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Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery (Review)

Forster RB, Lethaby A, Maxwell H, Acosta S, Prins MH

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	4
OBJECTIVES	4
METHODS	4
RESULTS	6
Figure 1.	7
Figure 2.	9
Figure 3.	10
DISCUSSION	14
AUTHORS' CONCLUSIONS	16
ACKNOWLEDGEMENTS	16
REFERENCES	17
CHARACTERISTICS OF STUDIES	20
DATA AND ANALYSES	43
Analysis 1.1. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 1: Primary graft patency at 12 months ..	44
Analysis 1.2. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 2: Side effects and complications	45
Analysis 1.3. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 3: Limb amputation	46
Analysis 1.4. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 4: Cardiovascular events	46
Analysis 1.5. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 5: Mortality	46
Analysis 2.1. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 1: Primary graft patency, venous grafts, 1 month	47
Analysis 2.2. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 2: Primary graft patency, venous grafts, 3 months	47
Analysis 2.3. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 3: Primary graft patency, venous grafts, 6 months	48
Analysis 2.4. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 4: Primary graft patency, venous grafts, 12 months	48
Analysis 2.5. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 5: Primary graft patency, venous grafts, 24 months	48
Analysis 2.6. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 6: Primary graft patency, prosthetic grafts, 1 month	49
Analysis 2.7. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 7: Primary graft patency, prosthetic grafts, 3 months	49
Analysis 2.8. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 8: Primary graft patency, prosthetic grafts, 6 months	49
Analysis 2.9. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 9: Primary graft patency, prosthetic grafts, 9 months	50
Analysis 2.10. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 10: Primary graft patency, prosthetic grafts, 12 months	50
Analysis 3.1. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 1: Primary graft patency, 1 month ..	51
Analysis 3.2. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 2: Primary graft patency, 3 months ..	51
Analysis 3.3. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 3: Primary graft patency, 6 months ..	51
Analysis 3.4. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 4: Primary graft patency, 12 months ..	51
Analysis 3.5. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 5: Side effects	52
Analysis 3.6. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 6: Limb amputation	52
Analysis 3.7. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 7: Mortality	52
Analysis 4.1. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 1: Primary graft patency, 3 months	53
Analysis 4.2. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 2: Primary graft patency, 6 months	53
Analysis 4.3. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 3: Primary graft patency, 9 months	53
Analysis 4.4. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 4: Primary graft patency, 12 months	54
Analysis 5.1. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 1: Primary graft patency, 3 months	54

Analysis 5.2. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 2: Primary graft patency, 6 months	55
Analysis 5.3. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 3: Primary graft patency, 12 months	55
Analysis 5.4. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 4: Primary graft patency, 24 months	55
Analysis 5.5. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 5: Limb amputation	55
Analysis 5.6. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 6: Cardiovascular events	56
Analysis 5.7. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 7: Mortality	56
Analysis 6.1. Comparison 6: ASA/DIP versus LMWH, all grafts, Outcome 1: Primary graft patency, 6 months	56
Analysis 6.2. Comparison 6: ASA/DIP versus LMWH, all grafts, Outcome 2: Primary graft patency, 12 months	57
Analysis 6.3. Comparison 6: ASA/DIP versus LMWH, all grafts, Outcome 3: Mortality	57
Analysis 7.1. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 1: Primary graft patency, 1 month	57
Analysis 7.2. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 2: Primary graft patency, 6 months	58
Analysis 7.3. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 3: Primary graft patency, 12 months	58
Analysis 7.4. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 4: Primary graft patency, 24 months	58
Analysis 8.1. Comparison 8: ASA versus prostaglandin (PGE1), venous grafts, Outcome 1: Early occlusion	59
Analysis 9.1. Comparison 9: ASA versus naftidrofuryl, Outcome 1: Primary graft patency at 12 months	59
Analysis 9.2. Comparison 9: ASA versus naftidrofuryl, Outcome 2: Side effects	60
Analysis 9.3. Comparison 9: ASA versus naftidrofuryl, Outcome 3: Mortality	60
Analysis 10.1. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 1: Primary graft patency at 24 months	61
Analysis 10.2. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 2: Side effects	61
Analysis 10.3. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 3: Limb amputation	61
Analysis 10.4. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 4: Mortality	62
Analysis 11.1. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 1: Primary graft patency, venous grafts, 24 months	63
Analysis 11.2. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 2: Primary graft patency, prosthetic grafts, 24 months	63
Analysis 11.3. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 3: Side effects	64
Analysis 11.4. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 4: Limb amputation	64
Analysis 11.5. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 5: Mortality	65
ADDITIONAL TABLES	66
APPENDICES	68
FEEDBACK	70
WHAT'S NEW	70
HISTORY	71
CONTRIBUTIONS OF AUTHORS	71
DECLARATIONS OF INTEREST	71
SOURCES OF SUPPORT	71
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	72
INDEX TERMS	72

[Intervention Review]

Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery

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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) may cause occlusions (blockages) in the main arteries of lower limbs. One treatment option is bypass surgery using autologous (the patient's own tissue) vein graft or prosthetic (artificial) graft. A number of factors influence occlusion rates in these patients, including the material used. To prevent graft occlusion patients are usually treated with antiplatelet, antithrombotic drugs, or a combination of both.

Objectives

To determine the effects of antiplatelet agents for the prevention of thrombosis in people with lower limb atherosclerosis who were undergoing femoropopliteal or femorodistal bypass grafting. Outcomes included the overall success of therapy (graft patency and limb salvage rates) and complications of treatment.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched June 2014) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 5). We sought additional trials through screening the reference lists of relevant papers.

Selection criteria

Two review authors, RB and AL, independently reviewed studies found in the search and evaluated them based on the inclusion and exclusion criteria, resolving disagreements through discussion.

Data collection and analysis

RB and AL independently extracted details of the selected studies for the update. We compared the treatment and control groups for important prognostic factors and differences described. If any data were unavailable, we sought further information from study authors. We synthesised data by comparing group results. We addressed unit of analysis issues by subgroup analysis.

Main results

We include 16 studies with 5683 randomised participants. Nine different treatment groups were evaluated: aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus placebo or nothing (six studies); ASA or ASA/DIP versus pentoxifylline (two studies); ASA/DIP versus indobufen (one study); ASA or ASA/DIP versus vitamin K antagonists (two studies); ASA/DIP versus low molecular weight heparin (one study); ticlopidine versus placebo (one study); ASA versus prostaglandin E1 (one study); ASA versus naftidrofuryl (one study); and clopidogrel and ASA versus ASA alone (one study). The treatment comparisons were evaluated separately, and, where possible, we performed subgroup analysis for venous grafts and prosthetic grafts and at different follow-up time points. The quality of evidence was low to moderate as many of the treatment comparisons had very few studies to contribute data, several of the included studies had unit of analysis issues, the treatment dosages varied between studies, and data for many outcomes important to this review were not given in any of the studies, or differed greatly between studies. Overall study quality was moderate, with the largest problem being that the majority of studies did not describe their methods of randomisation, allocation concealment or blinding of outcome assessors, leading to risk ratings of 'unclear'. The other main issue with study quality was studies not blinding participants or personnel.

The treatment comparison with the most number of included studies, which allowed for robust conclusions, was that of aspirin (ASA) or ASA and dipyridamole (ASA/DIP) versus placebo or nothing, covered by six studies. For this treatment group, there was improved graft patency in the ASA or ASA/DIP treatment group, odds ratio (OR) 0.42 (95% confidence interval (CI) 0.22 to 0.83; $P = 0.01$; 952 participants). This effect was not seen for venous grafts alone at any of the time points, but was observed for all time points in prosthetic grafts, including the final time point of 12 months (OR 0.19, 95% CI 0.10 to 0.36; $P < 0.00001$; 222 participants). Only a single study evaluated secondary patency, for which there was no difference between treatment groups. For the comparison ASA or ASA/DIP versus placebo or nothing there was no difference for any of the side effects, including general, gastrointestinal, bleeding and wound/graft infection. Amputations, cardiovascular events and mortality were also similar between the treatment groups. The comparison of ASA or ASA/DIP versus vitamin K antagonists included two studies, one of which was very large, with over 2000 participants. There were no differences between treatment for primary graft patency at three, six, 12 or 24 months, and there was also no evidence of a difference for limb amputation, cardiovascular events or mortality. One large study (851 participants) evaluated clopidogrel and ASA versus ASA alone, and for all grafts there was no evidence of a difference of primary patency at 24 months. There was evidence of increased total bleeding in the clopidogrel and ASA group (OR 2.65, 95% CI 1.69 to 4.15) from an increase in mild (OR 2.34, 95% CI 1.37 to 4.00), and moderate bleeding (OR 4.13, 95% CI 1.37 to 12.45), but no difference in severe or fatal bleeding. There was no difference between the treatment groups for limb amputation or mortality. For the remaining treatment comparisons there is not currently enough evidence to draw any robust conclusions about the efficacy or safety of the treatment on graft patency after peripheral bypass.

Authors' conclusions

Antiplatelet therapy with aspirin or with aspirin plus dipyridamole had a beneficial effect on primary patency of peripheral bypass grafts compared to placebo or no treatment. This effect was not evident when evaluating venous grafts alone, but antiplatelet therapy did have a beneficial effect on patency in those who had prosthetic grafts. There was no evidence of differences in side effects (including general, gastrointestinal, bleeding or infection), amputation, cardiovascular events or mortality between the treatment groups. However, the number of participants included in this analysis might be too small to detect a statistically significant effect for side effects, amputation, cardiovascular morbidity or mortality. We found no difference in primary graft patency when aspirin or aspirin with dipyridamole was compared to a vitamin K antagonist or when clopidogrel with aspirin was compared to aspirin alone. However, there was evidence of increase bleeding in the clopidogrel with aspirin group for the latter comparison. The remaining six treatment comparisons did not include enough data to draw any robust conclusions about their efficacy or safety at this time.

PLAIN LANGUAGE SUMMARY

Antiplatelet agents for preventing failure of peripheral arterial grafts

Background

Symptomatic peripheral arterial disease in people with atherosclerosis can present as intermittent claudication, disabling pain on walking, or as critical limb ischaemia with pain at rest, ulceration, gangrene and the risk of losing a leg. One treatment option is to implant a graft or makeshift blood vessel to bypass a blockage in the main artery of the thigh. Using a section of the vein from the patient's leg is often better than artificial or prosthetic materials such as Dacron or polytetrafluoroethylene, which take up platelets that could lead to clotting that could block the graft. Other factors affecting the patency of the graft (how long the bypass remains open) include length of the bypass, site where the graft connects to the existing artery and blood flow out of the graft. Stenosis (narrowing) of the graft most frequently occurs at the surgical connections because of hyperplasia, or an increase in the number of smooth muscle cells, into the inner layer of the vessel, often followed by the formation of a thrombosis (clot) at the stenotic site.

Study characteristics

We include 16 studies in this review with 5683 randomised participants. Nine different treatment groups were evaluated: Aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus placebo or nothing (six studies); ASA or ASA/DIP versus pentoxifylline (two studies); ASA/DIP versus indobufen (one study); ASA or ASA/DIP versus vitamin K antagonists (two studies); ASA/DIP versus low molecular weight heparin (one study); ticlopidine versus placebo (one study); ASA versus prostaglandin E1 (one study); ASA versus naftidrofuryl (one study); and

clopidogrel and ASA versus ASA alone (one study). We evaluated the different treatment comparisons separately, and, where possible, we evaluated separately those participants who received different types of grafts, venous or prosthetic.

Quality of the evidence

The quality of evidence from the review was low to moderate, as there were few studies to provide evidence for the different comparisons; several of the included studies randomised and analysed participants in a way that could introduce bias; and many of the prespecified outcomes of the review were not addressed within the studies, or were reported on in different ways between studies. Also, the treatment dosages varied between studies. Overall study quality was moderate, with the largest problem being that the majority of studies did not describe their methods of randomisation or blinding of those that evaluated the outcomes. The other main issue with study quality was not blinding participants or personnel to the treatment received.

Key results

The comparison of ASA or ASA and dipyridamole (ASA/DIP) versus placebo or nothing, included the most studies (six), which allowed for robust analysis. For this treatment group, there was improved graft patency in the ASA or ASA/DIP treatment group. There was an improvement in those that received prosthetic grafts, but not in those that received venous grafts. Only a single study evaluated secondary patency, for which there was no difference between treatment groups. For this comparison there was no difference for any of the side effects, including general, gastrointestinal, bleeding and wound/graft infection. Amputations, cardiovascular events and death from any cause were also similar between the treatment groups. The comparison of ASA or ASA/DIP versus vitamin K antagonists included two studies, one of which was very large, with over 2000 participants. There were no differences between treatment for primary graft patency at three, six, 12 or 24 months, and there was also no evidence of a difference for limb amputation, cardiovascular events or mortality. One large study evaluated clopidogrel and ASA versus ASA alone, and for all grafts (including prosthetic and venous grafts) there was no evidence of a difference of primary patency at 24 months. There was evidence of increased total bleeding in the clopidogrel and ASA group, from an increase in mild and moderate bleeding, but there was no difference in severe or fatal bleeding. There was no difference between the treatment groups for limb amputation or death from any cause. For the remaining treatment comparisons there is not currently enough evidence to draw any robust conclusions about the efficacy or safety of the treatment on graft patency after peripheral bypass.

BACKGROUND

Description of the condition

Symptomatic, chronic peripheral arterial disease (PAD) of the lower extremities may present either as intermittent claudication (IC), pain on walking, or as critical limb ischaemia (CLI), which is a more progressive stage with pain at rest, ulceration and gangrene (Becker 2011). The implantation of a femoropopliteal or femorodistal bypass graft (a makeshift blood vessel used to bypass a blockage in the main artery of the thigh) is one treatment option for people who are at risk of losing a limb or whose walking ability is greatly impaired because of the disease. By placing a graft in the groin area (an infrainguinal graft) the blocked arterial segment is bypassed, thereby improving blood flow in the limb. This then relieves the symptoms of claudication or rest pain and decreases the potential for amputation due to ulceration and gangrene, termed limb salvage.

The patency rate for femoropopliteal and femorodistal grafts, or the number of bypasses remaining open after a certain period of time, depends on several risk factors. These include whether or not the patient has acute lower limb ischaemia (Baril 2013), graft material, length of the bypass, site of the distal anastomosis (surgical connection of the graft to the existing artery), outflow conditions in the calf (flow of blood out of the graft) and female gender (Cooper 1990; Tangelder 2000). Autologous saphenous vein (using a vein from the patient's calf or thigh or both) is superior to prosthetic (artificial) materials such as Dacron or polytetrafluoroethylene (PTFE) (Rutherford 1988). Where the distal anastomosis is above the knee there is a lower risk of graft failure, and patients with two or three patent calf arteries have a better outcome than those with only one patent artery. Graft failure most frequently occurs at the site of either the distal or proximal anastomosis, when smooth muscle cells of the medial (middle) layer of the vessel wall grow into the intimal (inner) layer, which is known as intimal hyperplasia. This in turn causes the diameter of the perfused graft to become smaller, known as stenosis. When blood flow through the vessel is significantly reduced intermittent claudication may be experienced. Graft occlusion (closure) can occur by formation of a thrombosis (clot) at the stenotic site. If blood flow in the failed graft cannot be restored and further bypass surgery is not possible, then blood flow may be so poor that the limb cannot remain viable and amputation is required. Successful prevention of graft failure and thus the need for surgical re-intervention is of major clinical and economic importance. Occlusion rates one year after the operation vary between 15% and 75% depending on the various risk factors described above (Abbott 1997; Consensus 1991). In addition, patients with lower limb atherosclerosis (progressive hardening of the arteries) frequently experience increased platelet aggregation, leading to clot formation. Moreover, the body's physiological stress response to surgery is a prothrombotic state (where the body is preparing to form a blood clot).

Description of the intervention

Antiplatelet treatment is used to prevent formation of blood clots by preventing platelet aggregation (NICE 2013). Antiplatelet agents work by improving blood rheology and also by suppressing the advancement of in- and outflow atherosclerosis (reducing the rate of development of stenosis) as well as coronary artery atherosclerosis, indirectly optimising cardiac function and circulation.

For patients receiving bypass surgery, the intensity of platelet uptake by the graft material has been shown to be inversely related to graft patency at one year, indicating the need for antiplatelet intervention. In animal experiments, antiplatelet drug administration started before bypass surgery has been shown to increase patency in prosthetic grafts when compared to no treatment (Fujitani 1988).

To prevent graft occlusion patients are usually treated with either an antiplatelet or an anticoagulant drug, or a combination of both. It is not known which regimen is best to prevent infrainguinal graft occlusion. The aim of this review was to evaluate whether antiplatelet treatment improves graft patency, limb salvage and survival in patients with chronic PAD who are undergoing infrainguinal bypass surgery.

Why it is important to do this review

Another Cochrane review was recently undertaken to also evaluate the prevention of thrombosis after infrainguinal arterial bypass, but this review focused on the use of antithrombotic therapies (Geraghty 2011). Overall their findings were inconclusive, with a possible benefit of antithrombotics for autologous vein grafts. Also, there may be higher economic costs and adverse haemorrhagic events associated with the use of anticoagulants compared with antiplatelet therapy. If the efficacy of antiplatelets is acceptable then it may be a more economical alternative to anticoagulant therapy following bypass graft surgery in the legs.

OBJECTIVES

To determine the effects of antiplatelet agents for the prevention of thrombosis in patients with lower limb atherosclerosis who were undergoing femoropopliteal or femorodistal bypass grafting. Outcomes include the overall success of therapy (graft patency and limb salvage rates) and complications of treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Trials in which participants were randomly allocated to receive either antiplatelet therapy versus placebo, one antiplatelet regimen versus another or antiplatelet therapy versus an alternative treatment. We include trials using alternation (allocation of treatment alternating between two interventions) and consider them as quasi-randomised clinical trials (qRCTs).

Types of participants

All people undergoing femoropopliteal or femorodistal bypass grafting for the treatment of intermittent claudication and critical limb ischaemia. We excluded people undergoing bypass surgery for trauma.

Types of interventions

Antiplatelet therapy versus placebo, one antiplatelet regimen versus another, or antiplatelet therapy versus an alternative treatment. We excluded studies that included the same antiplatelet agent in both treatment groups, unless another antiplatelet was also used, but in only one treatment arm. We recorded the type

of therapy, dosage, time of starting compared to surgery (pre- or postoperatively) and duration of the therapy.

Types of outcome measures

Primary outcomes

- (1) Primary graft patency: patency rates after surgery with no further intervention, as determined by clinical examination, measurement of the ankle-brachial pressure index (ABPI), duplex ultrasonography, angiography.
- (2) Assisted primary patency: patency rates after intervention to improve blood flow in a graft which has not occluded.

We analysed primary patency and primary assisted patency for all grafts and for venous or prosthetic (artificial) grafts separately.

Secondary outcomes

1. Secondary graft patency: patency rates following secondary intervention to restore blood flow to the graft
2. Objective assessment of lower limb blood flow: ABPI, exercise tolerance test
3. Side effects of treatment and complications
4. Limb salvage rate: survival rates with limb intact (or limb amputation)
5. Incidence of other cardiovascular events and mortality
6. Participants' quality of life

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched June 2014) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2014, Issue 5, 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, 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*.

Searching other resources

We scanned reference lists of studies and reviews identified by the search for relevant studies.

Data collection and analysis

Selection of studies

In this update, Rachel Bedenis (RB) and Anne Lethaby (AL) independently selected trials for inclusion or exclusion, resolving disagreements by discussion between them.

Data extraction and management

For newly-included studies RB and AL independently extracted the number of participants originally allocated to each treatment group and performed an intention-to-treat analysis. Data collection on each trial consisted of: inclusion and exclusion criteria;

participant details (age, gender, co-morbidity); severity of arterial occlusive disease (as determined by the ABPI and the European Consensus ([Consensus 1991](#)) definition of critical limb ischaemia); type of graft (autologous vein, prosthetic, human umbilical vein, composite graft); level of proximal graft anastomosis (common superficial femoral artery) and distal anastomosis (above-knee popliteal, below-knee popliteal, distal arteries); type of antiplatelet therapy used (dose, commencement of therapy relative to surgery, duration of therapy, compliance); and outcome (as mentioned in the section '[Criteria for considering studies for this review](#)'). We compared the treatment and control groups for important prognostic factors. If any of the above data were not available, we sought further information from the authors.

Assessment of risk of bias in included studies

RB and AL independently assessed the methodological quality of included trials, using the 'Risk of bias' tool from The Cochrane Collaboration ([Higgins 2011](#)). We assessed the following five domains: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel and blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other potential sources of bias. We classified the domains as being at low risk of bias, high risk of bias or unclear risk of bias according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The two review authors assessing bias resolved disagreements by discussion.

Measures of treatment effect

We extracted dichotomous data and transformed them into odds ratios (ORs) with 95% confidence intervals (CIs) in the meta-analysis.

Unit of analysis issues

The majority of the included studies use individual participants as the unit of analysis, although four studies were not consistent in this method ([Clyne 1987](#); [Donaldson 1985](#); [Kohler 1984](#); [Lucas 1984](#)). [Kohler 1984](#) reported on grafts rather than participants: 14 participants were re-entered and re-randomised after graft failure; participants with bilateral reconstructions were followed for patency of both grafts but were randomised only after the first reconstruction. There were 102 grafts in 88 participants in this study. In [Donaldson 1985](#), the aspirin group recorded 35 grafts in 33 participants and the placebo group recorded 38 grafts in 32 participants. These additional grafts were due to bilateral grafts. In [Clyne 1987](#), 148 grafts were undertaken in 140 participants. [Lucas 1984](#) examined a mixture of single and multiple bypasses, using different materials, and also included thromboendarterectomy; there were considerable sources of heterogeneity within this study. The remaining papers appeared to report on one graft per individual.

For the meta-analyses, we used the number of participants randomised where possible and not the number of grafts, in order to maintain consistency with the majority of included studies. We have included the four studies using grafts as the unit of analysis ([Clyne 1987](#); [Donaldson 1985](#); [Kohler 1984](#); [Lucas 1984](#)) in the meta-analysis, but we have excluded them from a subsequent sensitivity analysis, to assess the influence these studies may have on the overall results.

Dealing with missing data

Where data were missing, we contacted study authors for more information. Where possible, we performed analyses on an intention-to-treat basis.

Assessment of heterogeneity

To test for heterogeneity, we used the I^2 statistic (Higgins 2003). Where heterogeneity was high ($I^2 > 50\%$), we used a random-effects model for data synthesis.

Assessment of reporting biases

We obtained data from full papers, conference abstracts and unpublished sources, where found. If at least ten studies were included in a meta-analysis, we constructed a funnel plot to look at issues around publication bias.

Data synthesis

Where possible, we calculated the number of events occurring within the sample for each of the outcomes. We generated ORs

with 95% CIs to evaluate the effect of treatment, using a fixed-effect model. Where heterogeneity was high ($I^2 > 50\%$) we used a random-effects model for data synthesis.

Subgroup analysis and investigation of heterogeneity

We subgrouped data for graft patency at follow-up (that is, at 1, 3, 6, 9, 12 and 24 months, where data were available) and for whether the graft was venous or prosthetic.

Sensitivity analysis

We performed sensitivity analysis to evaluate the effect of studies with unit of analysis concerns. Please see [Unit of analysis issues](#) for more detail.

RESULTS**Description of studies****Results of the search**

See [Figure 1](#) for study flow diagram.

Figure 1. Study flow diagram.

