6: Suloctidil plus VKA (phenprocoumon) versus VKA (phenprocoumon), Outcome 2: Primary restenosis, 12 months

Analysis 6.3. Comparison 6: Suloctidil plus VKA (phenprocoumon) versus VKA (phenprocoumon), Outcome 3: Primary occlusion, 12 months

Comparison 7. Ticlopidine versus VKA (phenprocoumon)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Primary occlusion, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.2 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Ticlopidine versus VKA (phenprocoumon), Outcome 1: Primary occlusion, 12 months

Analysis 7.2. Comparison 7: Ticlopidine versus VKA (phenprocoumon), Outcome 2: Side effects

Comparison 8. Cilostazol plus aspirin versus ticlopidine plus aspirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Occlusion/restenosis, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Occlusion/restenosis, 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.3 Occlusion/restenosis, 36 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.4 Amputation, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.5 Death, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.6 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Cilostazol plus aspirin versus ticlopidine plus aspirin, Outcome 1: Occlusion/restenosis, 12 months

Analysis 8.2. Comparison 8: Cilostazol plus aspirin versus ticlopidine plus aspirin, Outcome 2: Occlusion/restenosis, 24 months

Analysis 8.3. Comparison 8: Cilostazol plus aspirin versus ticlopidine plus aspirin, Outcome 3: Occlusion/restenosis, 36 months

Analysis 8.4. Comparison 8: Cilostazol plus aspirin versus ticlopidine plus aspirin, Outcome 4: Amputation, all

Analysis 8.5. Comparison 8: Cilostazol plus aspirin versus ticlopidine plus aspirin, Outcome 5: Death, all

Analysis 8.6. Comparison 8: Cilostazol plus aspirin versus ticlopidine plus aspirin, Outcome 6: Side effects

Comparison 9. Taprostene versus ASA/DIP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Early occlusion, 72 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1.1 Low-dose taprostene	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1.2 High-dose taprostene	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2 Primary occlusion, 3 months (high-dose and low-dose taprostene)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Taprostene versus ASA/DIP, Outcome 1: Early occlusion, 72 hours

Analysis 9.2. Comparison 9: Taprostene versus ASA/DIP, Outcome 2: Primary occlusion, 3 months (high-dose and low-dose taprostene)

Comparison 10. Abciximab versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Immediate occlusion, 24 hours	2	168	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.17, 1.08]
10.2 Early occlusion, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.3 Primary occlusion, 3 months	2	168	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.25, 1.34]
10.4 Primary occlusion, 6 months	2	490	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.64]
10.5 Amputation, 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.6 Severe bleeding 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.7 Bleeding at groin access site, 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.8 Major bleeding, 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.9 Minor bleeding, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10: Abciximab versus control, Outcome 1: Immediate occlusion, 24 hours

Analysis 10.2. Comparison 10: Abciximab versus control, Outcome 2: Early occlusion, 1 month

Analysis 10.3. Comparison 10: Abciximab versus control, Outcome 3: Primary occlusion, 3 months

Analysis 10.4. Comparison 10: Abciximab versus control, Outcome 4: Primary occlusion, 6 months

Analysis 10.5. Comparison 10: Abciximab versus control, Outcome 5: Amputation, 3 months

Analysis 10.6. Comparison 10: Abciximab versus control, Outcome 6: Severe bleeding 30 days

Analysis 10.7. Comparison 10: Abciximab versus control, Outcome 7: Bleeding at groin access site, 30 days

Analysis 10.8. Comparison 10: Abciximab versus control, Outcome 8: Major bleeding, 3 months

Analysis 10.9. Comparison 10: Abciximab versus control, Outcome 9: Minor bleeding, 6 months

Comparison 11. LMWH (nadroparin calcium) versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Occlusion/restenosis more than 50%, 3 weeks, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.2 Occlusion/restenosis more than 50%, 3 weeks, by arteries	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.2.1 Pelvic arteries only	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.2.2 Femoropopliteal arteries only	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3 Occlusion/restenosis more than 50%, 3 months, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.4 Occlusion/restenosis more than 50%, 3 months, by arteries	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.4.1 Pelvic arteries only	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.4.2 Femoropopliteal arteries only	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.5 Occlusion/restenosis more than 50%, 6 months, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.6 Occlusion/restenosis more than 50%, 6 months, by arteries	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.6.1 Pelvic arteries only	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.6.2 Femoropopliteal arteries only	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.7 Haematoma more than 10 cm and spurious aneurysm, 3 weeks, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.8 Amputation, 6 months, all	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11: LMWH (nadroparin calcium) versus UFH, Outcome 1: Occlusion/restenosis more than 50%, 3 weeks, all

