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Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery (Review)

Geraghty AJ, Welch K

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[Intervention Review]

Antithrombotic agents for preventing thrombosis after infrainguinal 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Editorial note: This review has been superseded by Cochrane Reviews: 'Antithrombotics after infra-inguinal bypass grafting' (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) is frequently treated by either an infrainguinal autologous (using the patient's own veins) or synthetic graft bypass. The rate of occlusion of the graft after one year is between 12% and 60%. To prevent occlusion, patients are treated with an antiplatelet or antithrombotic drug, or a combination of both. Little is known about which drug is optimal to prevent infrainguinal graft occlusion. This is an update of a Cochrane review first published in 2003.

Objectives

To evaluate whether antithrombotic treatment improves graft patency, limb salvage and survival in patients with chronic PAD undergoing infrainguinal bypass surgery.

Search methods

The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched August 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3).

Selection criteria

Randomised, controlled trials; two review authors independently assessed the methodological quality of each trial using a standardised checklist.

Data collection and analysis

Data collected included patient details, inclusion and exclusion criteria, type of graft, antithrombotic therapy, outcomes, and side effects.

Main results

A total of 14 trials were included in this review; 4970 patient results were analysed. Four trials evaluating vitamin K antagonists (VKA) versus no VKA suggested that oral anticoagulation may favour autologous venous, but not artificial, graft patency as well as limb salvage and survival. Two other studies comparing VKA with aspirin (ASA) or aspirin and dipyridamole provided evidence to support a positive effect of VKA on the patency of venous but not artificial grafts. Three trials comparing low molecular weight heparin (LMWH) to unfractionated heparin (UFH) failed to demonstrate a significant difference on patency. One trial comparing LMWH with placebo found no significant improvement in graft patency over the first postoperative year in a population receiving aspirin. One trial showed an advantage for LMWH

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versus aspirin and dipyridamol at one year for patients undergoing limb salvage procedures. Perioperative administration of anicrod showed no greater benefit when compared to unfractionated heparin. Dextran 70 showed similar graft patency rates to LMWH but a significantly higher proportion of patients developed heart failure with dextran.

Authors' conclusions

Patients undergoing infrainguinal venous graft are more likely to benefit from treatment with VKA than platelet inhibitors. Patients receiving an artificial graft benefit from platelet inhibitors (aspirin). However, the evidence is not conclusive. Randomised controlled trials with larger patient numbers are needed in the future to compare antithrombotic therapies with either placebo or antiplatelet therapies.

PLAIN LANGUAGE SUMMARY

Antithrombotic drugs to prevent further blood vessel blockage after bypass surgery using vein grafts obtained from the same person (autologous) or artificial grafts in the legs

Lower limb atherosclerosis can lead to blocked blood vessels causing pain on walking (intermittent claudication) or, if more severe, pain at rest, ulceration and gangrene (critical limb ischaemia).

Surgery to bypass the blockage uses either a piece of vein from another part of the person's body or a synthetic graft. The bypass may help improve blood supply to the leg but the graft can also become blocked, even in the first year. To help prevent this, people are given aspirin (an antiplatelet drug) or a vitamin K antagonist (anti-blood clotting or antithrombotic drug), or both, to try to stop loss of blood flow through the graft (patency). The review of trials found that patients undergoing venous grafts were more likely to benefit from treatment with vitamin K antagonists than platelet inhibitors. Patients receiving an artificial graft may benefit from platelet inhibitors (aspirin). However, the evidence is not conclusive. Although a total of 14 randomised, controlled trials involving 4970 patients were included in the review, trials with larger patient numbers are needed. This is because there was considerable variation between the included trials in whether patients received both types of drugs, anticoagulation levels and how they were measured, and the indications for surgery, intermittent claudication or critical limb ischaemia.