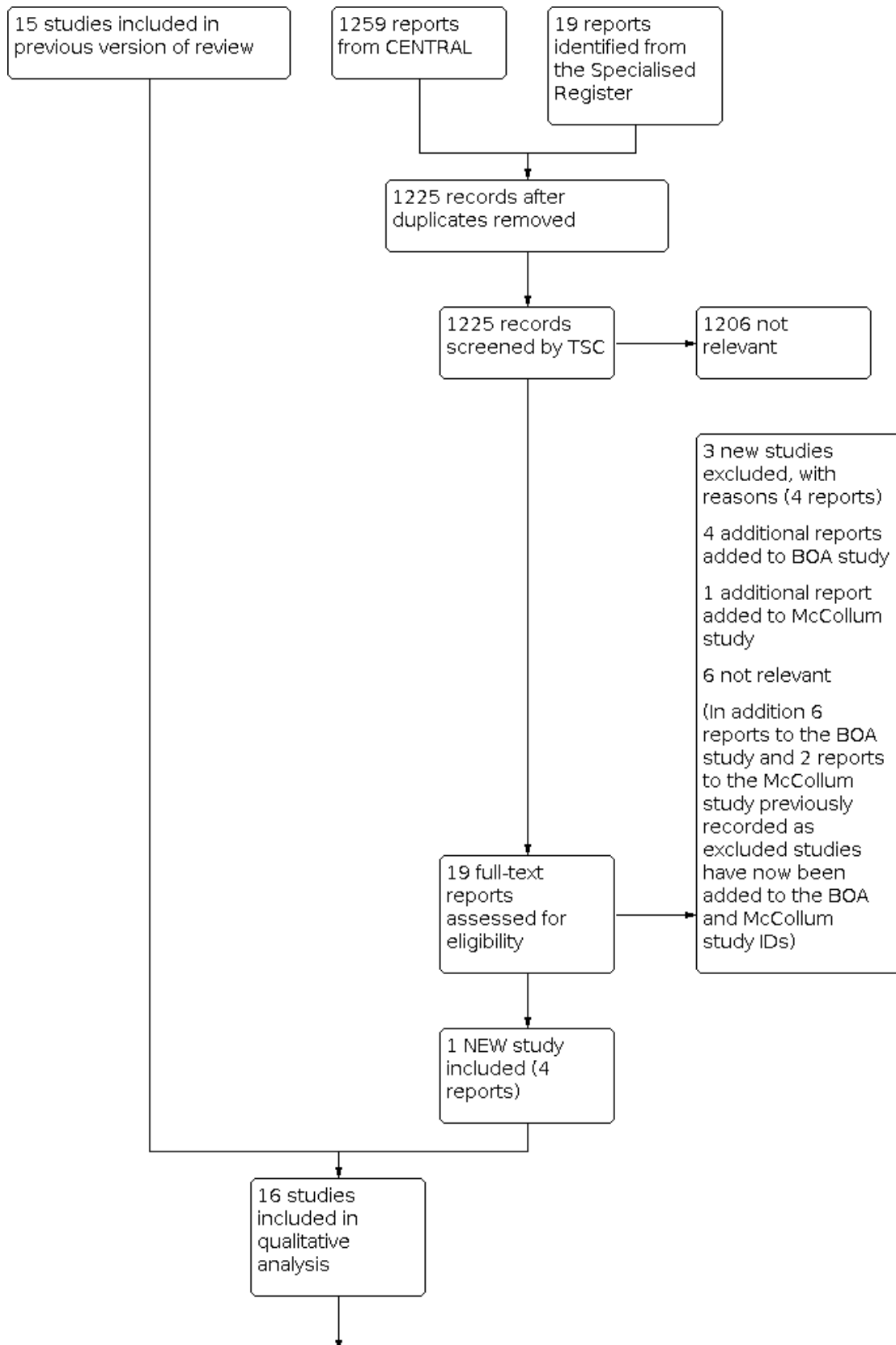
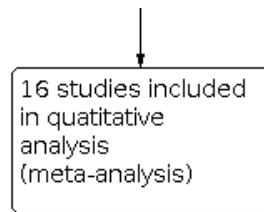


Figure 1. (Continued)



For the current update of the review, we considered 19 reports of 12 studies retrieved by the search. We included one additional study with four reports ([CASPAR 2010](#)). We deemed six studies with six citations not to be relevant, and we added another three studies with four reports to the excluded studies ([Burdess 2010](#); [EUCTR2007 2008](#); [Monaco 2012](#)). We added five new reports of two studies to previously included studies ([BOA 2000](#); [McCollum 1991](#)) and eight previously excluded reports to two included studies ([BOA 2000](#); [McCollum 1991](#)).

Included studies

For this update there was one additional study included ([CASPAR 2010](#)) making a total of 16 studies ([Becquemin 1997](#); [BOA 2000](#); [CASPAR 2010](#); [Clyne 1987](#); [D'Addato 1992](#); [Donaldson 1985](#); [Edmondson 1994](#); [Goldman 1984](#); [Green 1982](#); [Gruss 1991](#); [Kohler 1984](#); [Lucas 1984](#); [McCollum 1991](#); [Noppene 1988](#); [Raithel 1987](#); [Schneider 1979](#)) which were included in this analysis. See [Characteristics of included studies](#) for full details.

We conducted comparisons of the following interventions:

1. Aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus placebo or nothing ([Clyne 1987](#); [Donaldson 1985](#); [Goldman 1984](#); [Green 1982](#); [Kohler 1984](#); [McCollum 1991](#))
2. ASA or ASA/DIP versus pentoxifylline (PTX) ([Lucas 1984](#); [Raithel 1987](#))
3. ASA/DIP versus indobufen (IND), a reversible cyclo-oxygenase inhibitor ([D'Addato 1992](#))
4. ASA or ASA/DIP versus vitamin K antagonists (VKA) ([BOA 2000](#); [Schneider 1979](#))
5. ASA/DIP versus low molecular weight heparin (LMWH) ([Edmondson 1994](#))
6. Ticlopidine (TIC) versus placebo ([Becquemin 1997](#))
7. ASA versus prostaglandin E1 ([Gruss 1991](#))
8. ASA versus naftidrofuryl ([Noppene 1988](#))
9. Clopidogrel and ASA versus ASA alone ([CASPAR 2010](#))

Details of the study designs are shown in the table '[Characteristics of included studies](#)' and in [Table 1](#).

Aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus placebo or nothing

In all six trials study medication was started prior to bypass surgery, mostly 48 hours before the operation ([Clyne 1987](#); [Donaldson 1985](#); [Goldman 1984](#); [Green 1982](#); [Kohler 1984](#); [McCollum 1991](#)). Doses ranged from 300 mg to 325 mg ASA and 75 mg DIP, given two and three times daily. Participants were randomised before surgery. Duration of treatment was six weeks in the [Clyne 1987](#) trial but at least 12 to 24 months in the other trials. The percentage of participants with critical leg ischaemia (CLI) ranged from 60% to

80%, with the exception of [Donaldson 1985](#) which only included participants with disabling intermittent claudication.

Aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus pentoxifylline (PTX)

Two studies were included, comparing 1000 mg or 1500 mg ASA to 1200 mg PTX daily ([Lucas 1984](#); [Raithel 1987](#)). Participant characteristics and graft type were similar in both trials. While [Raithel 1987](#)'s participants all received prosthetic grafts, [Lucas 1984](#) also included participants with venous grafts. More than 90% of [Raithel 1987](#)'s participants had CLI compared to only 55% in the [Lucas 1984](#) trial.

Aspirin and dipyridamole (ASA/DIP) versus indobufen (IND)

We found only one multicentre double-blind randomised clinical trial including participants operated on for a prosthetic polytetrafluoroethylene (PTFE) femoropopliteal graft for inclusion ([D'Addato 1992](#)).

Aspirin and dipyridamole (ASA/DIP) versus vitamin K antagonists (VKA)

We include two trials in this category ([BOA 2000](#); [Schneider 1979](#)), comparing ASA or ASA and DIP with VKA. The Dutch [BOA 2000](#) trial included a much higher number of participants than the [Schneider 1979](#) trial; prosthetic grafts were included in the [BOA 2000](#) trial. It should be noted that participants receiving ASA in the [BOA 2000](#) trial were treated with a dose of only 80 mg, while all other trials included in this review compared doses of 600 mg to 1500 mg daily, sometimes with additional DIP.

Aspirin and dipyridamole (ASA/DIP) versus low molecular weight heparin (LMWH)

We include one open, randomised clinical trial for comparison of LMWH (Fragmin) and ASA and DIP ([Edmondson 1994](#)). Participants were assessed for their clinical outcomes on the seventh postoperative day.

Ticlopidine (TIC) versus nothing

Only one double-blind trial ([Becquemin 1997](#)) could be included for analysis, which randomised 243 participants after surgery. All participants received autologous saphenous vein grafts.

Aspirin versus prostaglandin E1 (PGE1)

One open, randomised clinical trial compared ASA to PGE1 on a background of 15,000 IU of heparin for early graft occlusion, within three days postoperatively, in 100 participants who all received autologous saphenous vein grafts ([Gruss 1991](#)).

Aspirin versus naftidrofuryl

We could consider only one trial in the analysis that compared ASA to naftidrofuryl (Noppene 1988). This study, which commenced on postoperative day one, randomised 99 participants who all had prosthetic PTFE grafts.

Clopidogrel and ASA (Clopidogrel/ASA) versus ASA alone

A single trial evaluated the comparison between clopidogrel with ASA versus ASA alone (CASPAR 2010), which was a large trial of 851 randomised, receiving a mixture of venous and prosthetic grafts.

Excluded studies

For this update we excluded an additional three studies (Burdess 2010; EUCTR2007 2008; Monaco 2012), making a total of 20

excluded studies (Böhmig 1995; Burdess 2010; DeWeese 1971; Ehersmann 1977; EUCTR2007 2008; Gorter 2001; Harjola 1981; Jivegard 2005; Johnson 2002; Johnson 2004; Kibbe 2002; Lassila 1991; Monaco 2012; Nevelsteen 1991; Raithel 1987b; Reichle 1979; Rosenthal 1987; Satiani 1985; Shionoya 1990; Smout 2004).The reasons for exclusion varied and include, among others: lack of a control group, not a randomised controlled trial, a heterogeneous cohort of participants, intervention not within the scope of the review, and too little information to determine inclusion.

See [Characteristics of excluded studies](#) for full descriptions of excluded studies.

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#) for 'Risk of bias' evaluation.

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

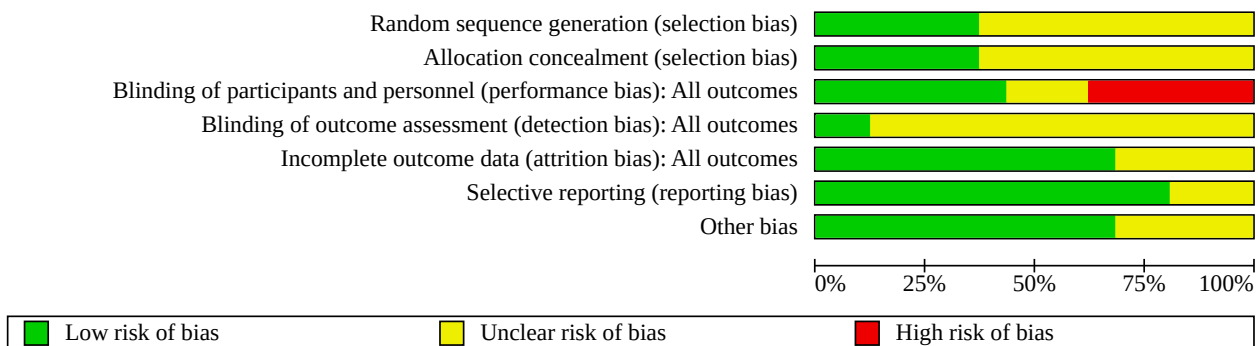


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Becquemin 1997	+	?	+	+	+	+	+
BOA 2000	+	+	-	?	+	+	+
CASPAR 2010	+	+	+	+	+	+	+
Clyne 1987	?	?	-	?	+	+	?
D'Addato 1992	?	?	?	?	+	+	+
Donaldson 1985	?	?	+	?	?	+	?
Edmondson 1994	+	+	-	?	+	+	+
Goldman 1984	?	?	+	?	+	+	?
Green 1982	?	+	+	?	+	?	+
Gruss 1991	?	?	-	?	?	?	+
Kohler 1984	+	?	+	?	?	+	+
Lucas 1984	+	+	?	?	+	+	+
McCollum 1991	?	+	+	?	+	+	?
Noppeney 1988	?	?	-	?	+	+	+
Raitchel 1987	?	?	-	?	?	+	?
Schneider 1979	?	?	?	?	?	?	+

Allocation

Random sequence generation methods were adequately described in six studies (Becquemin 1997; BOA 2000; CASPAR 2010; Edmondson 1994; Kohler 1984; Lucas 1984). The remaining 10 studies did not sufficiently describe how they generated their random sequence, leading to a rating of 'unclear' (Clyne 1987; D'Addato 1992; Donaldson 1985; Goldman 1984; Green 1982; Gruss 1991; McCollum 1991; Noppeney 1988; Raithel 1987; Schneider 1979).

Six studies described allocation concealment methods that were low-risk (BOA 2000; CASPAR 2010; Edmondson 1994; Green 1982; Lucas 1984; McCollum 1991), while the remaining 10 studies did not describe their methods adequately (Becquemin 1997; Clyne 1987; D'Addato 1992; Donaldson 1985; Goldman 1984; Gruss 1991; Kohler 1984; Noppeney 1988; Raithel 1987; Schneider 1979).

Blinding

Blinding of participants and personnel was adequate in seven studies (Becquemin 1997; CASPAR 2010; Donaldson 1985; Goldman 1984; Green 1982; Kohler 1984; McCollum 1991). Six studies were unblinded, leading to a high risk of performance bias (BOA 2000; Clyne 1987; Edmondson 1994; Gruss 1991; Noppeney 1988; Raithel 1987). The remaining three studies mentioned blinding but did not adequately describe their methods (D'Addato 1992; Lucas 1984; Schneider 1979), and are rated at unclear risk.

Blinding of outcome assessors was only described in two studies (Becquemin 1997; CASPAR 2010), while the remaining were at unclear risk of detection bias, with no description of assessor blinding.

Incomplete outcome data

The majority of studies had no issues with attrition bias, but five studies were at unclear risk, with Donaldson 1985 having a higher rate of drop-outs in the intervention arm, Gruss 1991 not reporting drop-outs or withdrawals, Kohler 1984 inconsistently reporting drop-outs between treatment groups, Raithel 1987 only reporting participants available for follow-up but not the number initially randomised, and Schneider 1979 not having enough information for us to adequately assess whether attrition bias was a problem.

Selective reporting

Selective reporting was a concern in three studies, which we evaluated as 'unclear' (Green 1982; Gruss 1991; Schneider 1979). For Green 1982 adverse events were not clearly reported, and for both Gruss 1991 and Schneider 1979 there was not enough information in the text to determine the risk of reporting bias. All remaining studies were at low risk of reporting bias.

Other potential sources of bias

Other bias was a concern in five studies (Clyne 1987; Donaldson 1985; Goldman 1984; McCollum 1991; Raithel 1987), with the rest at low risk of other bias. For Clyne 1987 and Donaldson 1985 all the data were presented by number of bypasses and not by the number of participants. Goldman 1984, McCollum 1991, and Raithel 1987 had differences in the treatment groups at baseline, and McCollum 1991 may be at risk of being underpowered, as the study power calculation required a study population of 800

participants to detect a 10% reduction in occlusion rate, but only 549 participants were randomised.

Effects of interventions

For the outcome 'primary patency' the numbers recorded for analyses were actually the number of grafts that occluded during the specified time period as reported by the trialists. We used these numbers due to the properties of odds ratios (ORs), and we found this method more straightforward to interpret. Both patency and occlusion are used to describe the treatment outcomes within the included studies and within this review, which should be kept in mind when interpreting the presented data.

Analysis for secondary graft patency, side effects of treatment and complications, limb amputation, cardiovascular events and mortality are only described when sufficient data were available. Otherwise, these outcomes are not mentioned.

None of the included studies reported on assisted primary patency, objective assessment of lower limb blood flow or participant quality of life.

None of the meta-analyses included 10 or more studies, so we could not construct funnel plots to evaluate possible publication bias.

Aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus nothing or placebo

Primary graft patency

The effect of ASA or ASA/DIP on infrainguinal bypass patency was assessed in six trials (Clyne 1987; Donaldson 1985; Goldman 1984; Green 1982; Kohler 1984; McCollum 1991). The OR from the random-effects model for primary occlusion at 12 months for all grafts was 0.42 (95% confidence interval (CI) 0.22 to 0.83; $P = 0.01$, $I^2 = 72%$, participants = 952), showing a positive effect of ASA on infrainguinal grafts at one year (Analysis 1.1).

Three of these studies had unit of analysis issues, with multiple grafts or re-randomisation of participants (Clyne 1987; Donaldson 1985; Kohler 1984). The association becomes attenuated when these studies are excluded (OR 0.36, 95% CI 0.13 to 0.99; $P = 0.05$, participants = 651).

When we performed the analysis for venous grafts alone, there was no difference in primary graft patency between the treatment groups at one, three and six months (OR 0.76, 95% CI 0.26 to 2.25, $P = 0.62$; OR 0.85, 95% CI 0.54 to 1.35, $P = 0.50$; and OR 0.88, 95% CI 0.59 to 1.31; $P = 0.53$, respectively, participants = 642 for all) (all fixed-effect analyses) (Analysis 2.1; Analysis 2.2; Analysis 2.3). At 12 months post-operation there was a possible increase in occlusion in the control group (OR 0.69, 95% CI 0.48 to 0.99; $P = 0.05$, participants = 642) (fixed-effect), but this was not seen at 24 months in the random-effects model analysis, (OR 1.03; 95% CI 0.32 to 3.28; $P = 0.96$, $I^2 = 79%$, participants = 620) (Analysis 2.4; Analysis 2.5).

Analysis for prosthetic grafts, however, showed a much stronger positive effect of ASA on primary patency as calculated from four studies (Clyne 1987; Donaldson 1985; Goldman 1984; Green 1982): ORs of 0.14 (95% CI 0.04 to 0.51; $P = 0.003$, participants = 157) at one month; 0.31 (95% CI 0.14 to 0.66; $P = 0.003$, participants = 222) at three months; 0.21 (95% CI 0.11 to 0.41; $P < 0.00001$, participants = 222) at six months; and 0.19 (95% CI 0.10 to 0.36, participants = 222) at 12 months (Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.10). Primary patency at nine months was only evaluated in a single

study, with an OR of 0.17 (95% CI 0.04 to 0.67, participants = 65) (Analysis 2.9).

Removal of the trials associated with unit of analysis issues meant that we could not conduct data analysis for venous grafts at one, three, six, 12, and 24 months as only one study remained. For prosthetic grafts, the OR was 0.25 (95% CI 0.05 to 1.30; $P = 0.10$, participants = 102) at one month; 0.30 (95% CI 0.09 to 1.01; $P = 0.05$, participants = 102) at three months; 0.31 (95% CI 0.13 to 0.74; $P = 0.008$, participants = 102) at six months; and 0.23 (95% CI 0.10 to 0.54; $P = 0.0008$, participants = 102) at 12 months, all fixed-effect models. For all comparisons the overall effect was reduced, and for months one and three the association no longer favoured ASA or ASA/DIP.

Secondary graft patency

McCollum 1991 reported on secondary patency of the failed grafts, but the time frame of the reported cases is unclear. The study reported that of the 172 failed grafts (86 in each treatment group), eight in the ASA/DIP group and four in the placebo group were restored by re-operation but it is unclear if all failed grafts were re-operated. McCollum 1991 also reported that the cumulative secondary patency rate for the ASA/DIP group was 80% at one year, 73% at two years and 63% at three years, and 74%, 64% and 61% respectively for the placebo group. Because the number of participants that were included to derive these values was unclear, we cannot use them in meta-analysis.

Side effects of treatment and complications

Side effects were reported in five studies (Clyne 1987; Donaldson 1985; Green 1982; Kohler 1984; McCollum 1991) and the fixed-effect model found an OR of 1.55 (95% CI 1.00 to 2.41; $P = 0.05$, participants = 913) for general side effects (Analysis 1.2). However, when Clyne 1987, Donaldson 1985 and Kohler 1984 were removed due to unit of analysis issues the association was attenuated with an OR of 1.34 (95% CI 0.83 to 2.16; $P = 0.23$, participants = 598). Six studies evaluated side effects specific to the gastrointestinal tract (Clyne 1987; Donaldson 1985; Goldman 1984; Green 1982; Kohler 1984; McCollum 1991), and found no differences between the two treatment groups (OR 1.44, 95% CI 0.92 to 2.24; $P = 0.11$, participants = 952) in the fixed-effect model. When Clyne 1987, Donaldson 1985 and Kohler 1984 were removed due to unit of analysis issues there was very little change in the outcome (OR 1.38, 95% CI 0.87 to 2.21; $P = 0.17$, participants = 651).

Major bleeding was similar between the treatment groups for two trials (Green 1982; McCollum 1991) (OR 1.88, 95% CI 0.85 to 4.16; $P = 0.12$, participants = 598) in the fixed-effect model. Minor bleeding was only evaluated in one study (Clyne 1987), with an OR of 0.73 (95% CI 0.31 to 1.70, participants = 148). Wound or graft infection was only evaluated in McCollum 1991, with similar events in both treatment groups (OR 1.07, 95% CI 0.67 to 1.71, participants = 549).

Limb amputation

Clyne 1987 reported amputations with an OR of 0.55 (95% CI 0.21 to 1.44, grafts = 148), but it should be noted this was one of the studies with multiple grafts in some of the participants (148 grafts in 140 participants) (Analysis 1.3).

Cardiovascular events and mortality

Analysis of cardiovascular events was performed in four trials (Clyne 1987; Donaldson 1985; Green 1982; McCollum 1991) and the random-effects model found an OR of 1.27 (95% CI 0.43 to 3.80; $P = 0.66$, $I^2 = 52%$, participants = 811) (Analysis 1.4). When Clyne 1987 and Donaldson 1985 were removed for unit of analysis issues, the association was statistically significant, in favour of ASA or ASA/DIP (OR 0.58, 95% CI 0.37 to 0.91; $P = 0.02$, participants = 598), although it should be noted that McCollum 1991 then comprises 96% of the analysis.

The OR for postoperative death for the fixed-effect model, as evaluated in four studies (Clyne 1987; Goldman 1984; Green 1982; McCollum 1991) was 0.84 (95% CI 0.56 to 1.26; $P = 0.41$, participants = 799) (Analysis 1.5). When Clyne 1987 was removed for sensitivity analysis due to unit of analysis issues the resulting OR was 0.77 (95% CI 0.49 to 1.21; $P = 0.26$, participants = 651). Again McCollum 1991 accounted for a large majority of the weight.

Aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus pentoxifylline (PTX)

Primary graft patency

The effect of PTX on graft patency when compared to ASA or ASA/DIP treatment could only be evaluated in a formal analysis from two RCTs (Lucas 1984; Raithel 1987) at six months post-operation. The fixed-effect model had an OR of 1.32 (95% CI 0.56 to 3.11; $P = 0.52$, participants = 151) showing no difference between the treatment groups (Analysis 3.3). This analysis should be considered with caution as Lucas 1984 involved multiple grafts and there appeared to be substantial heterogeneity among the sample population. At other time points, only Raithel 1987 provided raw data and showed a similar effect of both drugs on graft patency: OR 2.04 (95% CI 0.18 to 23.07, participants = 118) at one month; OR 1.00 (95% CI 0.27 to 3.65, participants = 118) at three months; and OR 0.91 (95% CI 0.38 to 2.15, participants = 118) at 12 months (Analysis 3.1; Analysis 3.2; Analysis 3.4).

Side effects of treatment and complications

Raithel 1987 reported on side effects that included gastric intolerance, gastric haemorrhage and vertigo, with ORs of 18.04 (95% CI 5.07 to 64.17), 3.11 (95% CI 0.31 to 30.77) and 0.48 (95% CI 0.08 to 2.74) respectively, all with 118 participants (Analysis 3.5). It should be noted that side effects were extrapolated from graphs and therefore may not be completely accurate.

Limb amputation

Amputation was also only evaluated in the Raithel 1987 study, with an OR of 0.38 (95% CI 0.07 to 2.04, participants = 118) (Analysis 3.6).

Cardiovascular events and mortality

Reported only in Raithel 1987, there were six deaths in the ASA group and three in the PTX group, with an OR of 2.11 (95% CI 0.50 to 8.88, participants = 118) (Analysis 3.7). The authors reported that eight of the deaths were from myocardial infarction and one from cardiac failure, but they did not detail which treatment groups they came from.

Aspirin and dipyridamole (ASA/DIP) versus indobufen (IND)**Primary graft patency**

The one eligible RCT (D'Addato 1992) compared ASA/DIP to IND in receiving infrainguinal prosthetic PTFE grafts. The study had an OR of 1.67 (95% CI 0.51 to 5.44, participants = 113) for primary patency at three months, OR 1.60 (95% CI 0.60 to 4.27, participants = 113) at six months, OR 1.26 (95% CI 0.56 to 2.85, participants = 113) at nine months and OR 1.34 (95% CI 0.61 to 2.93, participants = 113) at 12 months (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4).