Analysis 11.2. Comparison 11: LMWH (nadroparin calcium) versus UFH, Outcome 2: Occlusion/restenosis more than 50%, 3 weeks, by arteries

Analysis 11.3. Comparison 11: LMWH (nadroparin calcium) versus UFH, Outcome 3: Occlusion/restenosis more than 50%, 3 months, all

Analysis 11.4. Comparison 11: LMWH (nadroparin calcium) versus UFH, Outcome 4: Occlusion/restenosis more than 50%, 3 months, by arteries

Analysis 11.5. Comparison 11: LMWH (nadroparin calcium) versus UFH, Outcome 5: Occlusion/restenosis more than 50%, 6 months, all

**Analysis 11.6. Comparison 11: LMWH (nadroparin calcium) versus UFH,
Outcome 6: Occlusion/restenosis more than 50%, 6 months, by arteries**

**Analysis 11.7. Comparison 11: LMWH (nadroparin calcium) versus UFH,
Outcome 7: Haematoma more than 10 cm and spurious aneurysm, 3 weeks, all**

Analysis 11.8. Comparison 11: LMWH (nadroparin calcium) versus UFH, Outcome 8: Amputation, 6 months, all

Comparison 12. LMWH (dalteparin) plus aspirin versus aspirin alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Occlusion/restenosis more than 50%, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1.1 Intermittent claudication (IC) patients	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1.2 Critical limb ischaemia (CLI) patients	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 12.1. Comparison 12: LMWH (dalteparin) plus aspirin versus aspirin alone, Outcome 1: Occlusion/restenosis more than 50%, 12 months

Comparison 13. Lipo-ecraprost versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Major amputation, ≤ 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.2 Death, ≤ 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.3 Non-fatal cardiovascular adverse events, ≤ 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.4 Adverse events, ≤ 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.4.1 Serious adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.4.2 Non-serious adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13: Lipo-ecraprost versus placebo, Outcome 1: Major amputation, ≤ 6 months

Analysis 13.2. Comparison 13: Lipo-ecraprost versus placebo, Outcome 2: Death, ≤ 6 months

Analysis 13.3. Comparison 13: Lipo-ecraprost versus placebo, Outcome 3: Non-fatal cardiovascular adverse events, ≤ 6 months

Analysis 13.4. Comparison 13: Lipo-ecraprost versus placebo, Outcome 4: Adverse events, ≤ 6 months

Comparison 14. Batroxobin plus aspirin versus aspirin alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Restenosis, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.2 Restenosis at 12 months, femoral popliteal lesion	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.3 Restenosis at 12 months, in-frapopliteal lesion	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.4 Restenosis at 12 months, lesion length < 10 cm	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.5 Restenosis at 12 months, lesion length > 10 cm	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.6 Amputation, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.7 Death, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 14.1. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 1: Restenosis, 12 months

Analysis 14.2. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 2: Restenosis at 12 months, femoral popliteal lesion

Analysis 14.3. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 3: Restenosis at 12 months, infrapopliteal lesion

Analysis 14.4. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 4: Restenosis at 12 months, lesion length < 10 cm

Analysis 14.5. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 5: Restenosis at 12 months, lesion length > 10 cm

Analysis 14.6. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 6: Amputation, 12 months

Analysis 14.7. Comparison 14: Batroxobin plus aspirin versus aspirin alone, Outcome 7: Death, 12 months

Comparison 15. Candesartan versus quinapril

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Restenosis, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.2 Adverse events, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 15.1. Comparison 15: Candesartan versus quinapril, Outcome 1: Restenosis, 6 months

Analysis 15.2. Comparison 15: Candesartan versus quinapril, Outcome 2: Adverse events, 6 months