BACKGROUND

Description of the condition

Lower limb atherosclerosis may manifest as pain on walking (intermittent claudication) or, if more severe, pain at rest, ulceration and gangrene (critical limb ischaemia). Intermittent claudication (IC) corresponds to Fontaine's classification (Fontaine 1954) stage II and critical limb ischaemia (CLI) refers to stages III and IV. In selected patients, treatment includes placement of a femoropopliteal or femorodistal bypass graft to divert blood past the occluded arterial segment, thereby improving blood perfusion of the limb, relieving the symptoms of claudication or rest pain, and avoiding amputation because of ulceration and gangrene (limb salvage). Several different materials may be used for bypass grafting. These include a section of the patient's own vein (autologous vein graft), an artificial graft material such as dacron or polytetrafluoroethylene (PTFE), treated human umbilical vein (taken from an umbilical cord), or a combination of these materials. Graft patency is dependent on many factors including the indication for surgery (IC or CLI), quality of arterial inflow and outflow, type of graft used (Cochrane 2010), operative technique, progression of atherosclerosis in the proximal or distal arteries, and graft stenosis due to remodelling and intimal hyperplasia (IH) (a narrowing of the graft due to excessive formation of cells in the inner lining).

Description of the intervention

There is evidence that patients with lower limb atherosclerosis frequently have a prothrombotic tendency (Swedenborg 1996; Woodburn 1996). The body's physiological stress response to surgery adds further to this. Additionally, platelets are implicated in the initial steps of IH development (Davies 1994). Therefore, a key question is whether postoperative treatment following infrainguinal bypass grafting should include long or short-term antiplatelet drugs or anticoagulants in order to prevent graft occlusion (Kretschmer 1999) and, if so, whether the same treatment is optimal for all kinds of grafts and patients. Several reviews have been published (Cochrane 2010; Girolami 2000; Kraiss 1995; Lindblad 1995; Tangelder 1999; Watson 1999) trying to address these questions. A separate Cochrane review has been published on antiplatelet treatment in patients with symptomatic PAD undergoing infrainguinal bypass (Cochrane 2008); this present review will focus on the role of anticoagulants.

Why it is important to do this review

The overall one year incidence of graft failure (graft occlusion) for above-knee femoropopliteal bypass grafts is 12% to 18% when a vein is used (Achermann 1998; Johnson 2000) and 20% to 25% when PTFE is used (Abbott 1997; Johnson 2000). These figures rise to approximately 30% and 40%, respectively, for below-knee popliteal grafts (Consensus 1991); 30% and 60% for femorotibial bypass grafts (Consensus 1991). Approximately 5% to 25% will fail within one month of the procedure (in the acute phase) depending on the type of graft material used; the highest failure rates are for prosthetic grafts to the tibial arteries (Parsons 1996). Almost 10% of early failures are due to the consequences of technical error (Alback 1998; Stept 1987) or to thrombogenic (clot forming) graft material (Hanson 1987). The remaining 5% to 10% are considered as unexpected early graft failures and might be caused by an increased prothrombotic state. Eighty per cent of all graft failures will occur

within the first two postoperative years, due to development of graft stenosis (Bandyk 1987). Stenosis continues to develop at a rate of approximately 5% to 7% per year causing late vein graft failure (Schoder 2001). The Transatlantic Inter-Society Consensus (TASC) for the management of peripheral arterial disease (Norgren 2007) states a five-year patency rate of infrainguinal above-knee bypass grafts of 74% to 76% for vein and 39% to 52% for PTFE grafts. If blood flow in the failed graft cannot be restored and further bypass surgery is not possible, then limb perfusion may, in some cases, be so poor that the limb cannot remain viable and amputation is required. Successful prevention of graft failure, and the need for surgical re-intervention, is of major clinical and economic importance (Robinson 1997).

OBJECTIVES

To determine the efficacy of pharmacotherapy using anticoagulant drugs in patients with lower limb atherosclerosis (Intermittent claudication (IC) and critical limb ischaemia (CLI)) undergoing femoropopliteal and femorodistal bypass grafting. Outcomes include the overall success of therapy (graft patency and limb salvage rates) and complications of treatment. The null hypothesis tested is that antithrombotic therapy does not improve graft patency and limb salvage rates after femoropopliteal and femorodistal bypass surgery for lower limb atherosclerosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials. Trials using alternation would be considered as quasi-randomised controlled trials if included and a sensitivity analysis restricted to randomised controlled trials carried out to ensure the validity of any results.

Types of participants

All patients undergoing femoropopliteal or femorodistal bypass grafting for the treatment of IC and CLI. Patients undergoing bypass surgery for trauma were excluded. Patients undergoing bypass procedures using autologous vein grafts, synthetic (polytetrafluoroethylene (PTFE) or Dacron) grafts, treated human umbilical vein, or a combination of these materials were included.