Aspirin and dipyridamole (ASA/DIP) versus vitamin K antagonists (VKA)**Primary graft patency**

This was reported in two trials (BOA 2000; Schneider 1979). Primary graft patency for all grafts showed no difference for coumarin versus aspirin, irrespective of time point: OR 0.88 (95% CI 0.68 to 1.14; $P = 0.34$, $I^2 = 0\%$) at three months, OR 0.72 (95% CI 0.27 to 1.96; $P = 0.52$, $I^2 = 61\%$) at six months, OR 0.68 (95% CI 0.27 to 1.69; $P = 0.40$, $I^2 = 67\%$) at 12 months; and OR 0.64 (95% CI 0.25 to 1.63; $P = 0.36$, $I^2 = 74\%$) at 24 months, with 2781 participants included in each outcome (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4). We used a fixed-effect model at three months, and random-effects models for months six, 12 and 24, due to high heterogeneity.

Side effects of treatment and complications

In the BOA 2000 trial, haemorrhage necessitating hospital admission was reported for 119 (9%) participants in the coumarin group and 59 (4.5%) in the aspirin group. A total of 16 (1.2%) participants died from fatal bleeding in the coumarin group and 12 (0.9%) participants in the aspirin group. In Schneider 1979 the adverse effects reported were: two participants (0.6%) who stopped coumarin treatment because of bleeding complications and 13 participants (21%) who stopped aspirin for differing reasons.

Limb amputation

The two trials (BOA 2000; Schneider 1979), did not report data on limb salvage or survival that was suitable for formal meta-analysis. However, in BOA 2000 limb amputation had to be performed in a similar number of participants in each treatment group, with an OR of 0.99 (95% CI 0.75 to 1.30, participants = 2690) (Analysis 5.5).

Cardiovascular events and mortality

Only BOA 2000 reported on cardiovascular events and mortality for this treatment comparison. Myocardial infarction and stroke were similar for both treatment groups, with slightly higher occurrences in the ASA/DIP group: OR 1.45 (95% CI 0.90 to 2.34) and OR 1.34 (95% CI 0.86 to 2.09) respectively; participants = 2690 (Analysis 5.6). Death from all causes, after two years, was similar in both treatment groups, with an OR of 1.02 (95% CI 0.83 to 1.26, participants = 2690) (Analysis 5.7).

Aspirin and dipyridamole (ASA/DIP) versus low molecular weight heparin (LMWH)**Primary graft patency**

In Edmondson 1994 primary patency was measured at six and 12 months with little difference between the treatment groups: OR 1.69 (95% CI 0.78 to 3.65, participants = 200), and OR 1.19 (95% CI

0.66 to 2.15, participants = 200), respectively (Analysis 6.1; Analysis 6.2).

Side effects of treatment and complications

No major bleedings or adverse events occurred.

Cardiovascular events and mortality

There were more deaths in the LMWH treatment group compared to the ASA/DIP group: OR 0.18 (95% CI 0.04 to 0.86, participants = 200) (Analysis 6.3).

Ticlopidine (TIC) versus nothing**Primary graft patency**

Intention-to-treat analysis of one trial (Becquemin 1997) involving participants undergoing bypass with venous grafts showed no difference in primary patency at one month between the treatment groups: OR 3.00 (95% CI 0.12 to 74.37, participants = 243), with a wide confidence interval as only one event occurred by this time point (Analysis 7.1). However, primary patency at six, 12 and 24 months showed increased patency in the TIC treatment group: OR 0.26 (95% CI 0.11 to 0.63, participants = 243) at six months; OR 0.38 (95% CI 0.19 to 0.75, participants = 243) at 12 months; and OR 0.37 (95% CI 0.21 to 0.67, participants = 243) at 24 months (Analysis 7.2; Analysis 7.3; Analysis 7.4).

Aspirin versus prostaglandin E1 (PGE1)**Primary graft patency**

One study (Gruss 1991) reported on the drug comparison of aspirin to PGE1 in participants receiving autologous venous grafts. Early occlusion, within the first three postoperative days, had few events, with an OR of 3.91 (95% CI 0.77 to 19.83, participants = 100) (Analysis 8.1). Longer-term patency was not reported.

Aspirin versus naftidrofuryl**Primary graft patency**

One study (Noppeney 1988) reported graft occlusion in seven of the 50 participants administered naftidrofuryl compared to 10 of the 49 given ASA, with an OR of 1.58 (95% CI 0.55 to 4.54, participants = 99) (Analysis 9.1).

Side effects of treatment and complications

More general side effects were experienced by the ASA group compared to naftidrofuryl: OR 13.86 (95% CI 3.80 to 50.60, participants = 99). Gastrointestinal side effects were also more common in the aspirin group: OR 28.45 (95% CI 3.61 to 223.97, participants = 99). Only two participants reported vertigo, both in the naftidrofuryl treatment group: OR 0.20 (95% CI 0.01 to 4.19, participants = 99). Stomach bleeding was reported in five participants, all in the aspirin treatment group: OR 12.48 (95% CI 0.67 to 232.14, participants = 99) (Analysis 9.2).

Cardiovascular events and mortality

Deaths occurred in both treatment groups, with an OR of 2.73 (95% CI 0.50 to 14.78, participants = 99) (Analysis 9.3).

Clopidogrel and ASA (clopidogrel/ASA) versus ASA alone

CASPAR 2010 was the only study to compare clopidogrel/ASA to ASA alone. Outcomes were reported at 24 months as a whole population

and split by subgroups based on whether participants received venous or prosthetic grafts.

Primary graft patency

Primary graft patency for all participants was similar between both treatment groups, OR 0.95 (95% CI 0.69 to 1.31, participants = 851) [Analysis 10.1](#). There were more cases of occlusion in the clopidogrel/ASA group, compared to ASA alone, when only venous grafts were included: OR 1.47 (95% CI 0.93 to 2.31, participants = 598), but higher occlusion rates in the ASA alone group for prosthetic grafts: OR 0.53 (95% CI 0.32 to 0.88, participants = 253) ([Analysis 11.1](#); [Analysis 11.2](#)).

Side effects of treatment and complications

Total cases of bleeding were fewer in the ASA alone group: OR 2.65 (95% CI 1.69 to 4.15, participants = 851), as were mild bleeding: OR 2.34 (95% CI 1.37 to 4.00, participants = 851) and moderate bleeding: OR 4.13 (95% CI 1.37 to 12.45, participants = 851). Cases of severe bleeding and fatal bleeding were few, and similar between the treatment groups: OR 1.82 (95% CI 0.61 to 5.48, participants = 851) and OR 2.01 (95% CI 0.18 to 22.24, participants = 851), respectively ([Analysis 10.2](#)).

When we evaluated graft subgroups, there was still less mild bleeding in the ASA alone group for venous grafts: OR 2.46 (95% CI 1.33 to 4.53, participants = 598), but the occurrence of mild bleeding events was more similar between the treatment groups for prosthetic grafts: OR 1.86 (95% CI 0.67 to 5.21, participants = 253). The same trend was seen for moderate bleeding: venous grafts: OR 5.75 (95% CI 1.26 to 26.17, participants = 598) and prosthetic grafts: OR 2.50 (95% CI 0.48 to 13.13, participants = 253). Severe bleeding was similar between treatment groups for both venous and prosthetic grafts: OR 2.75 (95% CI 0.72 to 10.47, participants = 598) and OR 0.48 (95% CI 0.04 to 5.41, participants = 253), respectively ([Analysis 11.3](#)).

Limb amputation

For all grafts, amputations were similar between groups, with slightly higher occurrence in the ASA alone group: OR 0.67 (95% CI 0.41 to 1.08, participants = 851) ([Analysis 10.3](#)). Amputation occurrence was also similar between treatment groups for venous grafts: OR 0.91 (95% CI 0.48 to 1.73, participants = 598), but more occurred in the ASA alone group for prosthetic grafts: OR 0.44 (95% CI 0.21 to 0.91, participants = 253) ([Analysis 11.4](#)).

Cardiovascular events and mortality

For all graft types, death was similar between both treatment groups: OR 1.44 (95% CI 0.76 to 2.72, participants = 851), which was also the case for both venous and prosthetic grafts: OR 1.43 (95% CI 0.69 to 2.97, participants = 598), and OR 1.49 (95% CI 0.41 to 5.40, participants = 253), respectively ([Analysis 10.4](#); [Analysis 11.5](#)).

DISCUSSION

Summary of main results

Antiplatelet therapy effect on bypass patency

In the present meta-analysis we evaluated the effect of postoperatively administered antiplatelet treatment in people with peripheral arterial disease (PAD) receiving infrainguinal bypasses. It was shown that antiplatelet treatment with aspirin (ASA) or a

combination of ASA and dipyridamole (ASA/DIP) has an overall positive effect on primary patency 12 months after the procedure. Interestingly, the size of the effect differed between participants receiving prosthetic grafts and those receiving venous grafts. When we limited the analysis to the subgroups receiving prosthetic (polytetrafluoroethylene (PTFE) or Dacron) grafts, the effect was statistically significant at all time points. In contrast, there was no evidence to support an effect of ASA or ASA/DIP in participants receiving venous graft bypasses. The evidence for secondary patency is too limited to draw any conclusions at this time. It should be noted that we did not perform a formal test for interaction to statistically demonstrate a differential effect of antiplatelet agents by graft type.

There was no difference in primary patency for the comparison between ASA/DIP versus pentoxifylline (PTX) at one, three, six and 12 months. However, for most of the time points we evaluated only a single study. For the comparisons between ASA and DIP versus indobufen (prosthetic grafts only), ASA or ASA/DIP versus vitamin K antagonists (VKA), as well as ASA/DIP versus low molecular weight heparin (LMWH), there were no differences between the treatment groups in primary patency at any time point. The analyses of indobufen and LMWH only had single study reporting and VKA included only two studies.

A single study evaluated ticlopidine versus placebo in participants receiving venous grafts only. Primary patency was significantly improved at six, 12 and 24 months after the procedure, but not in the first month post-procedure. Thus, ticlopidine seems to be the only antiplatelet agent achieving a favourable effect on venous graft patency. ASA versus prostaglandin E1, also only with venous grafts, was reported in a single study, with few outcome events and no difference between the treatment groups for early occlusions. Comparing ASA with naftidrofuryl in a single study, there was no difference in primary patency at 12 months.

Clopidogrel with ASA versus ASA alone was reported in a single study, with no difference in primary patency at 24 months for all participants, as well as no difference for venous grafts. Prosthetic grafts showed improvement in patency at 24 months for the clopidogrel with ASA group.

Side effects and limb amputations

For the comparison of ASA or ASA/DIP versus placebo or nothing, there were no differences between the treatment groups for any of the evaluated side effects, complications or amputations. Comparing ASA or ASA/DIP to PTX there was a possible increase in gastric intolerance, but no differences for gastric haemorrhage, vertigo or amputations. There were also no differences in amputation comparing ASA or ASA/DIP to VKA. Both general and gastrointestinal side effects were increased in the ASA group, compared with naftidrofuryl, but vertigo and stomach bleeding were similar between the two groups. Comparing clopidogrel/ASA with ASA alone, there were increased total, mild and moderate bleeding events in the one study that evaluated this treatment comparison, in all participants, but no difference for severe or fatal bleeding events. In venous grafts within this study, there was an increase in mild and moderate events, but no difference in severe bleeding events, and there was no difference in any of the bleeding categories for prosthetic grafts. Within this comparison, amputations were similar between treatment groups

for all participants, including venous grafts, but there was a slight decrease in amputations in the clopidogrel/ASA group.

Cardiovascular events and mortality

For the comparisons of ASA or ASA/DIP versus placebo or nothing and ASA or ASA/DIP versus VKA there were no differences between the treatment groups for cardiovascular events or mortality. There was also no difference in mortality when comparing ASA or ASA/DIP versus PTX, ASA versus naftidrofuryl, or clopidogrel/ASA versus ASA alone; cardiovascular events were not evaluated within these comparisons.

Although very few events were reported in the single study, there appeared to be decreased mortality in the ASA/DIP treatment group, compared with LMWH.

In conclusion, the results of our meta-analysis suggest that the administration of platelet inhibitors such as ASA or ASA/DIP could result in improved venous and prosthetic graft patency compared to no treatment. However, subgroup analysis by graft type, i.e. venous versus PTFE or Dacron, shows that participants receiving a prosthetic graft are likely to benefit more from ASA or ASA and DIP administration than those treated with a venous graft. For most of the comparisons included in this review, there is currently not enough data to draw any conclusions.

Overall completeness and applicability of evidence

With 16 studies included in the review and meta-analysis, there was much relevant data available to provide evidence for the review question. However, we separately evaluated a total of nine different comparisons, with only one comparison having more than two studies providing data for meta-analysis. Therefore, while this review does bring many trials together touching on many antiplatelet treatments, the review does not reach a meaningful level of evidence for all of the predefined comparisons. Also, none of the included studies addressed the outcomes of assisted primary patency, objective assessment of blood flow or quality of life, and many studies did not report on any of the other outcomes. Assisted primary patency as an outcome is of specific importance, as even a highly stenotic graft may remain patent, and a graft at a highly stenotic stage would be more easily treated, both technically and for the patient, than a fully occluded graft. Therefore, knowing whether antiplatelet treatments help reduce full occlusion and allow treatment at a stenotic but not occluded stage would be of clinical importance.

Data presentation did not distinguish by graft type for the site of the distal anastomosis. Furthermore, the number of grafts frequently differed from the number of participants, without appropriate explanation. Insufficient information was available in the included studies to assess the effects of antiplatelet agents in different clinical settings such as diabetes and other co-morbidities. Another concern with the applicability of evidence is the fact that different dosages of the various treatments were used between the included studies. Further information on the dosages can be found in [Characteristics of included studies](#) tables.

Quality of the evidence

This review included 16 studies with a total of 5683 randomised participants. Currently we can only draw a robust conclusion regarding antiplatelet agents for preventing thrombosis after

peripheral arterial bypass surgery for the comparison between ASA or ASA/DIP versus placebo or nothing, showing a positive reduction in occlusion at 12 months in participants who received ASA or ASA/DIP. The comparisons of ASA or ASA/DIP versus vitamin K antagonists and of clopidogrel and ASA versus ASA alone only included one or two studies, but they encompassed a large number of participants. Neither comparison found any difference in primary graft patency at any of the time points. All other comparisons only included one or two smaller studies. Also limiting the quality of the evidence is the fact that several included studies provided their results by the number of bypasses and not by the number of participants, indicating bilaterally-treated patients. This could alter results, although currently only a few studies provided results in this manner, with few participants in their study population receiving multiple bypasses. Also of concern is the reporting of outcomes at varying time points, which vary between studies. This reduces our ability to combine outcome data in the most robust way possible.

Overall, study quality was moderate, with the largest problem being that the majority of studies did not adequately describe their methods of randomisation or outcome assessor blinding. The other main issue with study quality was not blinding participants or personnel to the treatment received. These concerns, along with the previously reported issues with paucity of data for many of the comparisons, unit of analysis issues, variation of treatment dosages and lack of data on our review's prespecified outcomes, leaves the quality of the evidence of the review moderate to low. We expect that with future updates and more high-quality studies, the quality of evidence will improve.

Potential biases in the review process

In order to reduce potential bias two review authors assessed studies for inclusion and performed data extraction and quality assessment. We made every attempt to include all relevant studies, but it is still possible that we did not identify all studies.

The majority of included studies randomised individuals as the unit for analysis, but four studies included participants with multiple or bilateral reconstructions or re-randomised participants, and used grafts as the unit of analysis. In order to include these data we performed analyses with the four studies with unit of analyses issues, but also performed sensitivity analyses by excluding them to see if the results were affected. Only the comparison between ASA or ASA/DIP versus nothing or placebo contained enough studies to evaluate the effects of the unit of analysis issues by sensitivity analysis, and within this comparison we could not evaluate all outcomes. Overall there was very little change in the results when the studies were removed, but when the odds ratios (ORs) did change, it was an expected attenuation and decreasing of power due to a reduction in the overall number of participants included in the calculation. Readers should keep in mind our methods of addressing these unit of analysis issues when evaluating the results of this review, as other reviews may take a different approach.

For the outcome 'primary patency', the numbers recorded for analyses were actually the number of grafts that occluded during the specified time period as reported by the trialists. Both patency and occlusion are used to describe the treatment outcomes within the included studies and within this review, which should be kept in mind when interpreting the presented data. As assisted primary patency was not reported by the trialists of the included studies, it is

unclear if the reported occlusion is actual occlusion i.e. thrombosis of the graft, or if it also includes participants whose grafts were revised prior to occlusion/thrombosis.

We calculated data for graft failure from the survival curves if raw data were not reported or were unavailable after contacting the authors of the trials.

Agreements and disagreements with other studies or reviews

A systematic review and meta-analysis that was published in 1999 also set out to evaluate antiplatelet therapy (specifically aspirin) in the prevention of graft occlusion after infrainguinal bypass surgery (Tangelder 1999). This review differs from our own, as it was interested in oral anticoagulants, as well as antiplatelet agents, and they used risk ratios (RRs) and not odds ratios for their dichotomous outcomes. The Tangelder 1999 review included five studies that we also included in our own review, and an additional two studies, one of which was specific to oral anticoagulants, while the other compared an anticoagulant with aspirin to aspirin alone. The findings in Tangelder 1999 were similar to our own meta-analyses findings for the comparison between ASA or ASA/DIP versus nothing or placebo. They found a decrease in bypass occlusions in the aspirin group (RR 0.78, 95% CI 0.64 to 0.95), and no difference between the treatment groups for total mortality (RR 0.92, 95% CI 0.64 to 1.32).

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence to suggest that the administration of platelet inhibitors such as ASA or ASA/DIP will result in improved venous and prosthetic graft patency compared to no treatment. However, patients with a prosthetic graft may benefit more from ASA or ASA/DIP administration than those with a venous graft, but this needs further investigation. The results of this review should be interpreted with caution, due to the unit of analysis issues

described within the review, as well as the fact that many of the comparisons were only reported in a single study, and that the dosages often differed between studies.

Implications for research

Further high-quality randomised clinical trials, with adequate sample sizes, are required to evaluate the efficacy of antiplatelet medications for graft patency in infrainguinal venous and prosthetic grafts for all treatment comparisons. Presentation of data should be detailed and not only show survival curves for overall patency. Tables showing the raw data would improve the transparency of the trial performance and allow comparison of endpoints at consecutive time points. The reader would be able to identify the number of occlusions, or other endpoints, at different time points in each comparison group as well as in subgroups defined by bypass material, above- and below-knee anastomosis, and inflow and outflow conditions. Other concerns for research within this area would be determining the optimal dosage of antiplatelet medications and also outcome stratification by co-morbidities, such as diabetes. A more complete outcome profile should be evaluated, such as assisted primary patency. Uniformity of unit of analysis issues should be addressed in studies of peripheral vascular disease, as there needs to be clarity around single and multiple grafts and the time points at which these occurred.

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Dörffler-Melly J, Büller HR, Koopman MM, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No: CD000535. [DOI: [10.1002/14651858.CD000535](https://doi.org/10.1002/14651858.CD000535)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Becquemin 1997

Study characteristics

Methods	<p>Study type: Multicentre, double-blind, randomised controlled trial</p> <p>Study aim: To determine whether ticlopidine (TIC) could reduce the rate of late occlusion of saphenous-vein grafts below the knee</p> <p>Country: France</p>
Participants	<p>Number randomised: Total n = 243 (TIC n = 122; placebo n = 121)</p> <p>Age- mean years: TIC 67.1; placebo 67.7</p> <p>Gender n (M/F): TIC 96/26; placebo 92/29</p> <p>Inclusion criteria: All patients 18 to 80 years old who required femoropopliteal or femorotibial bypass graft for atheromatous occlusive disease; had a saphenous vein suitable for grafting</p> <p>Exclusion criteria: Acute ischaemia or aneurysm; marked stenosis in the ipsilateral iliac artery; previous arterial surgery on the same limb; reduced life expectancy; pregnancy; inability to comply with the protocol; associated conditions requiring treatment with platelet-inhibiting drugs or anticoagulants; abnormalities of haemostasis</p>

Becquemin 1997 (Continued)

Co-morbidity: current angina or previous MI (TIC 20.5%; placebo 24.8%), impaired left ventricular function (TIC 10.7%; placebo 7.4%), arrhythmia (TIC 9.0%; placebo 15.7%), carotid stenosis (TIC 22.1%; placebo 21.5%), hypertension (TIC 48.4%; placebo 53.7%), current smoker (TIC 25.4%; placebo 19.0%), diabetes (TIC 27.0%; placebo 21.5%), hyperlipidaemia (TIC 23.8%; placebo 25.6%), previous vascular surgery (TIC 32.8%; placebo 30.6%)

Severity of occlusive disease: Leriche-Fontaine stage of disease- stage IIb (TIC 27.0; placebo 22.3), stage III (TIC 30.3; placebo 41.3), stage IV (TIC 42.6; placebo 36.4)

Site of distal anastomosis: popliteal (TIC n = 66; placebo n = 82), tibial (TIC n = 56; placebo n = 39)

Type of graft: autologous saphenous-vein grafts

More than 70% of the participants in both groups suffered from critical limb ischaemia

Interventions	<p>Treatment: 250 mg ticlopidine in bottles with a 1-month supply; given in boxes containing 6-month supply dispensed on day 0 and at 6, 12 and 18 months; participants instructed to take 1 tablet twice a day for the 24 months of the study</p> <p>Control: placebo identically matched to treatment in bottles with a 1-month supply; given in boxes containing 6-month supply dispensed on day 0 and at 6, 12 and 18 months; participants instructed to take 1 tablet twice a day for the 24 months of the study</p> <p>Duration: 24 months</p>
Outcomes	<p>Primary endpoint was primary patency at 2 years postoperatively; Secondary endpoints were secondary graft patency, death from any cause, nonfatal MI, nonfatal stroke, limb ischaemia, mesenteric infarct, amputation of leg or thigh</p> <p>Evaluated at 1, 3, 6, 12, 18 and 24 months</p>
Notes	<p>Randomisation took place between the 3rd and 14th postoperative day and follow-up continued for 2 years</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...according to a predetermined randomization list of numbers balanced in blocks of four"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment bottles containing a one-month supply of ticlopidine (250-mg tablets) or matching placebo were prepared by Sanofi and labelled according to a predetermined randomization list of number balanced in block of four"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All records concerning graft patency were reviewed by a validation committee that was unaware of the patients' treatment assignments. The clinical events were reviewed and adjudicated blindly by an independent panel..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete outcome data; used intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported on

Becquemin 1997 (Continued)

Other bias	Low risk	No indication of other bias
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BOA 2000
Study characteristics

Methods	<p>Study type: An open, randomised, multicentre clinical trial</p> <p>Study aim: To compare the effectiveness of oral anticoagulants with that of aspirin in the prevention of infrainguinal bypass-graft occlusion and other clinical events</p> <p>Country: the Netherlands</p>	
Participants	<p>Number randomised: Total n = 2690 (ASA n = 1351; coumarin n = 1339)</p> <p>Age- mean years (SD): ASA 69 (10); coumarin 69 (10)</p> <p>Gender- M%: ASA 63%; coumarin 65%</p> <p>Inclusion criteria: All patients who required an infrainguinal bypass graft for obstructive arterial disease</p> <p>Exclusion criteria: Contraindication or absolute indication for one of the trial medications; substantially shortened life expectancy; MI or stroke within 1 month before surgery; abnormalities of blood platelets or erythrocytes; anaemia; inability to adhere to the protocol; inability to give informed consent</p> <p>Co-morbidity: All participants: 54% smokers, 39% with hypertension, 26% with diabetes mellitus, and 16% with hyperlipidaemia</p> <p>Severity of occlusive disease: Claudicants (ASA 52%; coumarin 50%), Pain at rest (ASA 21%; coumarin 21%), Ischaemic ulceration (ASA 25%; coumarin 27%), gangrene (ASA 2%; coumarin 1%)</p> <p>Site of distal anastomosis: popliteal above knee (ASA 48%; coumarin 45%), popliteal below knee (ASA 32%; coumarin 36%), crural (ASA 19%; coumarin 18%), pedal (ASA 1%; coumarin 2%)</p> <p>Type of graft: vein (ASA 58%; coumarin 59%), biograft (ASA 6%; coumarin 6%), prosthetic (ASA 34%; coumarin 31%), composite (ASA 2%; coumarin 3%)</p>	
Interventions	<p>Treatment: Aspirin, 100 mg daily pulverised carbasalate calcium (equivalent to 80 mg daily), started within 5 days after surgery</p> <p>Control: coumarin derivatives (phenprocoumon or acenocoumarol) with intended International Normalised Ratio (INR) range was 3.0 - 4.5 (achieved in 50% of the observed patient years), started within 5 days after surgery</p> <p>Duration: unclear, but mean observation time was 21 months</p>	
Outcomes	<p>Primary endpoint was graft patency assessed clinically by Doppler flow measurement or duplex sonography, or by arteriography if indicated. Secondary endpoints were vascular death, MI, stroke, amputation, vascular intervention, and major haemorrhage. Follow-up was at 3, 6, 12, 18, and 24 months, with 6 monthly visits thereafter. Mean observation time was 21 months</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