ADDITIONAL TABLES

Table 1. Early patency rates

Trial	Treatment	Dose	Patency rate in %	Time point (days)
Study Group 1994	Placebo	-	80	30 d
Dörffler-Melly 2004	Placebo	-	80	30 d
Hess 1978	ASA	990	70	14 d
Minar 1995	ASA	1000	98	30 d
Ranke 1994	ASA	900	99	30 d
Weichert 1994	ASA	1000	90	30 d
Weichert 1994	ASA	300	94	30 d
Minar 1995	ASA	100	98	30 d
Ranke 1994	ASA	50	99	30 d
Hess 1978	ASA/DIP	990/225 mg	84	14 d
Pilger 1991	ASA/DIP	990/225 mg	93	30 d
Study Group 1994	ASA/DIP	50/400 mg	87	30 d

Table 1. Early patency rates *(Continued)*

Do 1994	ASA/DIP	50/400 mg	96	30 d
Do 1994	VKA	Standard	98	30 d
Pilger 1991	VKA	Standard	99	30 d
Dörffler-Melly 2004	Abciximab	Standard	96	30 d
Schweizer 2001	LMWH	Standard	80	30 d
Schweizer 2001	UFH	Standard	63	30 d

ASA: acetyl salicylic acid (aspirin)

DIP: dipyridamole

LMWH: low molecular weight heparin

UFH: unfractionated heparin

VKA: vitamin K antagonist

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor Graft Occlusion, Vascular explode all trees	499
#2	MeSH descriptor Arteriosclerosis, this term only	891
#3	MeSH descriptor Arteriosclerosis Obliterans, this term only	70
#4	MeSH descriptor Atherosclerosis, this term only	365
#5	MeSH descriptor Arterial Occlusive Diseases, this term only	743
#6	MeSH descriptor Intermittent Claudication, this term only	695
#7	MeSH descriptor Ischemia, this term only	732
#8	MeSH descriptor Peripheral Vascular Diseases explode all trees	2118
#9	MeSH descriptor Vascular Diseases, this term only	372
#10	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	16396
#11	(arter*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	4803
#12	(vascular) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	1311
#13	(vein*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	690
#14	(veno*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	966
#15	(peripher*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	1327

(Continued)

#16	peripheral near3 dis*	3091
#17	arteriopathic	6
#18	(claudic* or hinken*)	1406
#19	(isch* or CLI)	16439
#20	dysvascular*	14
#21	(leg or limb) near4 (obstruct* or occlus* or steno* or block* or oblitter*)	389
#22	restenosis or re-stenosis or reocclus* or re-occlus*	2244
#23	(lower near3 extrem*) near4 (obstruct* or occlus* or steno* or block* or oblitter*)	133
#24	(aort* or iliac or femoral or popliteal or femoropop* or fempop* or crural) near3 (obstruct* or occlus*)	316
#25	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)	39115
#26	MeSH descriptor Endovascular Procedures explode all trees	5106
#27	MeSH descriptor Stents explode all trees	2831
#28	MeSH descriptor Vascular Surgical Procedures, this term only	609
#29	MeSH descriptor Blood Vessel Prosthesis explode all trees	421
#30	MeSH descriptor Blood Vessel Prosthesis Implantation, this term only	443
#31	(endovasc*):ti,ab,kw	651
#32	(endograft*):ti,ab,kw	37
#33	*stent*	35463
#34	*graft*	14294
#35	TEVAR	15
#36	EVAR	91
#37	EVRAR	3
#38	RAAA	7
#39	endoprosthe*	217
#40	Palmaz	133
#41	Zenith or Dynalink or Luminex* or Memotherm or Wallstent	132

(Continued)