Types of interventions

Trials in which participants were randomly allocated to receive either anticoagulant therapy versus placebo, one anticoagulant regimen versus another, or anticoagulant therapy versus an alternative treatment. The type of therapy, dosage, time of starting in relation to surgery (pre or postoperatively), and duration of therapy were recorded.

Types of outcome measures

Primary outcomes

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

Secondary outcomes

- Secondary graft patency: patency rates following secondary intervention to restore blood flow to the graft.
- Objective assessment of lower limb blood flow: ankle-brachial pressure index, exercise tolerance test.
- Patient's quality of life.
- Limb salvage rate: survival rates with limb intact.
- Incidence of other cardiovascular events and mortality.
- Side effects of treatment.

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched August 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3), see [Appendix 1](#) for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the Trials Search Co-ordinator and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, and AMED; and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the [Specialised Register](#) section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library*. Details of the search strategy used for the 2003 version of the review are shown in [Appendix 2](#).

Searching other resources

Reference lists of papers and reports retrieved from the electronic searches were screened to identify potentially relevant additional studies.

Data collection and analysis

Selection of studies

Alistair Geraghty (AG) and Karen Welch (KW) independently selected which trials were suitable for the updated review. Disagreements were resolved by discussion. In the absence of consensus over the inclusion of a trial, a third opinion was sought.

Data extraction and management

For this update AG and KW independently extracted the following data using a standardised data extraction form.

- Inclusion and exclusion criteria; patient details (age, gender, comorbidity).
- Severity of arterial occlusive disease (as determined by the ankle-brachial pressure index and the European Consensus definition of critical limb ischaemia).
- Type of graft (autologous vein or synthetic); level of distal graft anastomosis (above-knee popliteal, below-knee popliteal, distal arteries). Type of anticoagulant therapy used (dose, commencement of therapy relative to surgery, duration of therapy, patient compliance).
- Outcomes (as mentioned in [Types of outcome measures](#)). Treatment and control groups were compared for important prognostic factors and any differences described. Quality control measures to assess the bypass graft (such as Doppler and

duplex sonography or angiography); the sites of the proximal and distal anastomosis; and the patients risk factors for graft occlusion were recorded.

Assessment of risk of bias in included studies

The authors used the criteria for assessing risk of bias as provided in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2008](#)). We considered the six domains listed below with three possible responses. 'Yes' indicated a low risk of bias, 'no' indicated a high risk of bias, and if insufficient detail was reported the judgement was 'unclear'. We assessed the new studies included in the updated review and we re-assessed the studies already included in the original review.

- Sequence generation
- Allocation concealment
- Blinding
- Incomplete data assessment
- Selective outcome reporting
- Other sources of bias

Assessment of heterogeneity

The I^2 statistic was used to assess the appropriateness of pooling the data. This describes the percentage of the total variation in effect estimates that is due to heterogeneity rather than by chance. Values of I^2 lie between 0% and 100% and can be categorized so that heterogeneity is low when I^2 has a value of 25%, moderate if I^2 has a value of 50%, and high when I^2 has a value of 75%.

Data synthesis

Data were processed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2008](#)) using RevMan 5 software, the Peto method, and a fixed-effect model unless there was substantial heterogeneity, in which case we used a random-effects model and the potential causes of heterogeneity were examined. For dichotomous data the numbers of events in the control and intervention groups of each study were calculated using the Peto odds ratio and 95% confidence interval.

RESULTS

Description of studies

See the [Characteristics of included studies](#) and [Characteristics of excluded studies](#) tables.

Results of the search

For this update 40 potential publications were retrieved from a search of the Peripheral Vascular Diseases Groups Specialised Register and 2700 from searching CENTRAL. These were screened for relevance by reading the titles and abstracts (if available) and full text copies of 21 were obtained and subjected to further evaluation. Of these, 16 were additional publications to studies which had already been included in the previous version of the review.

Included studies

For this update there were 14 eligible studies which investigated the efficacy of anticoagulant treatment in infrainguinal bypass surgery. Three additional studies were included in this update ([Jivegard](#)

2005; Logason 2001; Norgren 2004) and there were 11 studies which had already been included (Arfvidsson 1990; BOA 2000; Cole 1993; Edmondson 1994; Johnson 2002; Kretschmer 1992; Nydahl 1992; Samama 1994; Sarac 1998; Schneider 1979; Swedenborg 1996). A total of 4970 patients were included in the review analysis.