BOA 2000 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation was performed by telephone through a central trial office, using computer-generated sequences of numbers
Allocation concealment (selection bias)	Low risk	Performed by telephone through central trial office
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for drop-outs, and final numbers for each treatment group are similar
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

CASPAR 2010
Study characteristics

Methods	<p>Study type: Multicentre, prospective, randomised, placebo-controlled trial</p> <p>Study aim: To determine whether clopidogrel plus ASA had better limb outcomes compared to ASA alone, in patients undergoing below-knee bypass grafting</p> <p>Country: UK</p>
Participants	<p>Number randomised: Total n = 851 (Clopidogrel + ASA n = 425; ASA + placebo n = 426)</p> <p>Age- mean years (SD): Clopidogrel + ASA 66.5 (8.7); ASA + placebo 65.6 (8.5)</p> <p>Gender- M%: Clopidogrel + ASA 75.5%; ASA + placebo 75.8%</p> <p>Inclusion criteria: ≥ 40 and ≤ 80 years; informed consent obtained before conducting any study-related procedure; chronic background treatment with daily ASA of any dose, started at least 4 weeks before surgery; a post-randomisation dose of ASA between 75 and 100 mg/day; unilateral below-knee bypass graft for atherosclerotic PAD; patent index graft demonstrated during bypass surgery or between surgery and time of randomisation; no clinical evidence of graft occlusion at randomisation</p> <p>Exclusion criteria: Onset of PAD symptoms before age of 40; nonatherosclerotic vascular disease; patients receiving aortobifemoral, iliac-femoral or cross-over (femoral-femoral) grafts or undergoing peripheral transcatheter angioplasty during the same surgery; significant bleeding risk such as current active bleeding at the surgical site; withdrawal of an epidural catheter less than 12 hours before randomisation; peptic ulceration within 12 months of randomisation; previous or current intracranial haemorrhage or haemorrhagic stroke; any history of severe spontaneous bleeding; current warfarin therapy or anticipated need for warfarin; concomitant additional antiplatelet agents or thrombolytic agents</p> <p>Co-morbidity: Hypertension (Clopidogrel + ASA 70.1%, ASA + placebo 70.0%); Hyperlipidemia (Clopidogrel + ASA 50.4%, ASA + placebo 48.8%); CAD and/or CRVD (Clopidogrel + ASA 38.4%, ASA + placebo</p>

CASPAR 2010 (Continued)

31.0%); Diabetes (Clopidogrel + ASA 37.4%, ASA + placebo 38.0%), claudication only (Clopidogrel + ASA 34.1%, ASA + placebo 32.6%), rest pain (Clopidogrel + ASA 26.1%, ASA + placebo 26.5%), ulcers/gangrene (Clopidogrel + ASA 39.3%, ASA + placebo 39.9%)

Severity of occlusive disease (determined by ABPI): ABPI (SD) - Clopidogrel + ASA 0.44 (0.25), ASA + placebo 0.46 (0.26)

Site of distal anastomosis: Below-knee popliteal (Clopidogrel + ASA 75.5%, ASA + placebo 74.8%); below-knee popliteal crural (Clopidogrel + ASA 20.7%, ASA + placebo 22.1%); beyond popliteal pedal (Clopidogrel + ASA 3.8%, ASA + placebo 3.1%)

Type of graft: venous and prosthetic grafts (Clopidogrel + ASA venous = 297 prosthetic = 128; ASA + placebo venous = 301 prosthetic = 125)

Interventions	<p>Treatment: Clopidogrel + ASA: ASA 75 - 100 mg/day plus clopidogrel 75 mg/day</p> <p>Control: ASA + placebo: ASA 75 - 100 mg/day plus placebo 1 tablet/day</p> <p>Duration: Beginning 2- 4 days after bypass surgery; follow-up from 6 to 24 months after surgery; Follow-up evaluations at 1 month and then every 6 months thereafter</p>	
Outcomes	<p>Primary efficacy: composite of index-graft occlusion or revascularisation, above-ankle amputation of affect limb or death</p> <p>Primary safety: severe bleeding (GUSTO classification), moderate and mild bleeding</p> <p>ABPI</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used an interactive voice-response system with a pre-established randomisation scheme, stratified by graft type (venous or prosthetic)
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind" and used placebo tablets in ASA-only group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All occurrences of the primary endpoint were adjudicated on a blinded basis by the Clinical Endpoints Committee"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs and losses to follow up were clearly described and similar between groups; efficacy analysis performed on an intention-to-treat basis, with all randomised participants
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

Clyne 1987
Study characteristics

Methods	<p>Study type: Prospective randomised single-centre trial</p> <p>Study aim: To discover whether improved patency could be achieved by a short course of maximum thrombogenicity</p> <p>Country: UK</p>
Participants	<p>Number randomised: Total n = 140 (148 bypasses) (ASA/DIP = 78 bypasses; control = 70 bypasses)</p> <p>Age: not indicated</p> <p>Gender n (M/F): Total 107/41</p> <p>Inclusion criteria: patients undergoing femorodistal bypasses for rest pain or very short distance claudication</p> <p>Exclusion criteria: not indicated</p> <p>Co-morbidity: smoker (ASA/DIP 62%; control 61%), diabetes (ASA/DIP 13%; control 13%), duration of claudication- months (SD) (ASA/DIP 15.6 (24.9); control 24.7 (35)), rest pain (ASA/DIP = 42; control = 46)</p> <p>Severity of occlusive disease (determined by ABPI): ABPI (SD) - ASA/DIP 0.39 (0.25); control 0.35 (0.27)</p> <p>Site of distal anastomosis: below knee 119 (ASA/DIP = 64; control = 55)</p> <p>Type of graft: autogenous vein bypasses - 93 (63 %) (ASA/DIP = 49; control = 44), prosthetic including PTFE, Dacron and umbilical vein - 55 (ASA/DIP = 29; control = 26), 28 participants received secondary reconstructions</p>
Interventions	<p>Treatment: ASA/DIP - 200 mg twice daily DIP started 48 hours before surgery, continued on day of surgery and postoperatively 10 mg iv DIP; followed by 300 mg ASA and 200 mg DIP twice daily for 6 weeks after surgery. All participants received heparin perioperatively</p> <p>Control: no specific anti-thrombotic treatment or placebo</p> <p>Duration: 6 weeks</p>
Outcomes	<p>Primary endpoints were graft failure, limb loss, death at 12 months follow-up. Graft patency was assessed clinically and by Doppler ankle blood pressure before discharge, at 1, 3, 6, and 12 months post-operatively. Arteriography was performed when further operative treatment was considered</p>
Notes	<p>All data were related to the numbers of bypasses instead of numbers of participants (8 of 140 participants received 2 grafts)</p> <p>98 participants underwent operation for rest pain, 42 for claudication</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias)	High risk	Open trial

Clyne 1987 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete outcome data
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Unclear risk	All data were related to the numbers of bypasses instead of numbers of participants (8 of 140 participants received bilateral grafts)

D'Addato 1992
Study characteristics

Methods	<p>Study type:Multicentre, double-blind, randomised clinical trial</p> <p>Study aim:To compare the efficacy of indobufen (IND) and the combination of ASA/DIP in improving long-term patency of the femoropopliteal prosthetic bypass</p> <p>Country:Italy</p>
Participants	<p>Number randomised:Total n = 113 (ASA/DIP n = 57; IND n = 56)</p> <p>Age- mean years (SD):ASA/DIP 65.6 (8.4); IND 66.6 (8.4)</p> <p>Gender n (M/F):ASA/DIP 47/10; IND 49/7</p> <p>Inclusion criteria:Patients with vascular disease complaining of rest pain or trophic lesions or both; occlusion of the femoropoplitea-tibial tract; candidates for revascularising with PTFE bypass graft</p> <p>Exclusion criteria:Patients with severe obesity; severe or unstable diabetes; life expectancy < 12 months; hypertensive patients with mean arterial pressure > 115 mmHg not controllable by suitable therapy; patients with severe hepatic or renal insufficiency; chronic anaemia; haemorrhagic diathesis; present or previous peptic ulcer; need for treatment with drugs that could affect platelet aggregation or clotting or both</p> <p>Co-morbidity:Diabetes mellitus (ASA/DIP 15.8%; IND 14.3%), hypercholesterolaemia (ASA/DIP 14.0%; IND 7.2%), smoking (ASA/DIP 68.4%; IND 71.4%), hypertension (ASA/DIP 22.8%; IND 19.6%), critical ischaemia (ASA/DIP 75.4%; IND 66.1%)</p> <p>Severity of occlusive disease (determined by ABPI):not indicated</p> <p>Site of distal anastomosis:Above-knee anastomosis (ASA/DIP 29%; IND 35%), below-knee anastomosis (ASA/DIP 28%; IND 21%)</p> <p>Type of graft:PTFE</p>
Interventions	<p>Treatment:900 mg ASA combined with 225 mg DIP, started 2 days before surgery</p> <p>Control:400 mg IND daily, started 2 days before surgery</p> <p>7-day washout period during which no anticoagulants or inhibitors of prostaglandin synthesis were used</p>

D'Addato 1992 (Continued)

Duration:12 months

Outcomes	Graft patency was assessed by angiography 6 days and 12 months postoperatively, and clinically every 3 months by physical examination, Doppler ultrasound measurements on the graft, and by angiography if indicated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"...blindly assigned to treatment"; insufficient description of blinding methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for drop-outs, and final numbers for each treatment group are similar
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

Donaldson 1985
Study characteristics

Methods	<p>Study type:A randomised, double-blind clinical trial performed between 1979 and 1981</p> <p>Study aim:To evaluate the effect of a combination of ASA and DIP on the early patency of femoro-popliteal Dacron bypass grafts implanted to relieve disabling claudication</p> <p>Country:UK</p>
Participants	<p>Number randomised:Total n = 65 (73 grafts) (ASA/DIP n = 33 (35 grafts); placebo n = 32 (38 grafts))</p> <p>Age- mean years: ASA/DIP = 59.3; placebo 60.0</p> <p>Gender n (M/F):ASA/DIP 27/6; placebo 25/7</p> <p>Inclusion criteria:Patients with disabling intermittent claudication suitable for femoro-popliteal bypass</p> <p>Exclusion criteria:a history of dyspepsia, peptic ulceration or hypersensitivity to ASA or DIP</p>

Donaldson 1985 (Continued)

Co-morbidity:diabetic (ASA/DIP n = 3; placebo n = 2), mean MWD- m (ASA/DIP 61.2; placebo 54.7)

Severity of occlusive disease (determined by ABPI):ASA/DIP 0.63; placebo 0.61

Site of distal anastomosis:below the knee (ASA/DIP 11; placebo 10)

Type of graft:Dacron bypass grafts

Interventions	<p>Treatment:3 times daily 330 mg ASA and 75 mg DIP</p> <p>Control:placebo</p> <p>Duration:Therapy was started preoperatively. 1 trial capsule given on the evening prior to surgery then resumed as soon as oral intake was permitted postoperatively) and continued for 12 months postoperatively</p> <p>All participants received heparin intraoperatively</p>
Outcomes	<p>Assessment of graft patency was performed by a standardised treadmill test, ankle/brachial systolic pressure index (ABPI), Doppler ultrasound and by palpation at 3, 6, 9, and 12 months postoperatively. Plasma drug levels were measured for ASA and DIP. Graft patency by clinical examination, ABPI, Doppler on graft, maximum walking distance, platelet adhesion/aggregation, bleeding time</p>
Notes	<p>2 bilateral participants in the ASA/DIP group and 6 in the placebo group</p> <p>All concomitant antithrombotic therapy had been stopped at least 3 weeks prior to surgery</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patient sample was divided into two groups depending on whether the distal anastomosis was to be above or below the knee. Each group was then randomised to receive either placebo or active capsules...". Insufficient information to determine adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"... randomised to receive either placebo or active capsules..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although drop-out reasons given, withdrawals were much greater in the intervention treatment group
Selective reporting (reporting bias)	Low risk	All outcomes reported on; it should be noted that adverse events were only reported for those that withdrew from treatment and not the whole randomised group, but as adverse events were not a specified outcome, this would not increase reporting bias
Other bias	Unclear risk	All data were related to the numbers of bypasses instead of numbers of participants (2 participants received bilateral grafts)

Edmondson 1994
Study characteristics

Methods	<p>Study type:An open, multicentre, randomised controlled trial</p> <p>Study aim:To determine if low molecular weight heparin (LMWH) would be more effective than ASA and DIP in maintaining graft patency in patients undergoing femoropopliteal bypass grafting</p> <p>Country:UK</p>	
Participants	<p>Number randomised:Total n = 200 (ASA/DIP n = 106; LMWH n = 94)</p> <p>Age- mean years (SD):ASA/DIP 68.4 (9.6); LMWH 66.8 (9.2)</p> <p>Gender n (M/F):ASA/DIP 74/32; LMWH 61/33</p> <p>Inclusion criteria:> 40 years old; angiographically-proven arterial occlusive disease; scheduled to undergo femoropopliteal bypass surgery</p> <p>Exclusion criteria:currently taking oral anticoagulants; there was a known allergy to heparin, ASA or DIP; limb for operation had undergone previous femoropopliteal bypass grafting; the indication for bypass surgery was aneurysmal disease or trauma; there was a serious concomitant disease</p> <p>Co-morbidity:smoking (ASA/DIP 31.1%; LMWH 28.7%), diabetes (ASA/DIP 19.8%; LMWH 14.9%), hyperlipidaemia (ASA/DIP 6.6%; LMWH 5.3%)</p> <p>Severity of occlusive disease (determined by ABPI):not indicated</p> <p>Site of distal anastomosis:above-knee (ASA/DIP 69.8%; LMWH 68.1%), below-knee (ASA/DIP 27.4%; LMWH 27.7%), tibial vessels (ASA/DIP 2.8%; LMWH 4.3%)</p> <p>Type of graft:autologous vein (ASA/DIP 24.5%; LMWH 28.7%), prosthetic (PTFE and Dacron (ASA/DIP 46.2%; LMWH 30.9%))</p>	
Interventions	<p>Treatment:ASA/DIP- 300 mg ASA and 100 mg DIP, both 3 times per day</p> <p>Control:2500 IU LMWH (Fragmin) subcutaneously once daily</p> <p>Duration: 3 months</p> <p>All the participants received LMWH subcutaneously 2 hours preoperatively, continuing for 1 week post-operatively, and at 1 week participants were randomised to continue LMWH or receive ASA/DIP</p>	
Outcomes	<p>On the 7th postoperative day participants were assessed for primary graft occlusion, wound infection, thrombectomy, bleeding, and death. Total follow-up was 1 year with visits at 1, 3, 6, and 12 months. Graft patency was evaluated clinically and by ABPI, and, if indicated, supplemented by arteriography or duplex sonography</p>	
Notes	<p>Indication for surgery was disabling claudication in 107 participants and salvage in 93 participants</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central telephone randomisation using computer-generated random numbers was used 1 week after operation.
Allocation concealment (selection bias)	Low risk	Used central telephone service

Edmondson 1994 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; analysis on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

Goldman 1984
Study characteristics

Methods	<p>Study type: Double-blind, randomised controlled trial</p> <p>Study aim: To assess the effect of ASA and DIP on the patency of prosthetic femoropopliteal bypass grafts</p> <p>Country: UK</p>
Participants	<p>Number randomised: Total n = 53 (ASA/DIP n = 22; placebo n = 31)</p> <p>Age- mean years: ASA/DIP 64.3; placebo 63.2</p> <p>Gender n (M/F): ASA/DIP 16/6; placebo 27/4</p> <p>Inclusion criteria: patients awaiting femoropopliteal bypass for occlusive disease</p> <p>Exclusion criteria: patients already receiving platelet inhibitory drugs; with a significant history of dyspepsia</p> <p>Co-morbidity: Claudicants (ASA/DIP 3; placebo 8), rest pain/gangrene (ASA/DIP 19; placebo 23), smokers (ASA/DIP 19; placebo 24), diabetes mellitus (ASA/DIP 2; placebo 3) hypertension (ASA/DIP 4; placebo 6), ischaemic heart disease (ASA/DIP 7; placebo 11)</p> <p>Severity of occlusive disease (determined by ABPI): not indicated</p> <p>Site of distal anastomosis: above-knee anastomoses (ASA/DIP 10; placebo 19), below-knee anastomoses (ASA/DIP 12; placebo 12)</p> <p>Type of graft: prosthetic (Dacron or PTFE)</p>
Interventions	<p>Treatment: ASA/DIP- combination of 300 mg ASA and 75 mg DIP 3 times daily</p> <p>Control: placebo- identical to treatment drug</p> <p>Duration: started 48 h before surgery and continued for 12 months</p>
Outcomes	Graft patency was assessed in monthly follow-up visits up to 1 year based on reported symptoms, palpation, directional Doppler, and isotope angiography

Goldman 1984 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"... double blind to receive identical capsules containing either placebo or a combination of aspirin 300mg plus dipyridamole 75mg..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for drop-outs and all participants accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Unclear risk	Groups did not appear comparable at baseline (differences in gender and above-/below-knee proportions)

Green 1982
Study characteristics

Methods	<p>Study type: Double-blind, randomised controlled trial</p> <p>Study aim: To assess the effect of aspirin alone or in combination with DIP on the patency rates of expanded PTFE grafts placed in the infrainguinal position</p> <p>Country: US</p>
Participants	<p>Number randomised: Total n = 49 (ASA alone n = 16; ASA/DIP n = 16; placebo n = 17)</p> <p>Age: not indicated</p> <p>Gender: not indicated</p> <p>Inclusion criteria: All private patients of study authors RMG and JAD seen in the Peripheral Vascular Surgical Service of the University of Rochester Medical Center, Strong Memorial Hospital, beginning May 1979. 2 required an infrainguinal bypass</p> <p>Exclusion criteria: Patients with known sensitivity to ASA or DIP; platelet or clotting abnormalities; gastrointestinal disturbances with a tendency to bleeding; require ASA for other medical conditions; infrainguinal autogenous saphenous vein bypass available; concomitant inflow disease</p> <p>Co-morbidity: smoking (ASA 56%; ASA/DIP 56%; placebo 53%), diabetes (ASA 37%; ASA/DIP 50%; placebo 48%), previous femoropopliteal bypass (ASA 6%; ASA/DIP 19%; placebo 41%),</p>

Green 1982 (Continued)

Severity of occlusive disease: procedure performed for limb salvage (ASA 75%; ASA/DIP 87%; placebo 88%)

Site of distal anastomosis: below-knee (ASA 38%; ASA/DIP 56%; placebo 47%)

Type of graft: prosthetic PTFE grafts

Interventions	<p>Treatment:</p> <p>1) ASA alone- 325 mg ASA plus a red placebo tablet 3 times daily</p> <p>2) ASA/DIP- 325 mg ASA and 75 mg DIP 3 times daily</p> <p>Control: Placebo- received red and white placebo tablets 3 times daily</p> <p>Duration: Started preoperatively: DIP or matching placebo started 48 hours prior to operation and ASA or matching placebo started 24 hours prior to surgery, and then for 1 year</p> <p>Patients were randomised to either treatment with 325 mg ASA once daily plus a placebo 3 times daily or 325 mg ASA once daily combined with 75 mg DIP 3 times per day for 1 year. Medication was started 48 hours preoperatively and continued for 1 year</p>
Outcomes	Primary graft occlusion, withdrawal, and death were considered as treatment failures. Graft patency was assessed by clinical examination and ABPI change of 0.4 to 1.0. Follow-up visits were every 3 months, or when problems arose, until death or withdrawal or for at least 1 year
Notes	PTFE grafts when prosthetic graft was obligatory; all patients with available autologous saphenous veins for grafting were excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although authors state "key to the randomization was kept in a sealed envelope and was opened only on emergency basis by an independent observer", the sequence generation was not adequately described
Allocation concealment (selection bias)	Low risk	"The key to the randomization was kept in a sealed envelope and was opened only on emergency basis by an independent observer"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo group received red and white placebo tablets three times daily, the ASA group received 325 mg ASA and a red placebo tablet three times daily and the ASA/DIP group received 325 mg ASA and 75 mg DIP three times daily"; Use of coded bottles
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for drop-outs and all participants accounted for
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly reported
Other bias	Low risk	No indication of other bias

Gruss 1991
Study characteristics

Methods	<p>Study type:Prospective, randomised controlled trial</p> <p>Study aim:Can a permanent intra-arterial PGE1 therapy reduce the number of postoperative immediate and early closures in femoro-crural great saphenous vein in situ bypasses</p> <p>Country:Germany</p>
Participants	<p>Number randomised:Total n = 100 (ASA n = 50; PGE1 n = 50)</p> <p>Age:not indicated</p> <p>Gender (M/F):not indicated</p> <p>Inclusion criteria: patients with femorotibial greater saphenous vein in situ bypasses</p> <p>Exclusion criteria:not indicated</p> <p>Co-morbidity:not indicated</p> <p>Severity of occlusive disease (determined by ABPI):not indicated</p> <p>Site of distal anastomosis:not indicated</p> <p>Type of graft:autologous saphenous vein grafts</p>
Interventions	<p>Treatment:ASA, 0.5 g 3 times daily and 15,000 IU heparin continuously</p> <p>Control:Intra-arterial PGE1, 0.2 ng per kg body weight/min and 15,000 IU heparin continuously</p> <p>Duration:24 hours for the first 10 postoperative days</p>
Outcomes	Early graft occlusion was the primary outcome of this study
Notes	Study information came from a single abstract, with the majority of information in German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No indication of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is no discussion of drop-outs or withdrawals

Gruss 1991 (Continued)

Selective reporting (reporting bias)	Unclear risk	Not enough information in text to determine
Other bias	Low risk	No indication of other bias

Kohler 1984
Study characteristics

Methods	<p>Study type: Double-blind, randomised controlled trial performed from 1978 to 1982</p> <p>Study aim: To determine whether ASA and DIP administered postoperatively to patients with PTFE or autologous vein infrainguinal bypasses would improve graft patency during the first 24 months after operation</p> <p>Country: US</p>	
Participants	<p>Number randomised: Total n = 100 (grafts = 102) (ASA/DIP n = 44 (grafts = 51); placebo n = 44 (grafts = 51) 12 patients were not included in the study post-randomisation</p> <p>Age- mean years (SD): ASA/DIP 66 (12); placebo 66 (10)</p> <p>Gender n (M/F): ASA/DIP 34/10; placebo 34/10</p> <p>Inclusion criteria: Private patients at the Beth Israel or Brigham and Women's Hospital who were scheduled for infrainguinal bypass procedures with either autologous saphenous vein or expanded PTFE grafts</p> <p>Exclusion criteria: Concomitant inflow disease; hypersensitivity to ASA or DIP; gastrointestinal bleeding; recently taken platelet-activating drugs or anticoagulants for any reason; or if geographical inaccessibility prevented follow-up</p> <p>Co-morbidity: Diabetic (ASA/DIP n = 15; placebo n = 15), history of smoking (ASA/DIP n = 32; placebo n = 33), claudication indication for operation (ASA/DIP n = 16; placebo n = 19), threatened limb indication for operation (ASA/DIP n = 35; placebo n = 32)</p> <p>Severity of occlusive disease (determined by ABPI): not indicated</p> <p>Site of distal anastomosis: Tibial (ASA/DIP n = 8; placebo n = 10), proximal popliteal (ASA/DIP n = 21; placebo n = 22), distal popliteal (ASA/DIP n = 22; placebo n = 24)</p> <p>Type of graft: vein grafts (ASA/DIP n = 36; placebo n = 35), PTFE grafts (ASA/DIP n = 15; placebo n = 16)</p>	
Interventions	<p>Treatment: ASA/DIP- ASA 325 mg and DIP 75 mg 3 times daily, oral route</p> <p>Control: placebo- identical placebo tablets 3 time daily, oral route</p> <p>Duration: Starting on first day postoperatively, continuing 24 months</p>	
Outcomes	<p>Graft patency, the primary endpoint, was assessed at 3 and 6 weeks, further at 3, 6, 12, 18, 24 months postoperatively by evaluation of clinical symptoms, palpation of the graft, ABPI assessment, and if indicated by angiography</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Kohler 1984 (Continued)