#42	Viabahn or Nitinol or Hemobahn or Intracoil or Tantalum	132
#43	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	305
#44	MeSH descriptor Angioplasty explode all trees	3834
#45	(angioplas* or percutan* or PTA)	9444
#46	recanali*	513
#47	dilat*	6151
#48	balloon	5621
#49	(#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48)	61743
#50	MeSH descriptor Anticoagulants explode all trees	3245
#51	anticoagul* or anti-coagu*	5889
#52	LMWH OR heparin or UH or UFH	7637
#53	nadroparin* OR fraxiparin* OR enoxaparin OR Clexane OR klexane OR lovenox OR dalteparin	1661
#54	Fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR Innohep OR certoparin OR sandoparin OR reviparin OR clivarin*	548
#55	danaproid OR danaparoid or antixarin OR ardeparin* OR bemiparin* OR Zibor or seleparin* or tedeigliparin or parnaparin	129
#56	"cy 222" or cy222 or embolex OR monoembolex OR parnaparin* OR "rd 11885" Or tedelparin OR Kabi-2165 OR "Kabi 2165" or emt-966 or emt-967 or "pk-10 169" or pk-10169 or pk10169 or cy-216 or cy216	190
#57	wy90493 or "wy 90493" or "kb 101" or kb101 or lomoparan or organan or flux-um or lohepa or lowhepa or "op 2123" or parvoparin or AVE5026	62
#58	MeSH descriptor Platelet Aggregation Inhibitors explode all trees	2507
#59	MeSH descriptor Phosphodiesterase Inhibitors explode all trees	823
#60	phosphodiesterase near3 inhibitor	1102
#61	platelet near3 inhibitor	2768
#62	MeSH descriptor Tetrazoles explode all trees	2167
#63	cilosta*	280
#64	pletal or pletaal	11
#65	OPC-13013	7

(Continued)

#66	73963-72-1	1
#67	((cyclooxygenase or ADP) near3 inhib*)	1798
#68	aspirin	7767
#69	(acetyl near3 salicylic) or ASA or acetylsalicylic	6783
#70	clopidogrel* or Plavix	1246
#71	prasugrel or Effient or Efient or Prasita or Ticagrelor or Cangrelor or Portola or PRT060128	110
#72	ticlopidine or Ticlid or trapidil or thienopyridine	1445
#73	dipyridamo* or Persantin*	1180
#74	glycoprotein near3 (antagonist or inhibitor)	159
#75	GR144053 or GR-144053 or abciximab or tirofiban or eftifibatid or eptifibatide	906
#76	ReoPro or Integrilin or Aggrastat	170
#77	thrombo* near3 inhib*	632
#78	terutroban	11
#79	picotamide	59
#80	satigrel	11
#81	(#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80)	30610
#82	(#25 AND #49 AND #81)	1710

FEEDBACK

Anticoagulant feedback, February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at <http://www.editorial-unit.cochrane.org/anticoagulants-feedback>.

WHAT'S NEW

Date	Event	Description
23 January 2023	Amended	This review has been superseded by Cochrane Reviews: 'Antithrombotics after infra-inguinal bypass grafting' (http://doi.org/10.1002/14651858.CD015141) and 'Antithrombotics after infra-inguinal peripheral endovascular treatment' (http://doi.org/10.1002/14651858.CD015141)

Date	Event	Description
		s://doi.org/10.1002/14651858.CD015142) and will no longer be updated.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 1, 2005

Date	Event	Description
24 February 2012	New citation required but conclusions have not changed	New authors updated this review, eight new studies included, and one new study excluded, conclusions not changed.
24 February 2012	New search has been performed	Review updated, searches rerun, eight new studies included and one new study excluded.
14 February 2011	Amended	Link to anticoagulant feedback added.
14 January 2011	Amended	Explanations added to abbreviations in abstract.
25 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

LR: selected trials for the update, extracted data, assessed risk of bias for all included studies and wrote the updated review.

MG: selected trials for the update, extracted data, assessed risk of bias for all included studies and reviewed the updated paper.

FK: selected trials for the update, extracted data, assessed risk of bias for all included studies and reviewed the updated paper.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

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External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK

The PVD Group editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Difference between protocol and review

The only alterations made to the protocol were the inclusion of trials with intermediate and late-term patency outcomes. The review authors considered that analysing only early occlusions would not be clinically relevant.

Difference between previous and current version of the review

In the original review, the overall quality of studies was assessed using the Jadad score ([Jadad 1996](#)). For this update, the quality of all included studies was assessed using the 'Risk of bias' tool from the Cochrane Collaboration.

In 'Types of participants' we have clarified the definition of symptomatic chronic or acute PAD.

INDEX TERMS

Medical Subject Headings (MeSH)

Angioplasty, Balloon; Anticoagulants [*therapeutic use]; Constriction, Pathologic [*prevention & control] [therapy]; Peripheral Vascular Diseases [*prevention & control] [therapy]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Secondary Prevention

MeSH check words

Humans