Vitamin K antagonist (VKA) versus no VKA

Four open randomised clinical trials (RCTs) were identified for a comparison of treatment with vitamin K antagonists (VKA) versus no VKA (Arfvidsson 1990; Johnson 2002; Kretschmer 1992; Sarac 1998).

Arfvidsson 1990 included 116 patients suffering from intermittent claudication (IC) or severe arterial insufficiency. Ninety-two patients had critical or severe ischemia (peripheral arterial occlusive disease stages III and IV) and 24 patients suffered from claudication (stage IIb). Nine patients had femorodistal bypass, 25 had femoro-above knee popliteal bypass and 48 had femoro-below knee popliteal bypass. Forty-nine patients had saphenous vein grafts and 33 had polytetrafluoroethylene (PTFE) grafts. Sixty-one patients were assigned to treatment with dicoumarol and 55 patients to no anticoagulation. There were 34 patients who had thromboendarterectomy.

Johnson 2002 included 614 patients with ischaemic symptoms of disabling claudication, rest pain or tissue loss. Of these 207 patients had synthetic bypass grafts and 407 had vein bypass. Distal anastomosis site was above-knee popliteal in 260 patients, below-knee popliteal in 116 and tibial/peroneal in 238. Acetylsalicylic acid (ASA) (325 mg) was started one day preoperatively in both groups plus administration of warfarin (approximately 5 mg/day) in the treatment group on the first or second postoperative day.

Kretschmer 1992 involved a total of 130 patients: 62 with claudication (Fontaine stage II-III) and 68 requiring limb salvage (stage III-IV) underwent bypass procedures. All patients had femoropopliteal vein bypass grafts. Patients were assigned to treatment with coumarin derivatives (phenprocoumon) or no anticoagulation.

Sarac 1998 included 56 patients who underwent a total of 64 vein bypass grafts. There were 61 operations for rest pain or tissue loss, three were for short distance claudication. All these procedures were deemed high risk for occlusion with either a suboptimal venous conduit, poor arterial run-off, or patients were undergoing a re-do procedure. Patients were randomised to warfarin, starting on postoperative days two or three, with a target international normalised ratio (INR) of two to three and aspirin 325 mg/d or only aspirin 325 mg/d postoperatively.

In two of these trials patients received ASA (Johnson 2002; Sarac 1998) while in the other two studies patients did not receive any antiplatelet therapy (Arfvidsson 1990; Kretschmer 1992).

Vitamin K antagonist (VKA) versus acetylsalicylic acid (ASA) or dipyridamol (DIP)

Two RCTs were included comparing the administration of VKA versus ASA or DIP (BOA 2000; Schneider 1979).

BOA 2000 recruited 2690 patients of which 2650 completed the study; 51% of these patients had intermittent claudication and the remainder had pain at rest, ischaemic ulceration or gangrene.

Participants underwent bypass operations from the femoral artery to the above-knee popliteal (1222, 46%), below-knee popliteal (897, 34%), crural (490, 18%) or pedal (41, 2%) arteries. There were 1546 patients (58%) who had vein bypass grafts and the remainder had synthetic grafts. Patients were assigned to coumarin derivatives (phenprocoumon or acenocoumarol) or to aspirin 80 mg daily, started within five days after surgery.

Schneider 1979 included 213 patients, 91 of whom had femoropopliteal bypass using a vein graft and could be included in the review. The remainder had thromboendarterectomy only. Of the included patients 37.3% had Fontaine stage III or IV disease and 61.7% had stage II disease. Patients were allocated to either coumarins or aspirin, or aspirin and dipyridamole.

Unfractionated heparin (UFH) versus low molecular weight heparin (LMWH)

Three RCTs were included which compared UFH to LMWH (Norgren 2004; Samama 1994; Swedenborg 1996).

Norgren 2004 examined 849 patients undergoing vascular surgery for: critical limb ischaemia (464), intermittent claudication (201), abdominal aortic aneurysm (118), other aneurysms (43) or other indications (35). This included 313 patients who underwent femoropopliteal bypass with either autologous or synthetic grafts, who could be included in this review.

Samama 1994 included 199 patients who underwent femorodistal bypass operations. There were 135 patients who had autologous vein grafts, 47 who had PTFE grafts and 17 who had other types of graft.