Random sequence generation (selection bias)	Low risk	"...the research pharmacist randomized the patients to receive treatment or placebo according to a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Used identical placebo with same schedule as active treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Discussed drop-outs, but not consistently by which treatment group, drop-outs > 10%
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

Lucas 1984
Study characteristics

Methods	<p>Study type: Randomised controlled trial</p> <p>Study aim: To compare post-operative course over 6 months of 2 parallel cohorts of peripheral arteriopathy patients, 1 treated with pentoxifylline (PTX) and the other with conventional anti-aggregant medication, ASA and DIP, with regard to the incidence of rethrombosis</p> <p>Country: Argentina</p>
Participants	<p>Number randomised: Total n = 100 (ASA/DIP n = 49; PTX n = 48), three patients were excluded post-randomisation</p> <p>Age- mean years (SD): ASA/DIP 66.1 (9.9); PTX 68.5 (8.2)</p> <p>Gender: ASA/DIP 71.4% males; PTX 80% males</p> <p>Inclusion criteria: not indicated</p> <p>Exclusion criteria: not indicated</p> <p>Co-morbidity: Claudicants (ASA/DIP 28.6%; PTX 50%), ischaemia (ASA/DIP 71.4%; PTX 50%)</p> <p>Severity of occlusive disease (determined by ABPI): ASA/DIP 0.33 ± 0.33; PTX 0.46 ± 0.27</p> <p>Site of distal anastomosis: not indicated</p> <p>Type of graft: autologous vein (ASA/DIP 12; PTX 12), synthetic prosthetic- Dacron and Foretex (ASA/DIP 34; PTX 30)</p>
Interventions	<p>Treatment: ASA/DIP- 1050 mg/day ASA (divided into 3 doses) plus 150 mg/day DIP</p> <p>Control: PTX- 1200 mg/day (divided into 3 doses of 400 mg)</p>

Lucas 1984 (Continued)

Duration:6 months

Outcomes	Graft occlusion within 6 months was the primary endpoint, evaluated by clinical examination, ABPI, treadmill assessment of walking distance, and angiography. Follow-up controls were at 1, 3, 4, and 6 months
Notes	The study included patients with aortoiliac or femoropopliteal bypass or both; for the purposes of this review, only participants receiving femoropopliteal bypass were included and analysed; 14 participants were included in our analysis randomised to ASA/DIP and 19 to PTX

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned to one of the treatments using a random number table"
Allocation concealment (selection bias)	Low risk	"Once patients had been assigned, the individual envelope containing the treatment to be followed in each case was opened"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No indication of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis is performed with all randomised participants
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

McCollum 1991
Study characteristics

Methods	<p>Study type:Multicentre, double-blind, randomised controlled trial, performed between 1984 and 1989</p> <p>Study aim:To investigate whether ASA/DIP therapy improved graft patency in autologous saphenous vein femoropopliteal bypasses</p> <p>Country:UK</p>
Participants	<p>Number randomised:Total n = 549 (ASA/DIP n = 286; placebo n = 263)</p> <p>Age- mean years (SEM):ASA/DIP 66.8 (0.5); placebo 66.6 (0.6)</p> <p>Gender:ASA/DIP 75.5% men; placebo 74.9% men</p> <p>Inclusion criteria:All patients undergoing femoropopliteal bypass; informed consent given</p>

McCollum 1991 (Continued)

Exclusion criteria:Contraindication to ASA or DIP; patient taking drugs with platelet-inhibitory or anti-coagulant effects that could not be stopped; adequate follow-up could not be achieved

Co-morbidity:smoking (current) (ASA/DIP 42.2%; placebo 40.5%), hypertension (ASA/DIP 36.0%; placebo 35.0%), diabetes (ASA/DIP 18.2%; placebo 18.3%), IHD (ASA/DIP 26.2%; placebo 22.4%), claudication only (ASA/DIP 40.6%; placebo 39.6%), rest pain/gangrene (ASA/DIP 59.4%; placebo 60.4%)

Severity of occlusive disease (determined by ABPI):not indicated

Site of distal anastomosis:Above-knee (ASA/DIP 36%; placebo 46%)

Type of graft:autologous saphenous vein

Interventions	<p>Treatment:ASA/DIP- 300 mg ASA plus 150 mg DIP, twice daily orally</p> <p>Control: Identical placebo, twice daily orally</p> <p>Duration:Starting 48 h before surgery, taken indefinitely (mean follow-up was 35 months)</p>
Outcomes	Primary endpoints were graft occlusion, MI and stroke. Patency assessment was performed by pulse palpation, Doppler signal or duplex sonography, DSA, isotope angiography at 3-monthly intervals of follow-ups during the first year, and 6-monthly for 5 years
Notes	<p>Participants that required a prosthetic implant were given ASA/DIP and randomised to HUV or PTFE grafts; results of these participants are not currently reported</p> <p>Also known as the Femoropopliteal Bypass Trial</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was in batches of 10 to ensure that each hospital recruited similar numbers of patients on ASA + DPM or placebo"; Insufficient description of sequence generation
Allocation concealment (selection bias)	Low risk	Allocation centrally controlled by pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Used identical placebo with same schedule as active treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for drop-outs and all participants accounted for. Analysis on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Unclear risk	Power calculation reported a study population of 800 participants to detect a 10% reduction in occlusion rate, but only 549 patients were randomised; groups not comparable at baseline (proportions with above-knee grafts, which is a prognostic factor that can influence the outcomes)

Noppeney 1988
Study characteristics

Methods	<p>Study type: Randomised controlled trial</p> <p>Study aim: To evaluate the antithrombotic efficacy of naftidrofuryl in comparison to ASA</p> <p>Country: Germany</p>	
Participants	<p>Number randomised: Total n = 99 (ASA n = 49; naftidrofuryl n = 50)</p> <p>Age- years: 0 - 39 (ASA 2%; naftidrofuryl 0%), 40 - 49 (ASA 2%; naftidrofuryl 0%), 50 - 59 (ASA 27%; naftidrofuryl 12%), 60 - 69 (ASA 33%; naftidrofuryl 38%), 70 - 79 (ASA 33%; naftidrofuryl 48%), 80 - 89 (ASA 4%; naftidrofuryl 2%)</p> <p>Gender (M/F): not indicated</p> <p>Inclusion criteria: not indicated</p> <p>Exclusion criteria: not indicated</p> <p>Co-morbidity: Hypertension (ASA/DIP n = 25; naftidrofuryl n = 23), hyperlipidaemia (ASA/DIP n = 36; naftidrofuryl n = 34), hyperuricaemia (ASA/DIP n = 14; naftidrofuryl n = 12), diabetes mellitus (ASA/DIP n = 32; naftidrofuryl n = 28), obesity (ASA/DIP n = 10; naftidrofuryl n = 11), smoker (ASA/DIP n = 34; naftidrofuryl n = 38)</p> <p>Severity of occlusive disease (determined by ABPI): not indicated</p> <p>Site of distal anastomosis: not indicated</p> <p>Type of graft: PTFE grafts</p>	
Interventions	<p>Treatment: ASA 1500mg daily orally</p> <p>Control: naftidrofuryl 600 mg daily orally</p> <p>Duration: commenced on day 1 postoperatively for 12 months</p>	
Outcomes	<p>Graft occlusion within 12 months was the primary endpoint, also reported side effects and treatment withdrawal</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No indication of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessors not described

Noppeney 1988 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; analysis on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	No indication of other bias

Raithel 1987
Study characteristics

Methods	<p>Study type:Open, randomised controlled trial</p> <p>Study aim:To examine whether a protective effect associated with a low risk of side effects could be achieved with pentoxifylline (PTX), compared with ASA</p> <p>Country:Germany</p>	
Participants	<p>Number randomised:Total n = 118 (ASA n = 59; PTX n = 59)</p> <p>Age- mean years (range):Total study population 67.2 (42 to 87)</p> <p>Gender n (M/F):Total study population 88/30</p> <p>Inclusion criteria:Patients who had undergone a prosthetic bypass operation in the femoropopliteal region</p> <p>Exclusion criteria:not indicated</p> <p>Co-morbidity:Angina pectoris (ASA 15; PTX 21), myocardial infarction (ASA 39; PTX 42), coronary insufficiency (ASA 11; PTX 14), arrhythmias (ASA 5; PTX 8), hypertension (ASA 31; PTX 22), hyperlipidaemia (ASA 38; PTX 41), hyperuraemia (ASA 20; PTX 17), obesity (ASA 3; PTX 6), diabetes mellitus (ASA 45; PTX 32), smoking (ASA 42; PTX 46), operated on for critical ischemias (ASA 94.9 %; PTX 96.6%)</p> <p>Severity of occlusive disease (determined by ABPI):not indicated</p> <p>Site of distal anastomosis:not indicated</p> <p>Type of graft:prosthetic grafts</p>	
Interventions	<p>Treatment:ASA- 500 mg 3 times daily</p> <p>Control:PTX - 400 mg daily</p> <p>Duration:Starting 2 days before operation and continuing until 12 months postoperatively.</p>	
Outcomes	<p>Graft patency was assessed by clinical examination, pulses, Doppler pressure, and arteriography when indicated, before and 3, 6, 9, 12 months postoperatively.</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Raithel 1987 (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as an open study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors state: "One hundred eighteen patients... were available for the final assessment"; unclear how many were initially randomised, and whether the data are incomplete
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Unclear risk	Groups do not appear to be comparable at baseline with respect to risk factors

Schneider 1979
Study characteristics

Methods	<p>Study type:Single-centre, double-blind, randomised controlled trial, performed between 1974 and 1978</p> <p>Study aim:To evaluate the prophylactic value of long-term oral anticoagulation and inhibition of platelet aggregation</p> <p>Country:Switzerland</p>
Participants	<p>Number randomised:Total n = 213 randomised to femoropopliteal bypass or thromboendarterectomy (TEA); n = 91 randomised to femoropopliteal bypass (ASA or ASA/DIP n = 61; coumarin n = 30)</p> <p>Age- mean years (SD):All participants receiving femoropopliteal bypass 63.9 (8.8)</p> <p>Gender (M:F ratio):All participants receiving femoropopliteal bypass 3.3:1</p> <p>Inclusion criteria:Patients with atherosclerosis obliterans undergoing femoropopliteal reconstruction</p> <p>Exclusion criteria:not indicated</p> <p>Co-morbidity:not indicated</p> <p>Severity of occlusive disease (determined by ABPI):not indicated</p> <p>Site of distal anastomosis:not indicated</p> <p>Type of graft:not indicated</p>
Interventions	<p>Treatment:ASA or ASA/DIP- 1 g/day ASA or 1 g ASA and 225 mg DIP per day</p> <p>Control:coumarin - (Quick, aim 25 - 30%)</p>

Schneider 1979 (Continued)

Duration: 2 years

All participants were treated with therapeutic doses of heparin and coumarins in the first 1 to 2 postoperative weeks and were then randomly allocated to either coumarins (Quick, aim 25 - 30%) or aspirin, or aspirin/dipyridamole

Outcomes	Graft patency was assessed angiographically before dismissal, further by evaluation of segmental oscillography and a fall of the systolic pressure of at least 20 mm Hg; Signs of occlusions were measured angiographically; Follow-up period was 2 years with visits every 3 months during the first year and every 6 months in the second year; Drug assessment was performed by measurement of prothrombin time for coumarins and ASA levels in urine; Death and bleeding complications were recorded; Side effects like gastrointestinal bleeding or ulceration or pain or other bleeding complications could not be disclosed, as results were only presented for all participants, including those undergoing TEA
Notes	This study randomised patients to receive either femoropopliteal bypass or TEA; only patients receiving femoropopliteal bypass are considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors mention double-blinding but the methods are unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough descriptive information
Selective reporting (reporting bias)	Unclear risk	Not enough information in text to determine
Other bias	Low risk	No indication of other bias

ABPI: ankle brachial pressure index
 ASA: aspirin
 CAD: coronary artery disease
 CRVD: cerebrovascular disease
 DIP: dipyridamole
 DPM: dipyridamole (equivalent to DIP)
 DSA: digital subtraction angiography
 h: hour
 HUV: human umbilical vein
 IND: indobufen
 IU: international units
 iv: intravenous
 kg: kilograms
 LMWH: low molecular weight heparin

m: metre
 mg: milligram
 MI: myocardial infarction
 min: minute
 MWD: maximum walking distance
 ng: nanograms
 PAD: peripheral arterial disease
 PGE1: prostaglandin E1
 PTFE: polytetrafluoroethylene
 PTX: pentoxifylline
 SD: standard deviation
 TEA: thromboendarterectomy
 TIC: ticlopidine

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Böhmig 1995	Not a controlled trial. 20-year follow-up study of infrainguinal venous bypass grafts. All participants received 100 IU/kg heparin iv intraoperatively, followed by 5000 IU 4 times daily sc in the first post-operative days, then dicoumarol lifelong. No control group
Burdess 2010	Heterogeneous study population: bypass, femoral endarterectomy and lower limb amputation without stratification
DeWeese 1971	Non-randomised, non-controlled study on femoropopliteal venous bypass patency
Ehersmann 1977	Heterogeneous cohort of patients. Results not separated for infrainguinal bypass surgery
EUCTR2007 2008	Intervention is anticoagulant (fondaparinux) versus anticoagulant (enoxaparin) with no antiplatelet treatment
Gorter 2001	Comparison of 2 studies, one of which is the BOA 2000 trial
Harjola 1981	No clear distinction between bypass operations and other reconstructive therapies. No definition of 'major' and 'minor' injury. No details on claudicants, ischaemic participants, on distal insertion of the grafts, other risk factors like diabetes No description of randomisation procedure
Jivegard 2005	Intervention is anticoagulant (LMWH) versus placebo. All participants received 75 mg of ASA daily
Johnson 2002	Intervention is anticoagulant (warfarin) + ASA versus ASA alone i.e. both groups received ASA
Johnson 2004	Intervention is anticoagulant (warfarin) + ASA versus ASA alone i.e. both groups received ASA
Kibbe 2002	Intervention is anticoagulant (warfarin) + ASA versus ASA alone i.e. both groups received ASA
Lassila 1991	144 participants, randomised controlled trial. Mainly endarterectomy involved, ASA vs nothing. Results not presented separately
Monaco 2012	Intervention is anticoagulant + clopidogrel versus clopidogrel + ASA. Only 1 treatment group received the anticoagulant, so there could be a drug interaction between the clopidogrel and anticoagulant that would make it impossible to directly compare with ASA
Nevelsteen 1991	No relevant outcomes
Raithel 1987b	99 participants assigned to treatment by ASA or naftidrofuryl in a randomised trial. Time point and method of randomisation are unclear. Data are only presented in an abstract mentioning cumulative patency rate 12 months postoperatively, which was 80% in both groups without any significant

Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery (Review)

Study	Reason for exclusion
	differences. The authors state that side effects occurred in 23 participants of the ASA group versus 3 participants in the naftidrofuryl group, without describing the type of side effect. Too little information is available for inclusion in the present meta-analysis
Reichle 1979	Retrospective non-controlled, non-randomised study
Rosenthal 1987	Retrospective study
Satiani 1985	Excluded because of pseudo-randomisation (odd ages receiving ASA)
Shionoya 1990	Intention-to-treat analysis is not possible as the results are only analysed for operated arterial segments and not for number of participants. In addition, bias has been introduced by exclusion of prosthetic grafts when final data were analysed
Smout 2004	All patients received aspirin

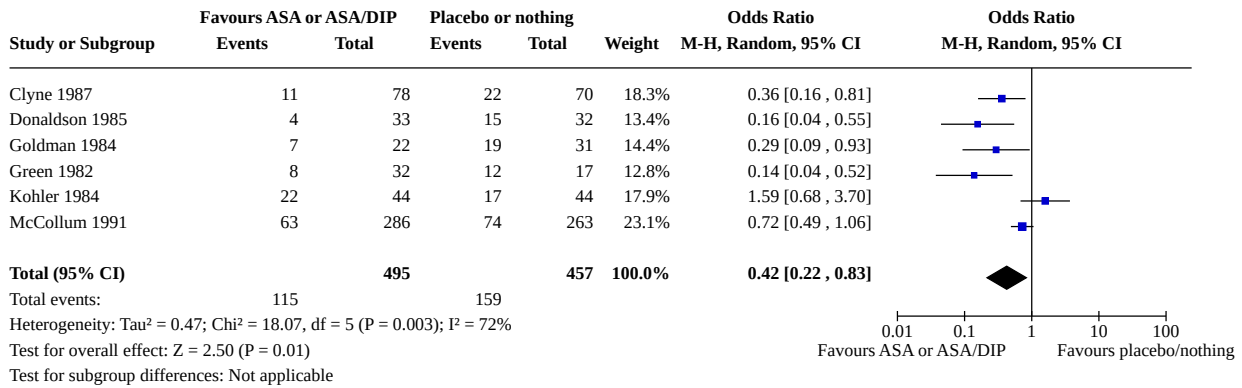
ASA: aspirin
 iv: intravenous
 LMWH: low molecular weight heparin
 sc: subcutaneous

DATA AND ANALYSES

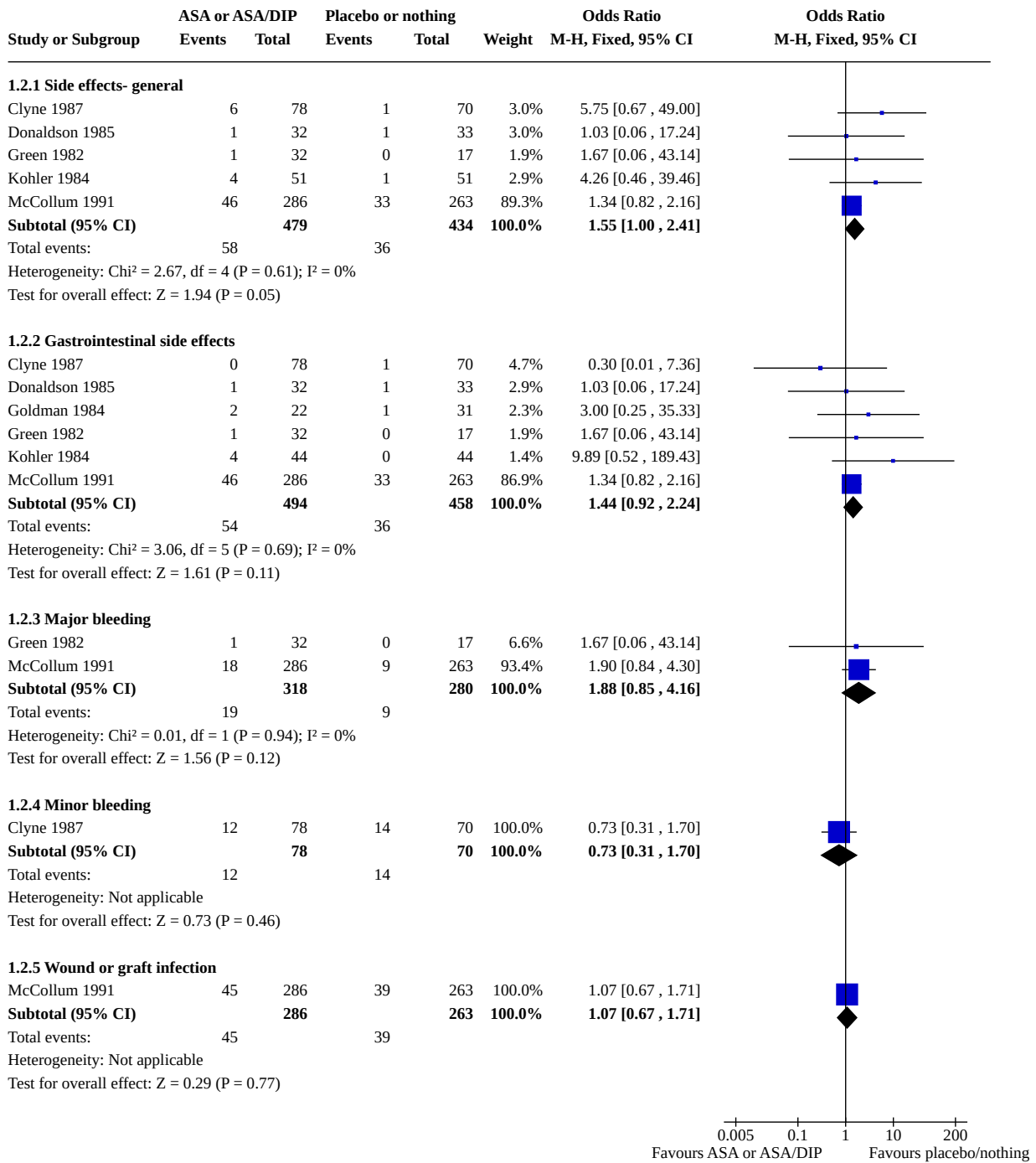
Comparison 1. ASA or ASA/DIP vs placebo or nothing, all grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Primary graft patency at 12 months	6	952	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.83]
1.2 Side effects and complications	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Side effects- general	5	913	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [1.00, 2.41]
1.2.2 Gastrointestinal side effects	6	952	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.92, 2.24]
1.2.3 Major bleeding	2	598	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.85, 4.16]
1.2.4 Minor bleeding	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.31, 1.70]
1.2.5 Wound or graft infection	1	549	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.67, 1.71]
1.3 Limb amputation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Cardiovascular events	4	811	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.43, 3.80]
1.5 Mortality	4	799	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.56, 1.26]

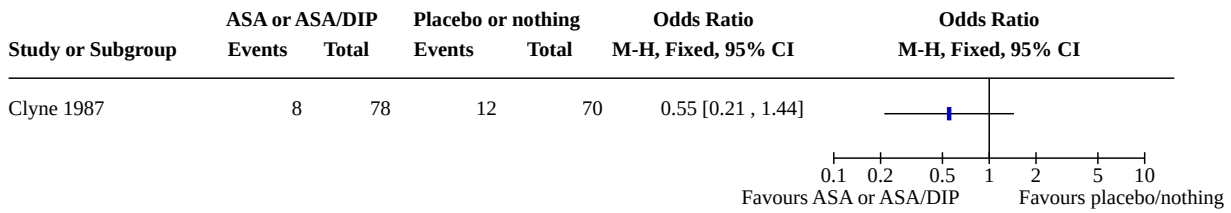
Analysis 1.1. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 1: Primary graft patency at 12 months



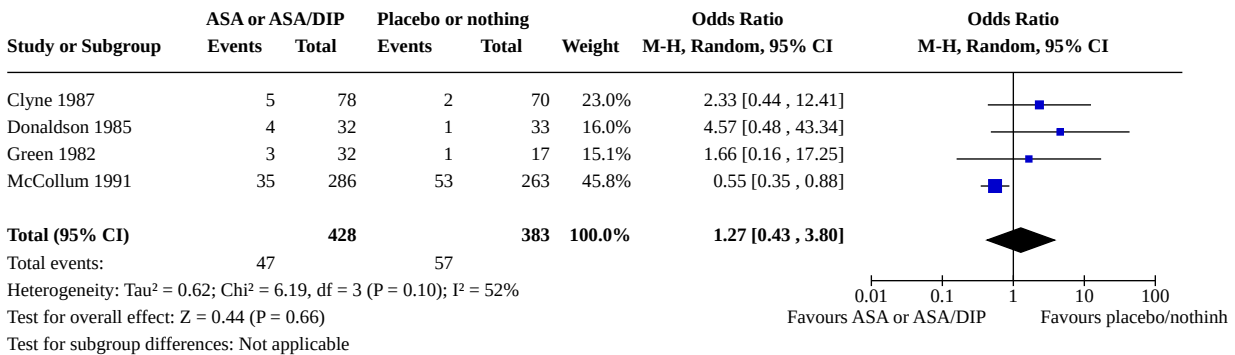
Analysis 1.2. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 2: Side effects and complications



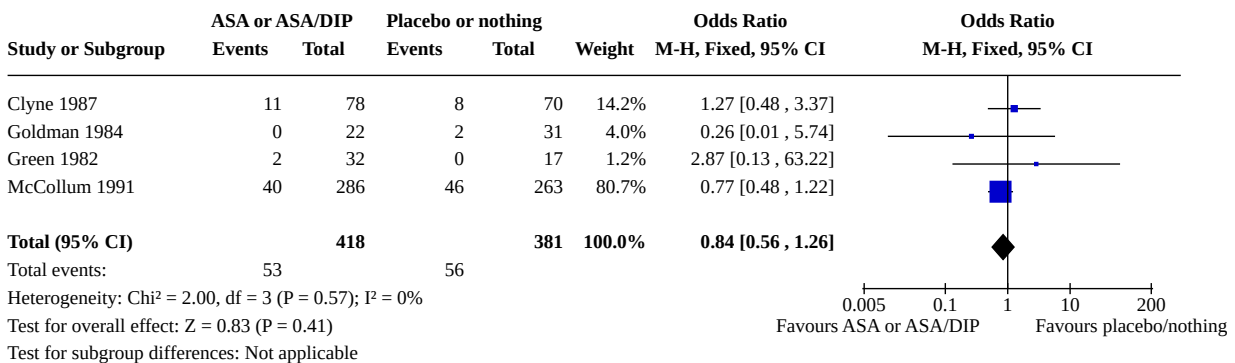
Analysis 1.3. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 3: Limb amputation



Analysis 1.4. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 4: Cardiovascular events



Analysis 1.5. Comparison 1: ASA or ASA/DIP vs placebo or nothing, all grafts, Outcome 5: Mortality

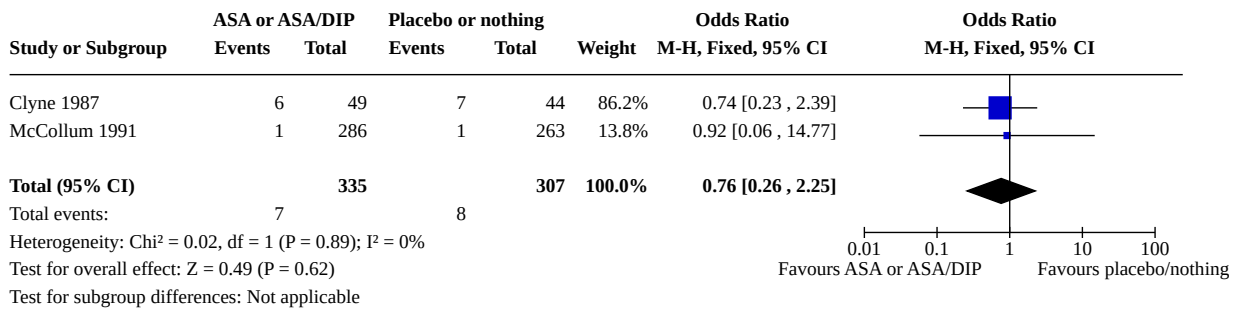


Comparison 2. ASA or ASA/DIP vs placebo or nothing, subgroups

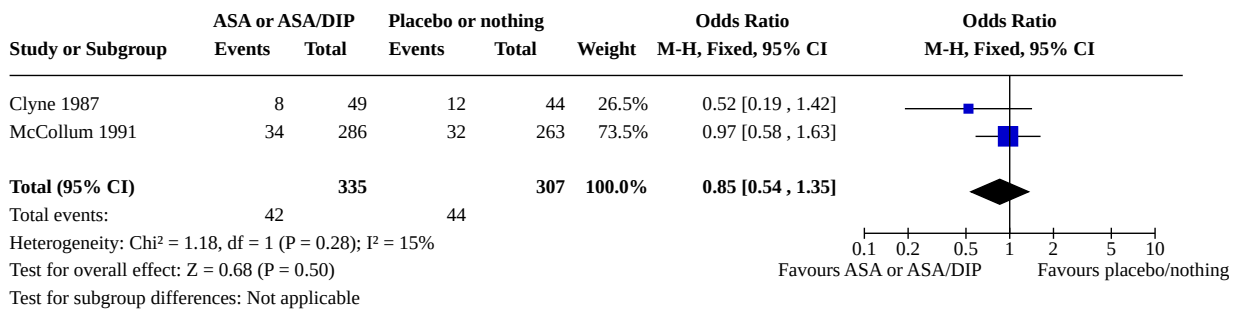
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Primary graft patency, venous grafts, 1 month	2	642	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.26, 2.25]
2.2 Primary graft patency, venous grafts, 3 months	2	642	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.54, 1.35]
2.3 Primary graft patency, venous grafts, 6 months	2	642	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Primary graft patency, venous grafts, 12 months	2	642	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.48, 0.99]
2.5 Primary graft patency, venous grafts, 24 months	2	620	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.32, 3.28]
2.6 Primary graft patency, prosthetic grafts, 1 month	3	157	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.04, 0.51]
2.7 Primary graft patency, prosthetic grafts, 3 months	4	222	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.14, 0.66]
2.8 Primary graft patency, prosthetic grafts, 6 months	4	222	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.11, 0.41]
2.9 Primary graft patency, prosthetic grafts, 9 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.10 Primary graft patency, prosthetic grafts, 12 months	4	222	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.10, 0.36]

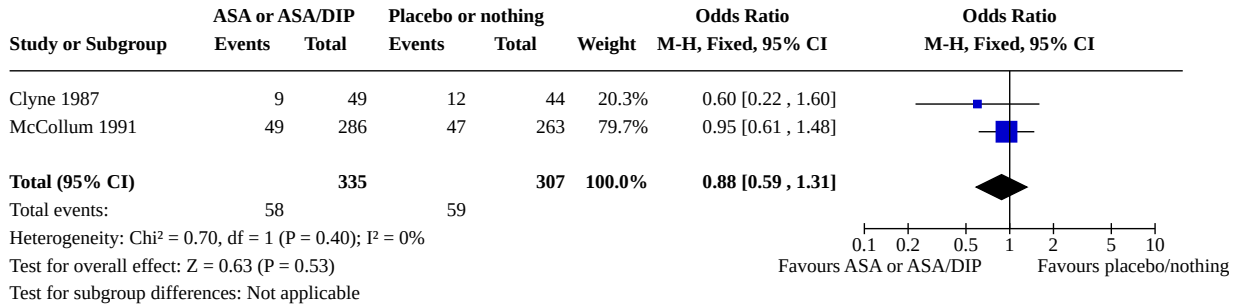
Analysis 2.1. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 1: Primary graft patency, venous grafts, 1 month



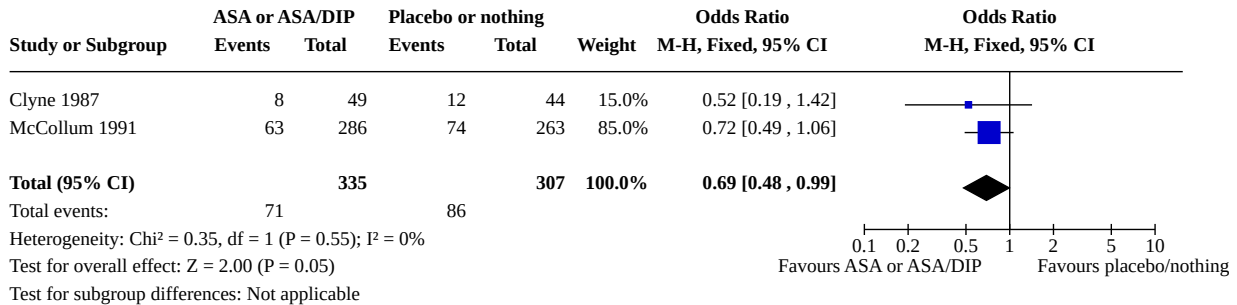
Analysis 2.2. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 2: Primary graft patency, venous grafts, 3 months



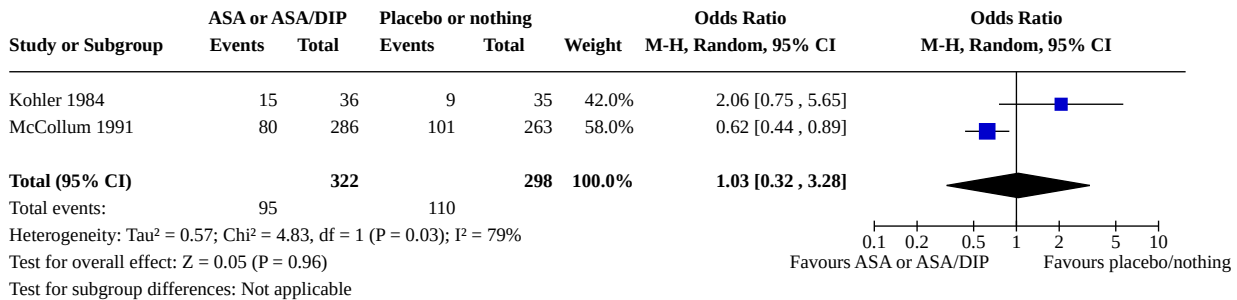
Analysis 2.3. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 3: Primary graft patency, venous grafts, 6 months



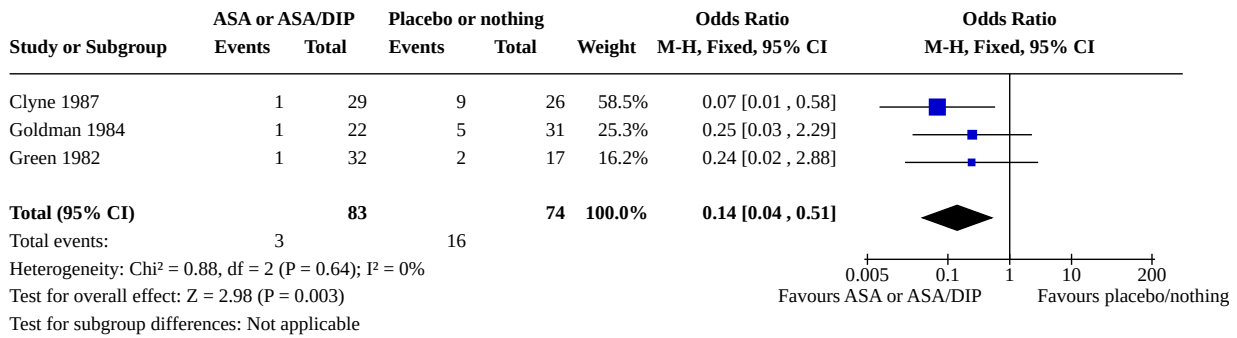
Analysis 2.4. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 4: Primary graft patency, venous grafts, 12 months



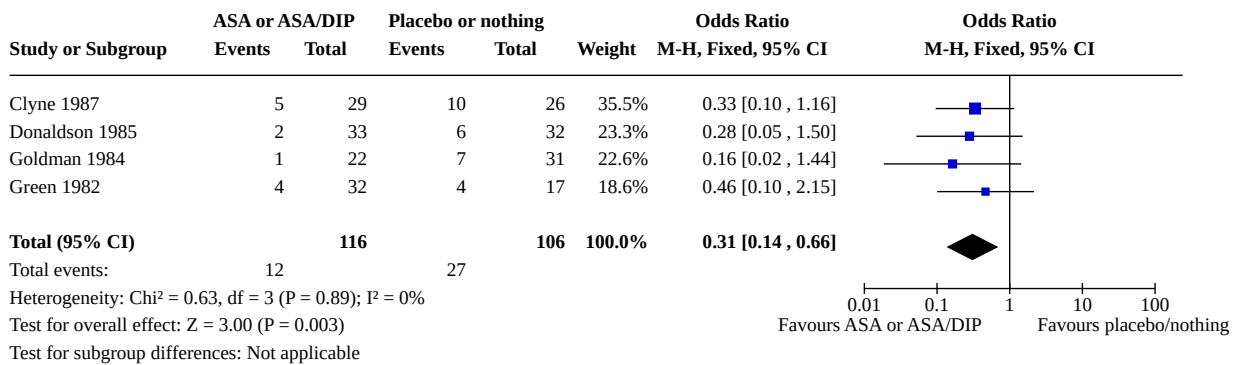
Analysis 2.5. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 5: Primary graft patency, venous grafts, 24 months



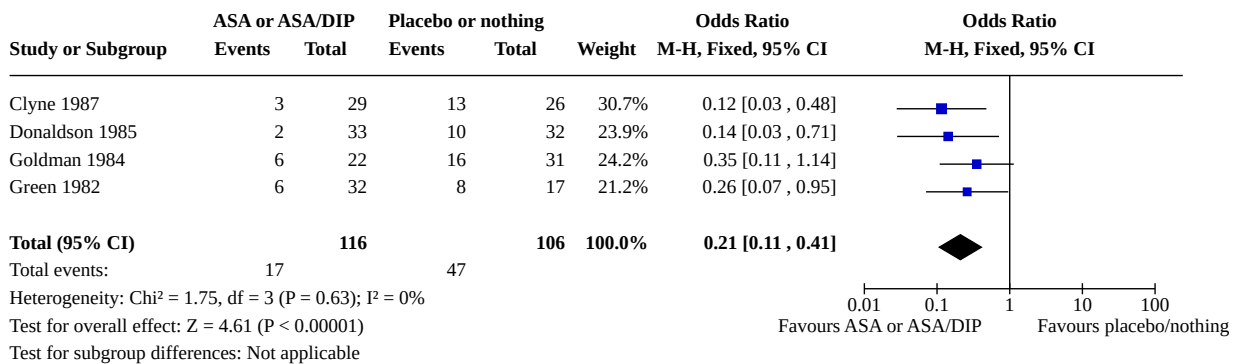
Analysis 2.6. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 6: Primary graft patency, prosthetic grafts, 1 month



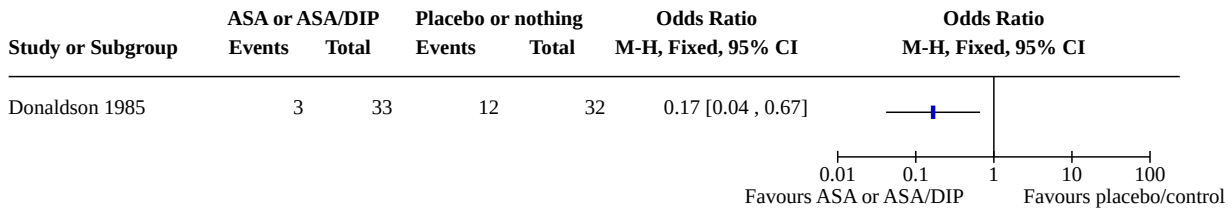
Analysis 2.7. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 7: Primary graft patency, prosthetic grafts, 3 months



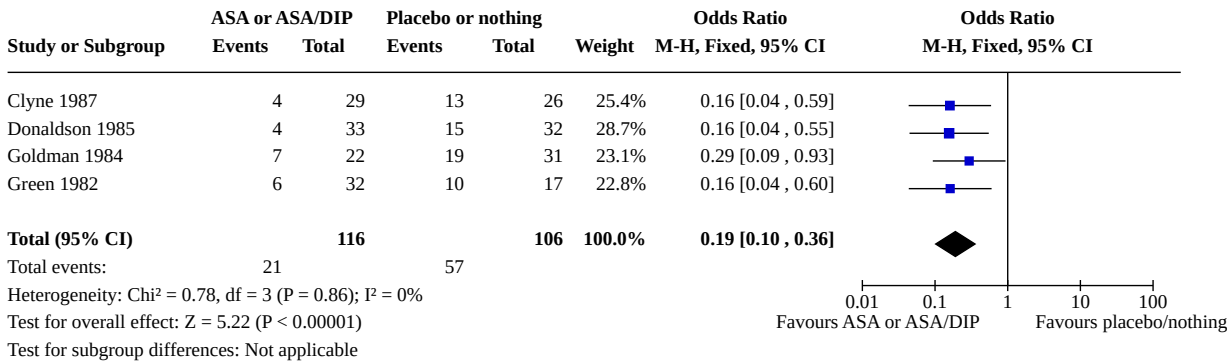
Analysis 2.8. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 8: Primary graft patency, prosthetic grafts, 6 months



Analysis 2.9. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 9: Primary graft patency, prosthetic grafts, 9 months



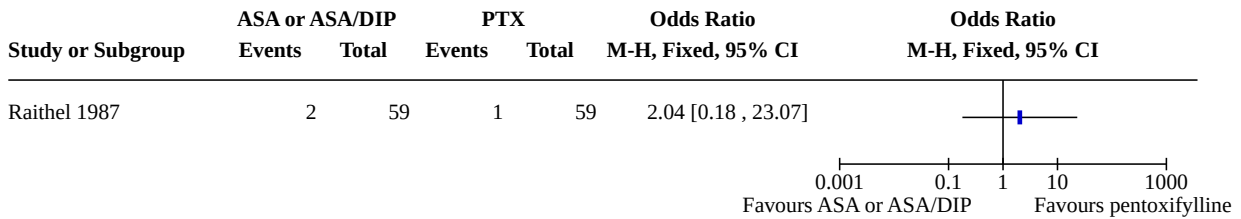
Analysis 2.10. Comparison 2: ASA or ASA/DIP vs placebo or nothing, subgroups, Outcome 10: Primary graft patency, prosthetic grafts, 12 months



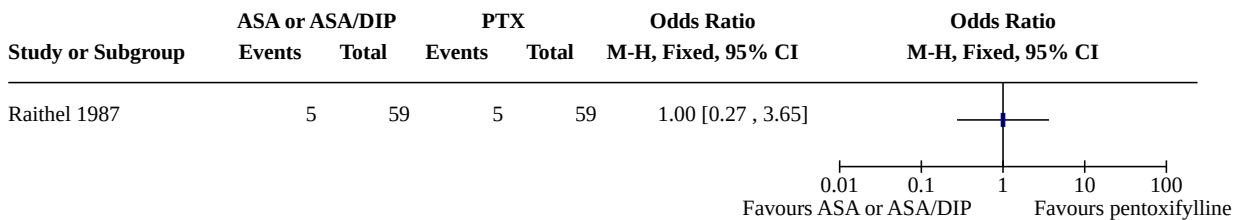
Comparison 3. ASA or ASA/DIP versus pentoxifylline (PTX), all grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Primary graft patency, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2 Primary graft patency, 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.3 Primary graft patency, 6 months	2	151	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.56, 3.11]
3.4 Primary graft patency, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5.1 Gastric intolerance	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5.2 Gastric haemorrhage	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5.3 Vertigo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6 Limb amputation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

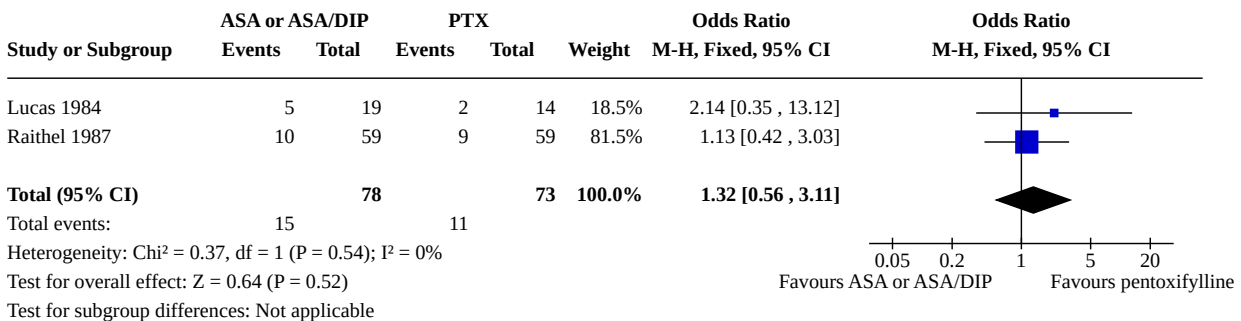
Analysis 3.1. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 1: Primary graft patency, 1 month



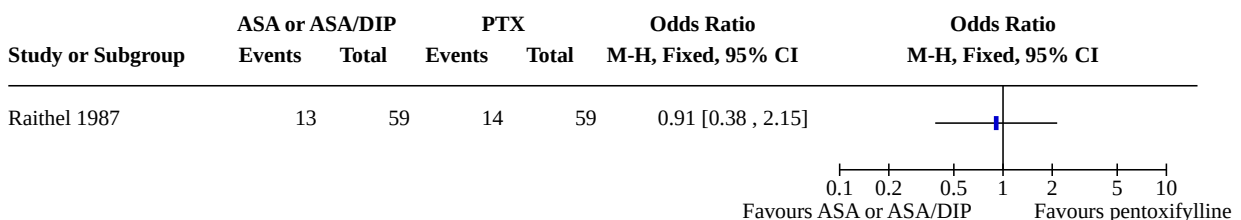
Analysis 3.2. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 2: Primary graft patency, 3 months



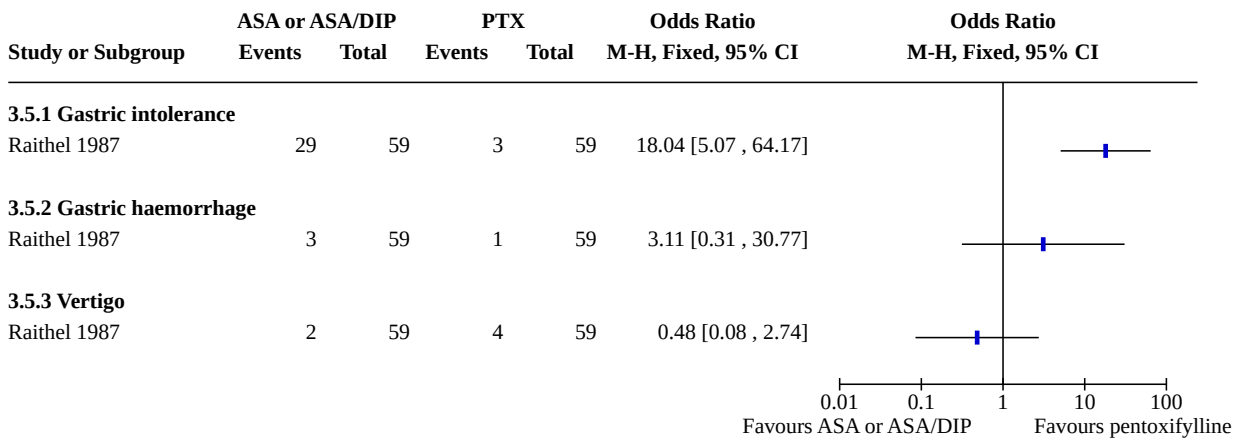
Analysis 3.3. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 3: Primary graft patency, 6 months



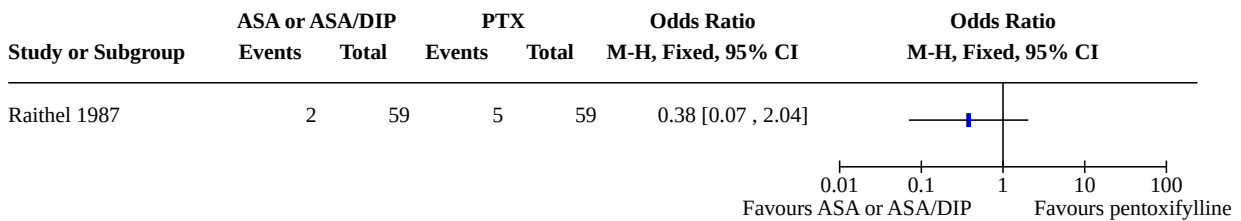
Analysis 3.4. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 4: Primary graft patency, 12 months



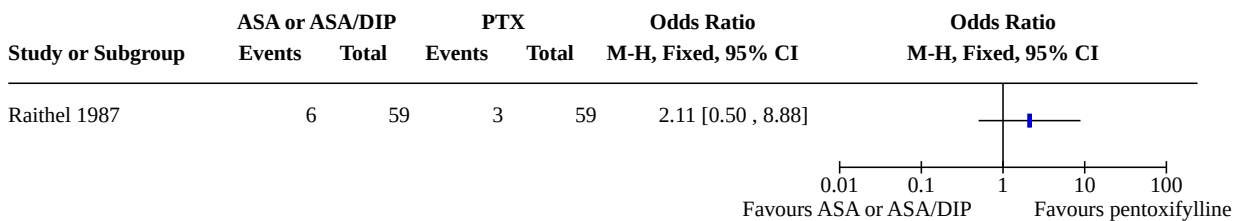
Analysis 3.5. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 5: Side effects