Swedenborg 1996 included 18 patients who underwent infrainguinal bypass using vein grafts; three patients had intermittent claudication, six had rest pain and nine had ulcers or gangrene.

Low molecular weight heparin (LMWH) versus acetylsalicylic acid and dipyridamol (ASA/DIP)

Edmondson 1994 compared LMWH with ASA/DIP in 200 patients; 107 with IC and 93 patients with CLI. A total of 53 patients had vein grafts with the remainder having PTFE or dacron grafts.

Low molecular weight heparin (LMWH) versus no LMWH

One trial (Jivegard 2005) compared LMWH to placebo in a study population who all received aspirin. The trial included 284 patients who had either supra or infrainguinal bypass operations for lower limb ischaemia. The trialists were contacted and provided data for 229 patients who had infrainguinal bypass surgery.

Heparin versus ancrod

Cole 1993 compared ancrod versus UFH in 28 patients receiving 'high risk' infrainguinal bypass; the patients had distal anastomosis to either blind popliteal segment or a single outflow tibial vessel. Twenty-five patients had vein grafts, two had PTFE grafts and one patient had a composite graft composed of both short saphenous veins.

Heparin versus antithrombin

In Nydahl 1992 12 patients undergoing infrainguinal bypass were randomised to perioperative treatment with UFH or antithrombin.

Heparin versus dextran

In [Logason 2001](#) 314 patients receiving infrainguinal bypass were randomised to receive either dextran 70 or LMWH in the perioperative period. Twenty-eight patients were excluded after randomisation. The indication for surgery was IC in 47, 86 had rest pain, 147 had ulcers or gangrene and six had acute ischaemia. One hundred and forty-nine patients had vein grafts, the remainder had synthetic or composite grafts.

Excluded studies

Thirteen studies were excluded for the reasons given in the [Characteristics of excluded studies](#) table. Two additional studies were excluded in this update ([Kujath 2002](#); [Waibel 1981](#)).

Risk of bias in included studies

The risk of bias for the included trials is summarised in [Figure 1](#) and [Figure 2](#) and in the [Characteristics of included studies](#) table.

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

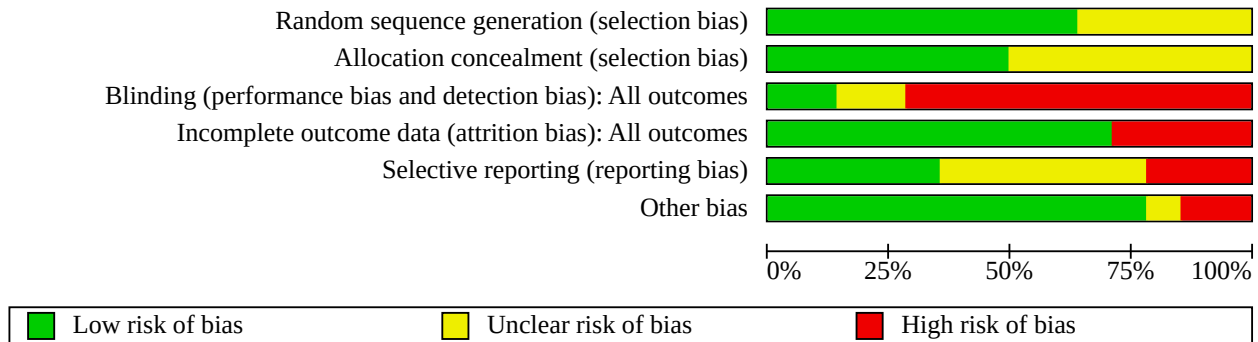


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Arfvidsson 1990	?	+	?	+	?	+
BOA 2000	+	+	-	+	+	+
Cole 1993	+	?	?	-	-	+
Edmondson 1994	+	+	-	+	?	+
Jivegard 2005	+	+	+	+	+	+
Johnson 2002	?	+	-	+	+	+
Kretschmer 1992	+	?	-	+	?	+
Logason 2001	+	+	+	+	+	+
Norgren 2004	+	+	-	-	+	?
Nydahl 1992	?	?	-	+	?	-
Samama 1994	+	?	-	+	?	+
Sarac 1998	+	?	-	-	?	+
Schneider 1979	?	?	-	-	-	+
Swedenborg 1996	?	?	-	+	-	-

Effects of interventions

Vitamin K antagonists (VKA) versus no VKA

(Arfvidsson 1990; Johnson 2002; Kretschmer 1992; Sarac 1998)

The number of events in these four studies were calculated from the survival curves when not otherwise reported.