Analysis 3.6. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 6: Limb amputation



Analysis 3.7. Comparison 3: ASA or ASA/DIP versus pentoxifylline (PTX), all grafts, Outcome 7: Mortality



Comparison 4. ASA/DIP versus indobufen, prosthetic grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Primary graft patency, 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2 Primary graft patency, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.3 Primary graft patency, 9 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
4.4 Primary graft patency, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 1: Primary graft patency, 3 months

Study or Subgroup	ASA/DIP		Indobufen		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
D'Addato 1992	8	57	5	56	1.67 [0.51, 5.44]	

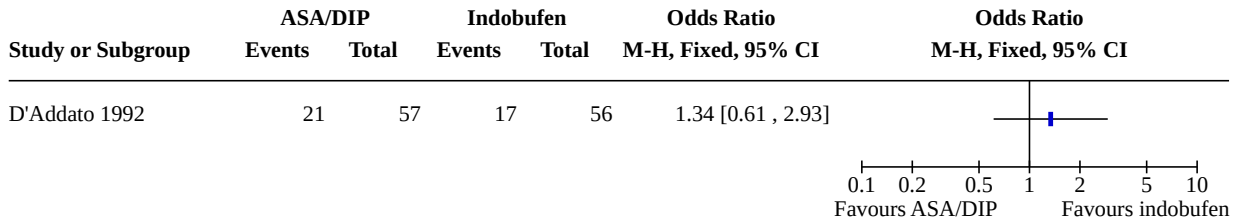
Analysis 4.2. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 2: Primary graft patency, 6 months

Study or Subgroup	ASA/DIP		Indobufen		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
D'Addato 1992	12	57	8	56	1.60 [0.60, 4.27]	

Analysis 4.3. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 3: Primary graft patency, 9 months

Study or Subgroup	ASA/DIP		Indobufen		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
D'Addato 1992	18	57	15	56	1.26 [0.56, 2.85]	

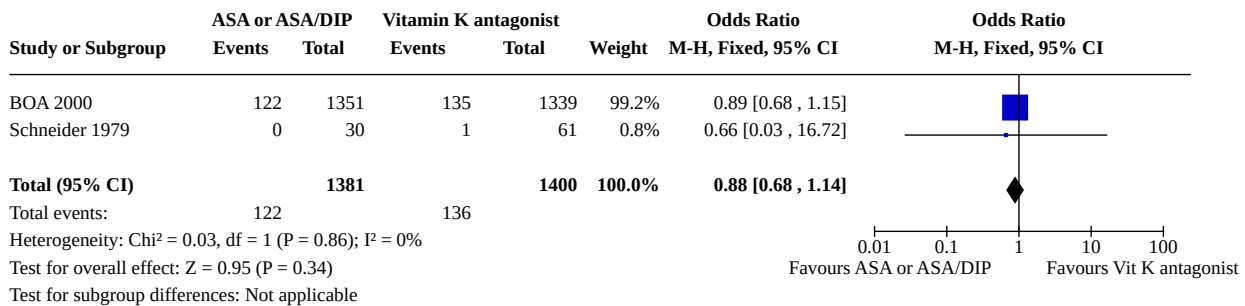
Analysis 4.4. Comparison 4: ASA/DIP versus indobufen, prosthetic grafts, Outcome 4: Primary graft patency, 12 months



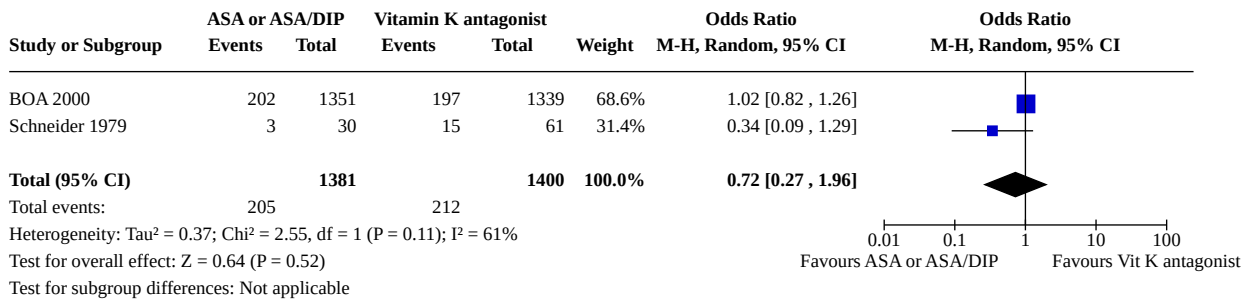
Comparison 5. ASA or ASA/DIP versus vitamin K antagonists, all grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Primary graft patency, 3 months	2	2781	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.68, 1.14]
5.2 Primary graft patency, 6 months	2	2781	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.27, 1.96]
5.3 Primary graft patency, 12 months	2	2781	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.27, 1.69]
5.4 Primary graft patency, 24 months	2	2781	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.25, 1.63]
5.5 Limb amputation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.6 Cardiovascular events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.6.1 Myocardial infarction	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.6.2 Stroke	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.7 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

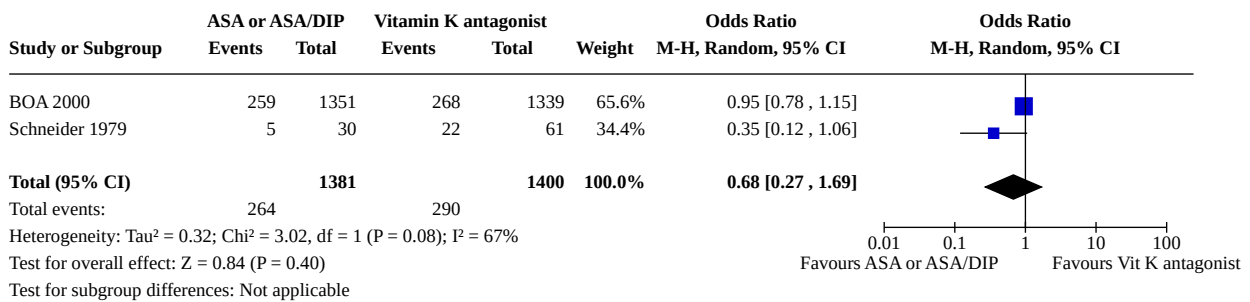
Analysis 5.1. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 1: Primary graft patency, 3 months



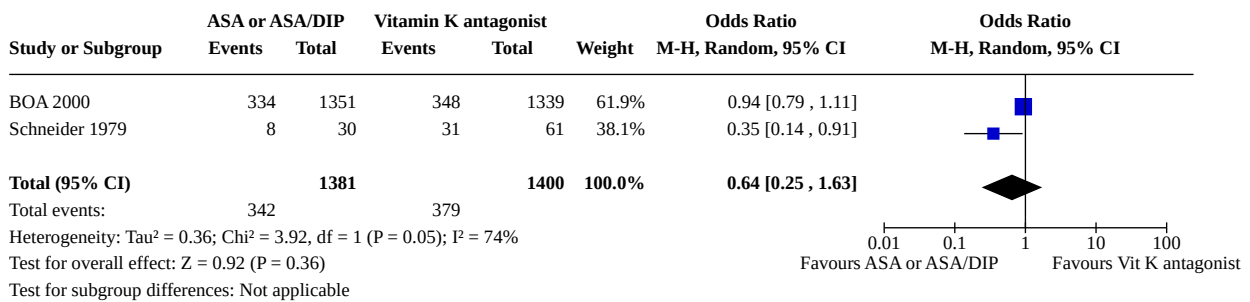
Analysis 5.2. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 2: Primary graft patency, 6 months



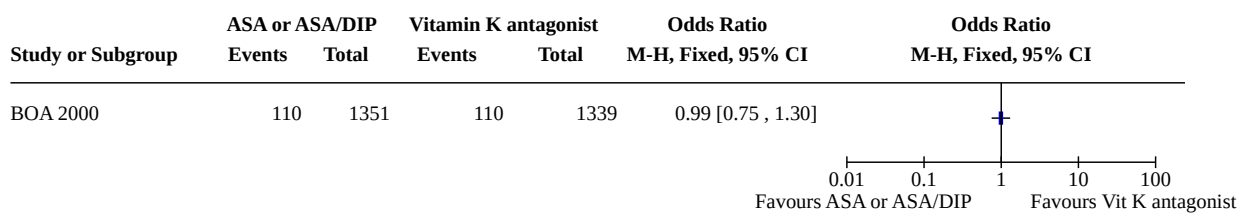
Analysis 5.3. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 3: Primary graft patency, 12 months



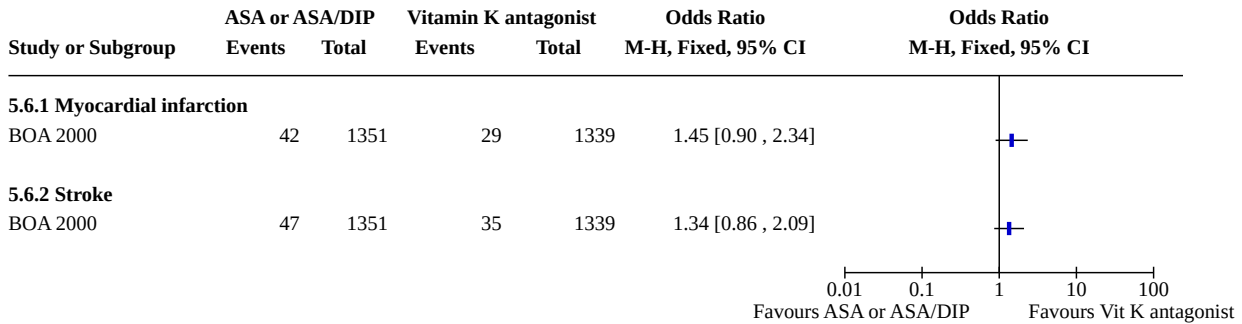
Analysis 5.4. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 4: Primary graft patency, 24 months



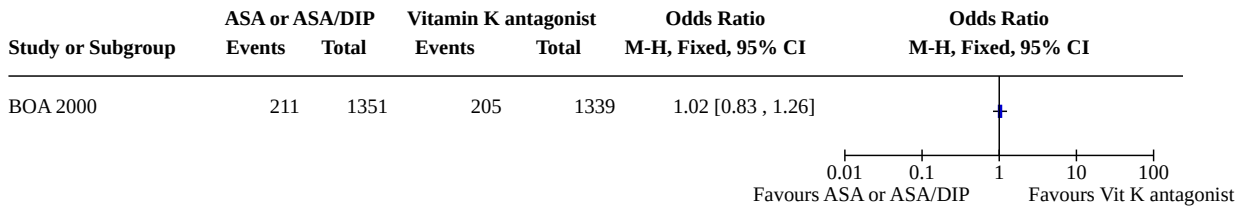
Analysis 5.5. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 5: Limb amputation



Analysis 5.6. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 6: Cardiovascular events



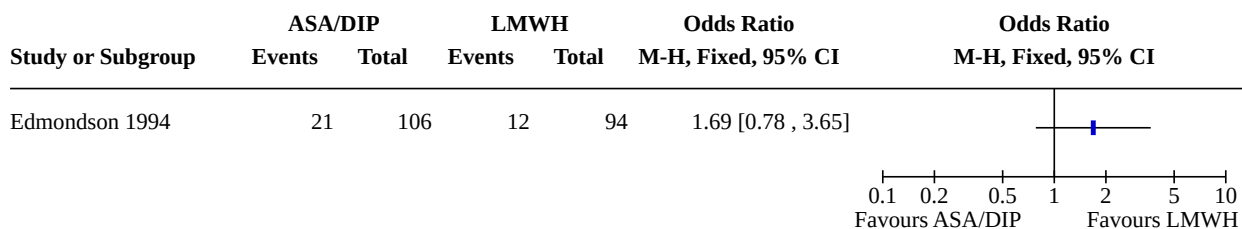
Analysis 5.7. Comparison 5: ASA or ASA/DIP versus vitamin K antagonists, all grafts, Outcome 7: Mortality



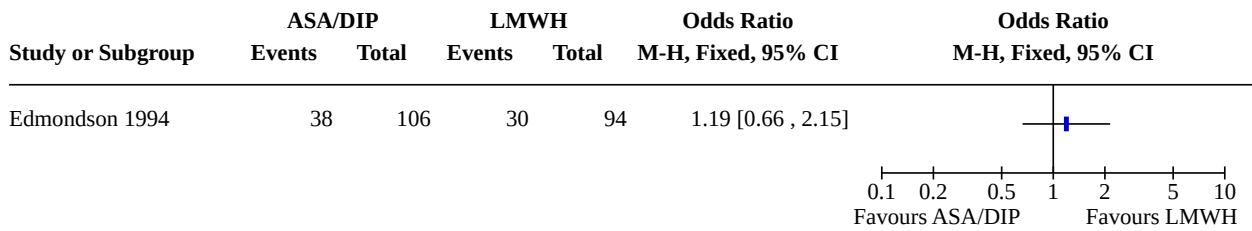
Comparison 6. ASA/DIP versus LMWH, all grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Primary graft patency, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Primary graft patency, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.3 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

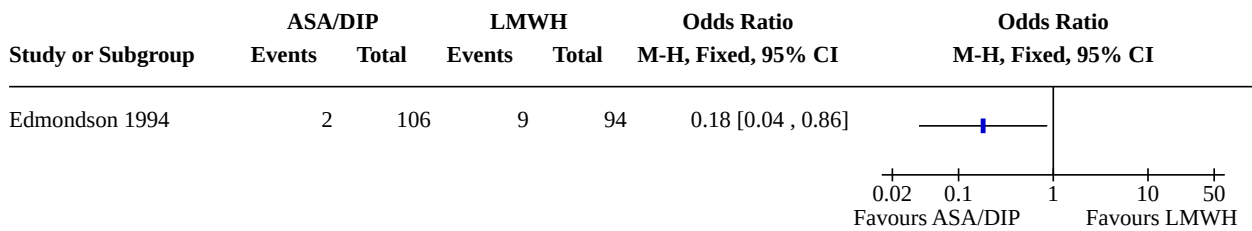
Analysis 6.1. Comparison 6: ASA/DIP versus LMWH, all grafts, Outcome 1: Primary graft patency, 6 months



Analysis 6.2. Comparison 6: ASA/DIP versus LMWH, all grafts, Outcome 2: Primary graft patency, 12 months



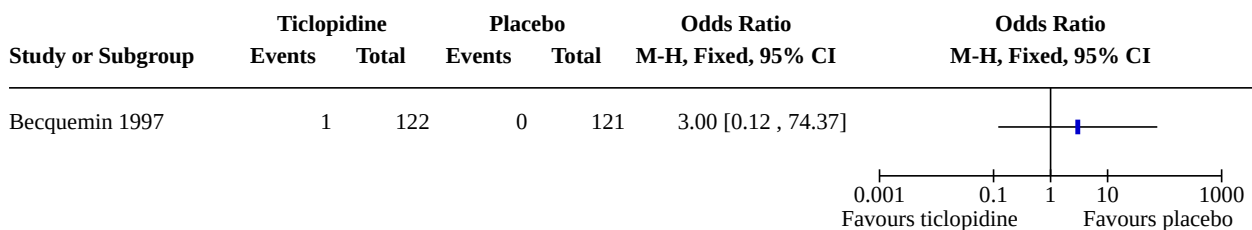
Analysis 6.3. Comparison 6: ASA/DIP versus LMWH, all grafts, Outcome 3: Mortality



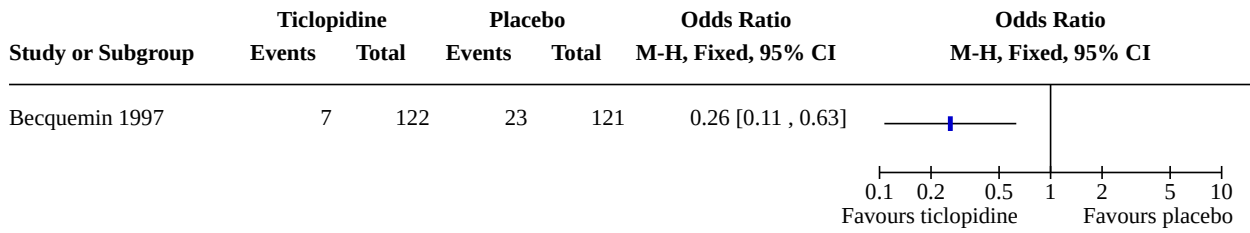
Comparison 7. Ticlopidine versus placebo, venous grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Primary graft patency, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.2 Primary graft patency, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.3 Primary graft patency, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.4 Primary graft patency, 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

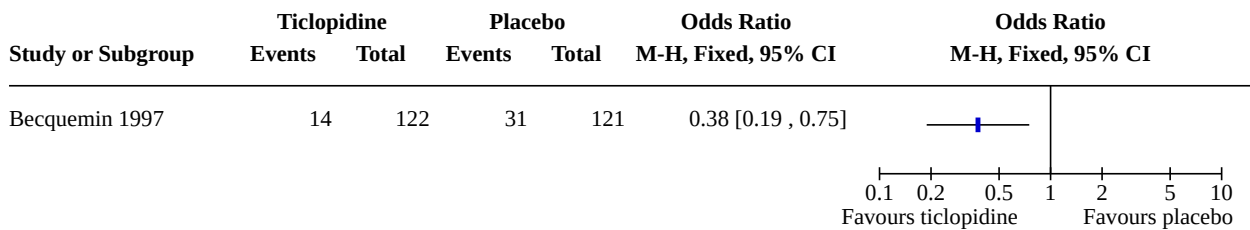
Analysis 7.1. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 1: Primary graft patency, 1 month



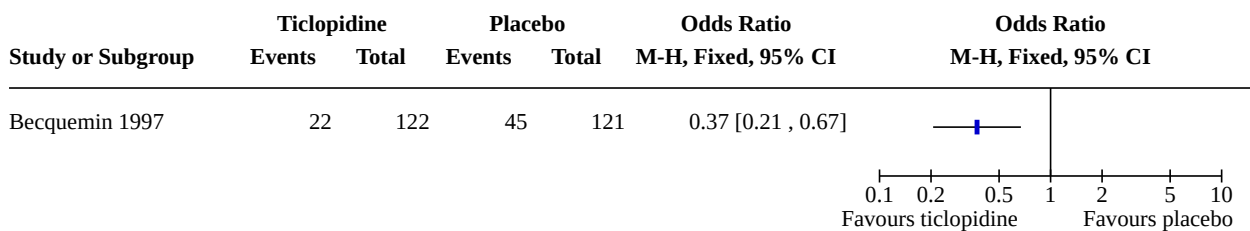
Analysis 7.2. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 2: Primary graft patency, 6 months



Analysis 7.3. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 3: Primary graft patency, 12 months



Analysis 7.4. Comparison 7: Ticlopidine versus placebo, venous grafts, Outcome 4: Primary graft patency, 24 months



Comparison 8. ASA versus prostaglandin (PGE1), venous grafts

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

Analysis 8.1. Comparison 8: ASA versus prostaglandin (PGE1), venous grafts, Outcome 1: Early occlusion

Study or Subgroup	ASA		PGE1		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gruss 1991	7	50	2	50	3.91 [0.77, 19.83]	

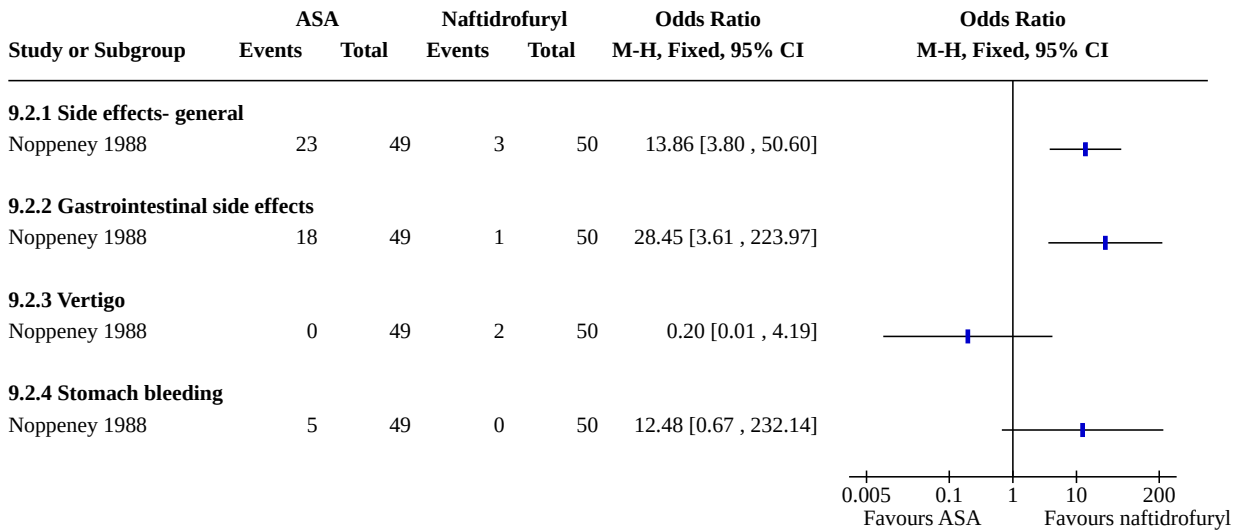
Comparison 9. ASA versus naftidrofuryl

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Primary graft patency at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2.1 Side effects- general	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2.2 Gastrointestinal side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2.3 Vertigo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2.4 Stomach bleeding	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

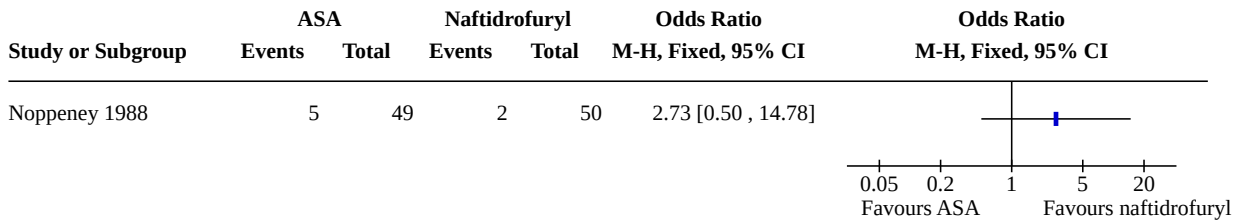
Analysis 9.1. Comparison 9: ASA versus naftidrofuryl, Outcome 1: Primary graft patency at 12 months

Study or Subgroup	ASA		Naftidrofuryl		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Noppeney 1988	10	49	7	50	1.58 [0.55, 4.54]	

Analysis 9.2. Comparison 9: ASA versus naftidrofuryl, Outcome 2: Side effects



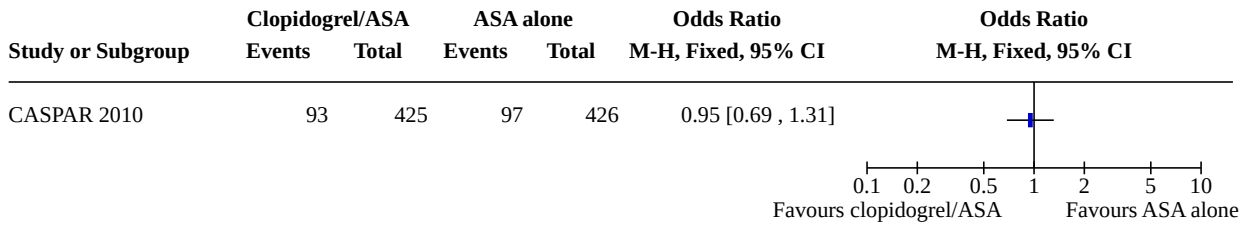
Analysis 9.3. Comparison 9: ASA versus naftidrofuryl, Outcome 3: Mortality