Primary patency rate

Primary patency rates were analysed at three, six, 12, 24 months, and five years postoperatively comparing anticoagulant with no anticoagulant treatment for all graft types. There was a statistically non-significant positive trend in favour of anticoagulant treatment on primary patency: odds ratio (OR) 0.65 (95% confidence interval (CI) 0.30 to 1.40) at three months (Analysis 1.1); OR 0.54 (95% CI 0.28 to 1.03) at six months (Analysis 1.2); OR 0.70 (95% CI 0.49 to 0.99) at 12 months (Analysis 1.3), OR 0.76 (95% CI 0.56 to 1.05) at 24 months (Analysis 1.4) and OR 0.80 (95% CI 0.61 to 1.07) at five years (Analysis 1.5).

When venous grafts were analysed separately in patients treated with VKA versus control patients, a more positive but non-significant effect for venous grafts was shown: OR 0.44 (95% CI 0.14 to 1.42) at three months (Analysis 4.1); OR 0.40 (95% CI 0.17 to 0.95) at six months (Analysis 4.2); OR 0.75 (95% CI 0.49 to 1.14) at 12 months (Analysis 4.3); OR 0.80 (95% CI 0.55 to 1.17) at 24 months (Analysis 4.4); and OR 1.00 (95% CI 0.71 to 1.40) at five years (Analysis 4.5). There was considerable heterogeneity between the trials as will be discussed later and the results were heavily weighted by the (Johnson 2002) study; but the effect measures did not vary significantly when a random-effects method was used (OR 0.80; 95% CI 0.35 to 1.81). In the (Johnson 2002) study warfarin therapy was withdrawn in most patients with a vein bypass when the data monitoring board found that there was no benefit on patency for vein bypass patients but a probable increase in morbidity.

In contrast, the effect in artificial conduits at the early time points was less pronounced: OR 0.89 (95% CI 0.13 to 5.95) at three months (Analysis 8.1); OR 0.87 (95% CI 0.20 to 3.82) at six months (Analysis 8.2). After 12 months and at later time points the antithrombotic effect seemed to be stronger in preventing bypass failure, with statistical significance after five years: OR 0.59 (95% CI 0.31 to 1.13; fixed) at 12 months; OR 0.72 (95% CI 0.40 to 1.29; fixed) at 24 months; and OR 0.43 (95% CI 0.26 to 0.73) at five years.

Limb salvage

The effect of VKAs on limb salvage was calculated for 139 patients in the treatment group and 129 controls. It should be noted that for seven patients with early occlusion in each group of the Arfvidsson 1990 study no follow-up data were provided. There was a tendency for coumarins to reduce limb loss during the observation time: OR 0.27 (95% CI 0.1 to 0.72) at three months (Analysis 2.1); OR 0.29 (95% CI 0.11 to 0.76) at six months (Analysis 2.2); OR 0.48 (95% CI 0.21 to 1.11) at 12 months (Analysis 2.3); OR 0.50 (95% CI 0.26 to 0.96) at 24 months (Analysis 2.4); and OR 0.36 (95% CI 0.19 to 0.69) at five years (Analysis 2.5). There was considerable heterogeneity (81%) in Analysis 2.5, which may have been due to there being a higher proportion of patients with critical or severe ischaemia in the Arfvidsson 1990 trial.

Survival

For survival, a non-significant trend was observed: OR 0.36 (95% CI 0.10 to 1.31) at six months (Analysis 3.2); OR 0.66 (95% CI 0.38 to 1.15) at 24 months (Analysis 3.4).

Analysis for assisted primary patency, secondary patency, site of distal anastomosis, and bleeding complications in the different patient groups could not be performed due to inaccessible raw data.

Overall, the effect of coumarins on patency, limb salvage, and survival was similar in the two trials (Arfvidsson 1990; Kretschmer 1992) in which patients did not receive aspirin. In the Sarac trial (Sarac 1998) all patients received aspirin and only venous grafts were used. In this cohort a similar effect was seen on primary patency as in the patients with a venous graft, who did not receive aspirin in the two other trials (Arfvidsson 1990; Kretschmer 1992). In addition, similar odds ratios for limb salvage and survival were observed.

Side effects

Bleeding complications requiring hospitalisation occurred in eight patients in the treatment group and in none in the control group in. One patient in the treatment group in Kretschmer 1992 had a lethal bleeding complication. In Sarac 1998 four (12.5%) patients in the treatment group required operative evacuation of wound haematoma compared with only one (4.2%) in the control group. Furthermore, in the VKA and ASA group one patient had gastrointestinal bleeding compared with three patients in the ASA group; one case in each group was reported with a bleeding event of the central nervous system, while three patients suffered from genitourinary bleeding in the VKA and ASA group compared with none in the control group.

Vitamin K antagonist (VKA) versus acetylsalicylic acid and dipyridamole (ASA/DIP)

(BOA 2000; Schneider 1979)

Primary graft patency

Primary graft patency for all grafts, including 1356 patients in the VKA group and 1385 in the ASA group, at three, six, 12, and 24 months postoperatively showed almost no difference for VKA versus ASA (OR 0.89; 95% CI 0.69 to 1.15 (Analysis 11.1); OR 0.99; 95% CI 0.81 to 1.22 (Analysis 11.2); OR 0.92; 95% CI 0.77 to 1.11 (Analysis 11.3); OR 0.91; 95% CI 0.77 to 1.08 (Analysis 11.4) respectively).

Intention-to-treat analysis for venous grafts included 814 patients randomised to VKA treatment versus 823 to ASA. Vitamin K antagonists had a statistically significant favourable effect on patency rates compared with antiplatelet treatment either with ASA alone or with a combination of ASA and DIP (OR 0.66; 95% CI 0.46 to 0.93 at three months (Analysis 12.1); OR 0.71; 95% CI 0.53 to 0.95 at six months (Analysis 12.2); OR 0.65; 95% CI 0.49 to 0.85 at 12 months (Analysis 12.3); OR 0.59; 95% CI 0.46 to 0.76 at 24 months (Analysis 12.4)). For patients treated with an artificial conduit, a group that had been analysed only by the BOA trialists (BOA 2000) (542 in the VKA group versus 562 in the ASA group), no statistically significant positive effect was found for VKAs (OR 1.32; 95% CI 0.89 to 1.95 at three months (Analysis 13.1); OR 1.47; 95% CI 1.08 to 1.99 at six months (Analysis 13.2); OR 1.33; 95% CI 1.02 to 1.74 at 12 months

(Analysis 13.3); OR 1.41; 95% CI 1.11 to 1.80 at 24 months (Analysis 13.4)).

No distinct data were reported for assisted primary patency or secondary patency rates.

Limb salvage and survival

Neither of the trials reported data on limb salvage or survival that were suitable for a formal meta-analysis. However, in the BOA trial (BOA 2000) limb amputation had to be performed in 100 (7.5%) coumarin-treated patients and 110 (8.3%) aspirin-treated patients.

Side effects

In the BOA 2000 trial, haemorrhage requiring hospital admittance was reported for 119 (9%) patients in the VKA group and 59 (4.5%) patients in the ASA group. Sixteen (1.2%) patients died from fatal bleeding in the VKA group compared with 12 (0.9%) patients in the ASA group. In the Schneider 1979 trial, adverse effects were reported for two patients (0.6%), who stopped VKA treatment for bleeding complications, and 13 patients (21%) who stopped ASA for varying reasons. Three patients in each group died within two years.

Unfractionated heparin (UFH) versus low molecular weight heparin (LMWH)

(Norgren 2004; Samama 1994; Swedenborg 1996)

Primary early graft patency

In the Norgren 2004 trial, analysis performed at 24 hours showed seven of 176 (3.9%) versus four of 137 (2.9%) occlusions in each group, which was a statistically insignificant difference (OR 1.38; 95% CI 0.39 to 4.8) (Analysis 14.1). This difference remained insignificant at 30 days with 18 of 174 (10.3%) versus 19 of 134 (14.2%) occlusions (OR 0.7; 95% CI 0.35 to 1.39) (Analysis 14.3).

An intention-to-treat analysis performed by Samama 1994 yielded eight of 99 (7.9%) versus 22 of 100 (22%) occlusions on day 10 (OR 0.34; 95% CI 0.16 to 0.74) (Analysis 14.2) and 11 of 99 (10.9%) versus 24 of 100 (24%) on day 30 (OR 0.41; 95% CI 0.20 to 0.85; fixed) (Analysis 14.3) showing a statistically significant positive effect for LMWH. In addition, a separate intra-protocol analysis was performed comparing 67 grafts in the LMWH group with 64 grafts in the UFH group. Early graft thrombosis within 10 days occurred in four and eight cases, for LMWH or UFH respectively; a difference that did not reach statistical significance.