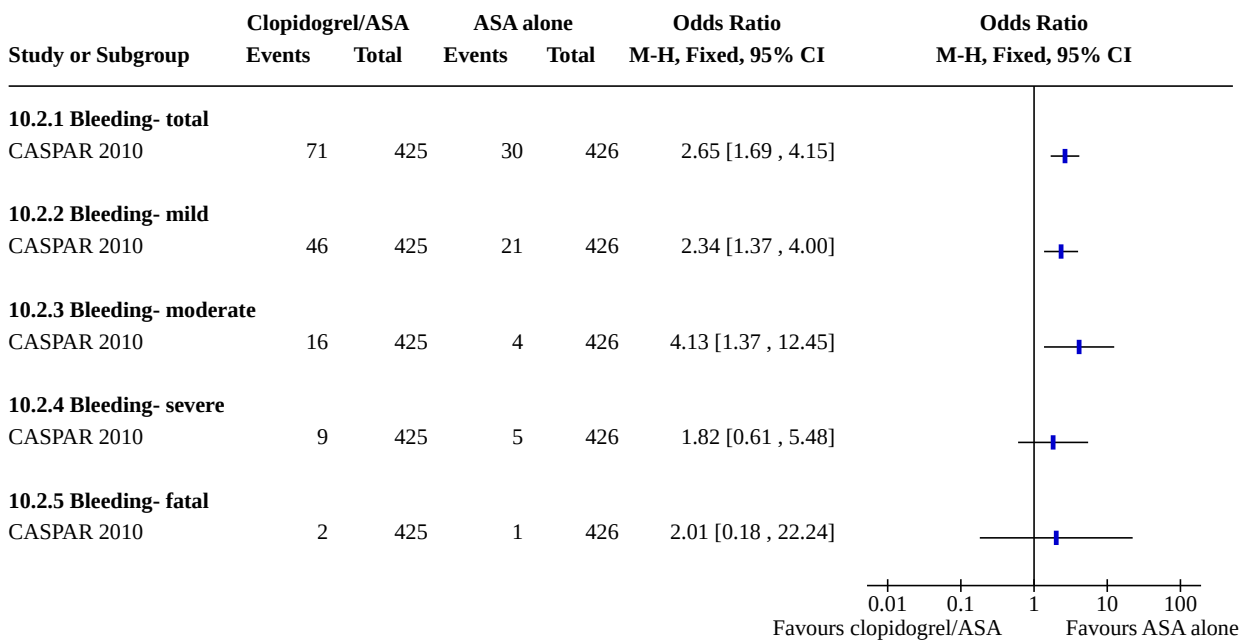
Comparison 10. Clopidogrel and ASA versus ASA alone, all grafts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Primary graft patency at 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.1 Bleeding- total	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.2 Bleeding- mild	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.3 Bleeding- moderate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.4 Bleeding- severe	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.5 Bleeding- fatal	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.3 Limb amputation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.4 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

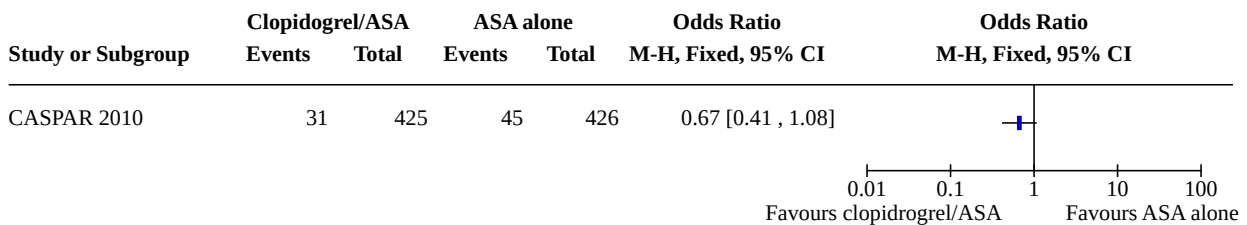
Analysis 10.1. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 1: Primary graft patency at 24 months



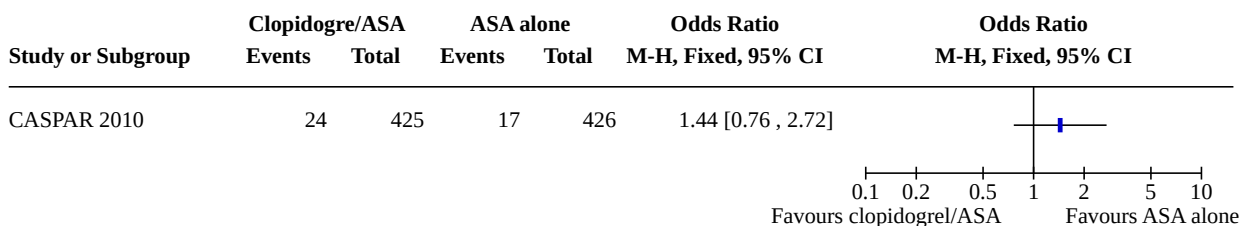
Analysis 10.2. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 2: Side effects



Analysis 10.3. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 3: Limb amputation



Analysis 10.4. Comparison 10: Clopidogrel and ASA versus ASA alone, all grafts, Outcome 4: Mortality

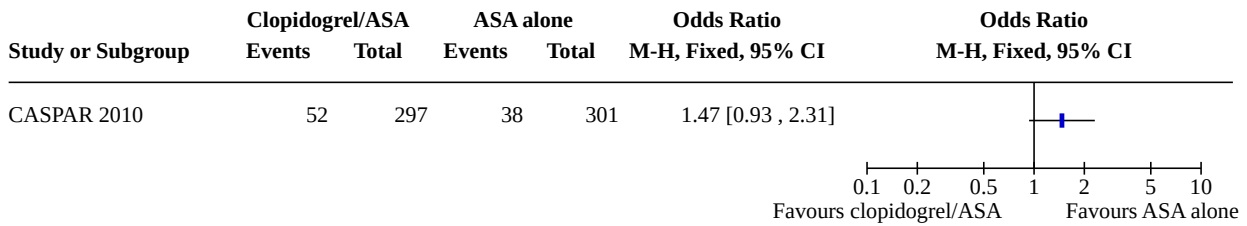


Comparison 11. Clopidogrel and ASA versus ASA alone, subgroups

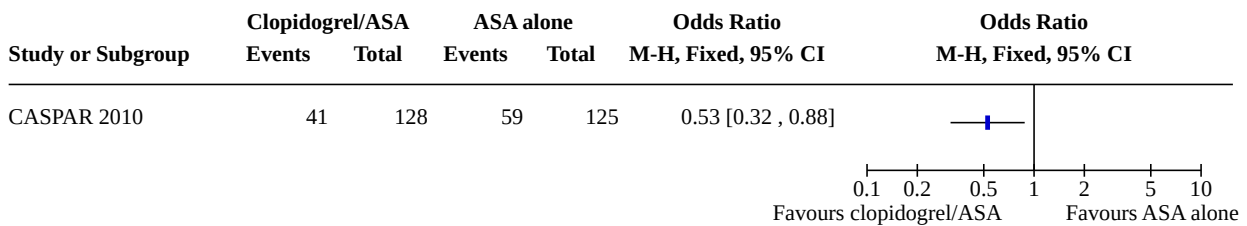
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Primary graft patency, venous grafts, 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.2 Primary graft patency, prosthetic grafts, 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3.1 Bleeding- mild, venous grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3.2 Bleeding- mild, prosthetic grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3.3 Bleeding- moderate, venous grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3.4 Bleeding- moderate, prosthetic grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3.5 Bleeding- severe, venous grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.3.6 Bleeding- severe, prosthetic grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.4 Limb amputation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.4.1 Amputation, venous grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.4.2 Amputation, prosthetic grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.5 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.5.1 Mortality, venous grafts	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
11.5.2 Mortality, prosthetic grafts	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

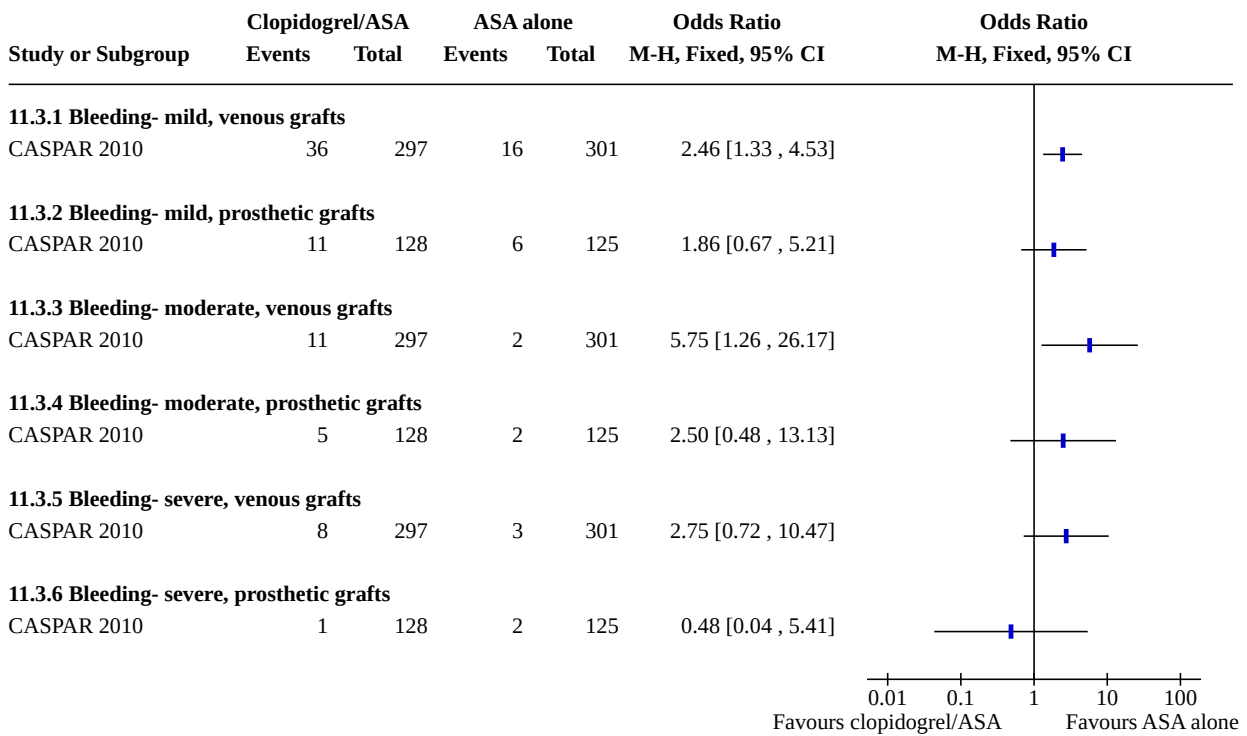
Analysis 11.1. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 1: Primary graft patency, venous grafts, 24 months



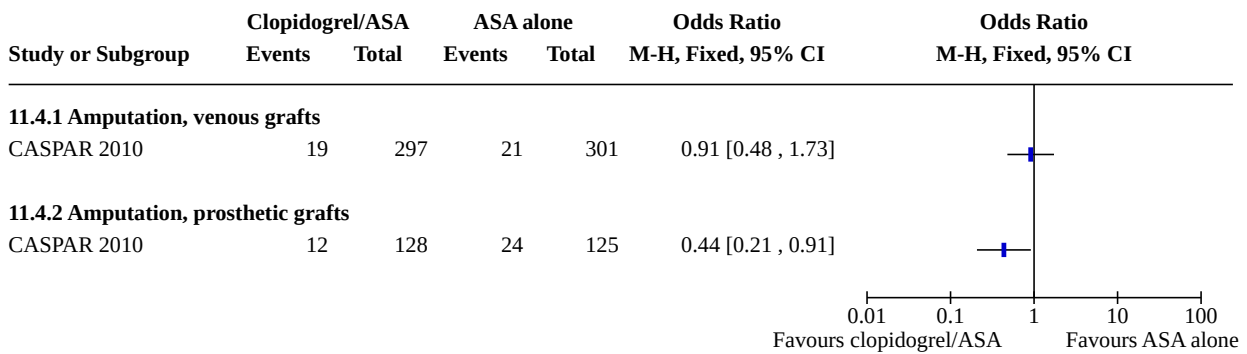
Analysis 11.2. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 2: Primary graft patency, prosthetic grafts, 24 months



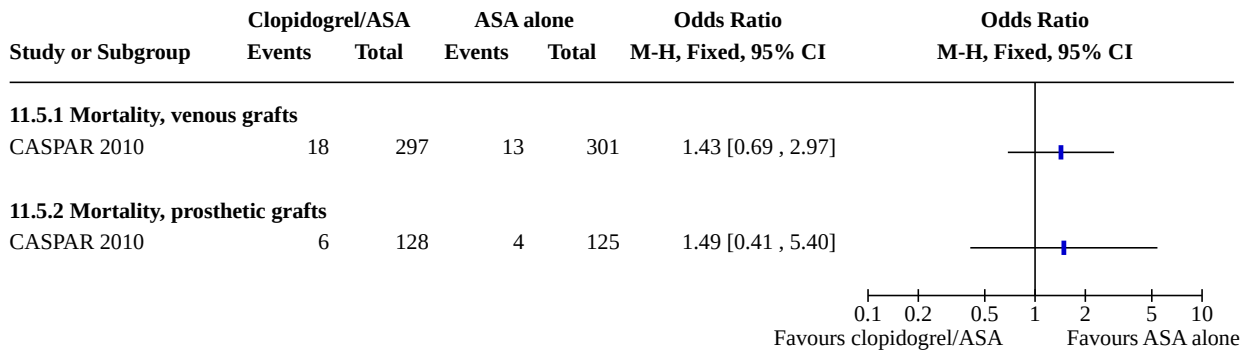
Analysis 11.3. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 3: Side effects



Analysis 11.4. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 4: Limb amputation



Analysis 11.5. Comparison 11: Clopidogrel and ASA versus ASA alone, subgroups, Outcome 5: Mortality



ADDITIONAL TABLES
Table 1. Patient characteristics

Study ID	% CLI	% below knee	% vein	% 1-ves-sel run-off	dose	preoperative start of treatment	treatment duration	randomisation	ABI pre-op to postop
Becquemini 1997	> 70	nd	100	nd	TIC 250 mg vs placebo	between the 3rd and 14th post-op day	24 months	post-op	nd
BOA 2000	50	52	58.5	nd	ASA 80 mg vs coumarin INR 3.0 - 4.5 reached in 50%	within 5 days until 1 month post-op	21 months	before surgery	nd
CASPAR 2010	66	100	70	nd	ASA 75 - 100 mg plus clopidogrel 75 mg vs ASA 75 - 100 mg plus placebo	2 to 4 days post-op	24 months	post-op	nd
Clyne 1987	70	85	63	24	ASA 2 x 300 mg, DIP 2 x 200 mg	48 hours pre-op	6 weeks	before surgery	0.38 to 0.78
D'Addato 1992	70	25	0	56	ASA 900 mg plus DIP 225 mg vs 400 mg IND	48 h	12 months	before surgery	nd
Donaldson 1985	0	32	0	37	ASA 3 x 330 mg plus DIP 75 mg	Evening prior to surgery	12 months	before surgery	0.62 to nd
Edmondson 1994	46	31	27	20	3 x 300 mg ASA plus 3 x 100 mg DIP versus 2500 IU LMWH	LMWH 2 hours pre-op; ASA/DIP 1 week post-op	3 months	post-op	nd
Goldman 1984	80	47	0	nd	ASA 3 x 300 mg plus DIP 3 x 75 mg	2 days ASA/DIP	12 months	before surgery	nd
Green 1982	82	47	0	nd	ASA 3 x 325 mg, or ASA 3 x 325 mg plus DIP 3 x 75 mg	2 days ASA/DIP	12 months	before surgery	0.42 to 1.01
Gruss 1991	nd	nd	100	nd	3 x 0.5 g ASA plus 15,000 IU heparin versus PGE1, 0.2 ng per kg body weight/min plus 15,000 IU heparin	post-op	10 days	nd	nd
Kohler 1984	76	52	69	nd	ASA 3 x 325 mg plus DIP 3 x 75 mg	first post-op day	24 months	before surgery	nd

Table 1. Patient characteristics (Continued)

Lucas 1984	55	nd	27	nd	ASA 1050 mg, DIP 150 mg or 1200 mg PTX	pre-op	6 months	before surgery	0.4
McCollum 1991	60	59	100	nd; vein < 4 mm:38	ASA 2 x 300 mg plus DIP 2 x 150 mg	2 days ASA/DIP	continuing indefinite- ly	before surgery	0.47 to nd
Noppene 1988	nd	nd	nd	nd	ASA 1500 mg vs naftidrofuryl 600 mg daily orally	day 1 post-op	12 months	before surgery	nd
Raithel 1987	95	nd	0	56	ASA 1500 mg vs PTX 1200 mg	48 h	12 months	before surgery	nd
Schneider 1979	nd	nd	100	nd	ASA 1000 mg, or ASA 1000 mg plus DIP 225 mg vs coumarin	post-op	24 months	post-op	nd

ASA: Aspirin

CLI: critical limb ischaemia

DIP: dipyridamole

h: hour

IU: international unit

LMWH: low molecular weight heparin

mg: milligram

nd: no data

ng: nanogram

PGE1: prostaglandin E1

PTX: pentoxifylline

TIC: ticlopidine

vs: versus

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Arteriosclerosis] this term only	895
#2	MeSH descriptor: [Arteriolosclerosis] this term only	0
#3	MeSH descriptor: [Arteriosclerosis Obliterans] this term only	73
#4	MeSH descriptor: [Atherosclerosis] this term only	513
#5	MeSH descriptor: [Arterial Occlusive Diseases] this term only	810
#6	MeSH descriptor: [Intermittent Claudication] this term only	768
#7	MeSH descriptor: [Ischemia] this term only	814
#8	MeSH descriptor: [Peripheral Vascular Diseases] explode all trees	2293
#9	MeSH descriptor: [Vascular Diseases] this term only	424
#10	MeSH descriptor: [Leg] explode all trees and with qualifier(s): [Blood supply - BS]	1145
#11	MeSH descriptor: [Femoral Artery] explode all trees	796
#12	MeSH descriptor: [Popliteal Artery] explode all trees	289
#13	MeSH descriptor: [Iliac Artery] explode all trees	159
#14	MeSH descriptor: [Tibial Arteries] explode all trees	32
#15	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	19399
#16	(arter*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	6127
#17	(vascular) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1656
#18	(vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	951
#19	(veno*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1174
#20	(peripher*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1631
#21	peripheral near/3 dis*	3705
#22	arteriopathic	25
#23	(claudic* or hinken*)	1600
#24	(isch* or CLI)	20013
#25	dysvascular*	35

(Continued)

#26	leg near/4 (obstruct* or occlus* or steno* or block* or oblitter*)	201
#27	limb near/4 (obstruct* or occlus* or steno* or block* or oblitter*)	261
#28	(lower near/3 extrem*) near/4 (obstruct* or occlus* or steno* or block* or oblitter*)	158
#29	(aort* or iliac or femoral or popliteal or femoro* or fempop* or crural or *inguinal) near/3 (obstruct* or occlus*)	402
#30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29	46395
#31	bypass*:ti,ab,kw (Word variations have been searched)	11328
#32	MeSH descriptor: [Vascular Grafting] explode all trees	6012
#33	MeSH descriptor: [Blood Vessel Prosthesis] explode all trees	472
#34	MeSH descriptor: [Blood Vessel Prosthesis Implantation] explode all trees	536
#35	revascul*:ti,ab,kw (Word variations have been searched)	4850
#36	graft*:ti,ab,kw (Word variations have been searched)	13673
#37	reconstruct*:ti,ab,kw (Word variations have been searched)	9
#38	#31 or #32 or #33 or #34 or #35 or #36 or #37	23761
#39	#30 and #38 in Trials	5278
#40	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees	3038
#41	MeSH descriptor: [Phosphodiesterase Inhibitors] explode all trees	970
#42	MeSH descriptor: [Tetrazoles] this term only	1681
#43	antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*:ti,ab,kw (Word variations have been searched)	2314
#44	((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) near/3 (antagonist or inhibitor)):ti,ab,kw (Word variations have been searched)	6624
#45	(gp* or glycoprotein* or protease or P2Y12 or TXA2) near/3 inhibit*:ti,ab,kw (Word variations have been searched)	2401
#46	thienopyridine:ti,ab,kw (Word variations have been searched)	144
#47	ticlopidine or Ticlid:ti,ab,kw (Word variations have been searched)	1583
#48	clopidogrel or Plavix:ti,ab,kw (Word variations have been searched)	1849
#49	Prasugrel or Effient or Efiend or Prasita:ti,ab,kw (Word variations have been searched)	182

(Continued)

#50	ticagrelor or AZD6140 or Brilinta:ti,ab,kw (Word variations have been searched)	126
#51	elinogrel or PRT060128 or PRT-060128:ti,ab,kw (Word variations have been searched)	7
#52	cangrelor or AR-C6993* or ARC6993*:ti,ab,kw (Word variations have been searched)	25
#53	SCH530348 or SCH-530348:ti,ab,kw (Word variations have been searched)	11
#54	E5555:ti,ab,kw (Word variations have been searched)	3
#55	terutroban or Triplion:ti,ab,kw (Word variations have been searched)	11
#56	(aspirin* or nitroaspirin or ASA or "acetyl salicylic acid*" or "acetylsalicylic acid" or "acetyl-salicylic acid"):ti,ab,kw (Word variations have been searched)	15346
#57	triflusal or disgren:ti,ab,kw (Word variations have been searched)	88
#58	Cilostazol or Pletal or Pletaal:ti,ab,kw (Word variations have been searched)	356
#59	dipyridamol* or Persantine:ti,ab,kw (Word variations have been searched)	1086
#60	OPC-13013 or OPC13013:ti,ab,kw (Word variations have been searched)	5
#61	picotamide or picotinamide:ti,ab,kw (Word variations have been searched)	43
#62	satigrel:ti,ab,kw (Word variations have been searched)	4
#63	vorapaxar:ti,ab,kw (Word variations have been searched)	22
#64	indobufen	102
#65	#40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #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	25325
#66	39 and #65 in Trials	1259

FEEDBACK

Anticoagulant feedback, 14 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: 'Anti-thrombotics after infra-inguinal bypass grafting' (https://doi.org/10.1002/14651858.CD015141) and 'Anti-thrombotics

Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery (Review)

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Date	Event	Description
		after infra-inguinal peripheral endovascular treatment' (https://doi.org/10.1002/14651858.CD015142) and will no longer be updated.

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 3, 2003

Date	Event	Description
2 September 2014	New search has been performed	Searches rerun, one new study included, three new studies excluded
2 September 2014	New citation required but conclusions have not changed	Searches rerun, one new study included, three new studies excluded, risk of bias tables completed, two new authors joined review team. Conclusions not changed
14 February 2011	Amended	Link to anticoagulant feedback added
23 April 2008	Amended	Converted to new review format.
23 April 2008	New citation required and conclusions have changed	This review was updated in 2008. New studies were identified and added to the included and excluded tables.
26 May 2004	Amended	Graph created and text amended
18 August 2003	Amended	Published note added to effect that Donald Adam wrote protocol but did not have any involvement with the review

CONTRIBUTIONS OF AUTHORS

RB: performed study selection, data extraction and quality assessment and wrote the review update

AL: performed study selection, data extraction and quality assessment

HM: provided support in updating the manuscript

SA: provided support in updating the manuscript

MP: provided support in updating the manuscript

DECLARATIONS OF INTEREST

RB: none known

AL: none known

HM: none known

SA: none known

MP: Prof Prins' institution has received a grant from ZON-MW (not-for-profit organisation) for demonstrating cost-effectiveness on the topic of this review. Prof Prins' institution has received funding for his board membership of clinical studies and consultancy from Bayer, Boeringer Ingelheim, Daiichi Sankyo, Pfizer and ISIS Pharmaceuticals. These were not related to this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

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

We amended the outcome 'Limb salvage rate: survival rates with limb intact' to included 'or limb amputation', as most studies reported amputations, but not necessarily limb salvage rate.

We amended the outcome 'Side effects of treatment' to include 'and complications', as in several studies these two outcome types were grouped together.

INDEX TERMS

Medical Subject Headings (MeSH)

Anastomosis, Surgical [adverse effects] [methods]; Anticoagulants [therapeutic use]; Arteriosclerosis [surgery]; Aspirin [therapeutic use]; Dipyridamole [therapeutic use]; Graft Occlusion, Vascular [etiology] [*prevention & control]; Intermittent Claudication [surgery]; Peripheral Vascular Diseases [*surgery]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Thrombosis [*prevention & control]; Vascular Patency

MeSH check words

Humans