In the Swedenborg 1996 trial early graft occlusion occurred in two cases in each group. No time points were included and so the data could not be included in the meta-analysis.

Combined analysis of the Norgren 2004 and Samama 1994 trials regarding primary graft patency showed an OR of 0.54 (95% CI 0.33 to 0.90; fixed) for day 30, marginally favouring LMWH versus UFH for early graft thrombosis.

Low molecular weight heparin (LMWH) versus acetylsalicylic acid and dipyridamol (ASA/DIP)

(Edmondson 1994)

Primary patency

In the 94 patients randomised to LMWH and the 106 patients to ASA/DIP, there were 12 versus 30 occlusions at six months (OR 0.39;

95% CI 0.20 to 0.78) (Analysis 15.1) and 21 versus 38 occlusions at 12 months (OR 0.52; 95% CI 0.29 to 0.96) (Analysis 15.2), showing a significant positive effect for LMWH. Further subgroup analysis found that this positive effect was only significant in patients undergoing operations for limb salvage and not in patients having operations for claudication.

Nine patients in the LMWH group (four with patent grafts) and two in the aspirin group died during follow up. No major bleeding or adverse events occurred.

Low molecular weight heparin (LMWH) versus no LMWH

(Jivegard 2005)

Of the 229 patients with infrainguinal bypasses 116 were randomised to receive LMWH, 113 received placebos, and all received aspirin. At one month there were eight versus 11 occlusions (OR 0.69; 95% CI 0.27 to 1.78) (Analysis 16.1); at three months there were 20 versus 25 occlusions (OR 0.75; 95% CI 0.39 to 1.44) (Analysis 16.2); and at 12 months 44 versus 46 occlusions (OR 0.97; 95% CI 0.56 to 1.69) (Analysis 16.3); and therefore no statistically significant difference between groups at each time point.

Heparin versus anicrod

(Cole 1993)

Among the 14 patients randomised to either heparin or anicrod, one graft in each group occluded within 24 hours postoperatively. One patient suffered from postoperative bleeding and graft failure in the anicrod group. No further events occurred during one month follow up. Primary patency at one month was 12/13 and 13/14 with an OR of 1.08 (95% CI 0.06 to 18.18; fixed). Anicrod was equally efficient as UFH. No data on limb salvage, survival, or primary assisted patency were reported.

Heparin versus antithrombin (AT)

(Nydahl 1992)

In five out of six patients in the AT group graft thrombosis occurred intraoperatively, whereas no occlusion occurred in the heparin group. The study was stopped before completion. One patient in the heparin group suffered from major bleeding; and one patient in the heparin group died from myocardial infarction on the second postoperative day.

Heparin versus dextran

(Logason 2001)

In 314 patients randomised to receive either Dextran 70 or enoxaparin in the perioperative period for femorodistal bypass, there were no significant differences in graft patency rates at days one, five to seven, 30, and at three months. However, there was a significant increase in the number of patients developing heart failure in the dextran group (12.8% versus 0.7%, $P < 0.001$).

DISCUSSION

Summary of main results

Differences in patency between venous and artificial grafts have been apparent for many years, with artificial grafts having a higher rate of occlusion than their venous counterparts (Abbott 1997; Achermann 1998; Parsons 1996). This review demonstrates

that antithrombotic drug treatments also vary in their effects on patency depending on the type of graft used. The initial pooled analyses ([Analysis 1.1](#) to [Analysis 1.3](#)) would suggest that all patients undergoing infrainguinal bypass surgery might benefit from VKA in terms of patency rates, limb salvage and survival at three, six, 12 and 24 months regardless of graft type (although the effect does not reach statistical significance for graft occlusion or survival). However, since graft type has a major influence on patency the effects of antithrombotic treatments on venous and artificial grafts must be considered separately.

For venous grafts, meta-analysis suggests that VKA may have a positive effect on patency compared to no VKA ([Analysis 4.1](#) to [Analysis 4.5](#)), however at no point did this result reach statistical significance. In fact of the four included trials ([Arfvidsson 1990](#); [Johnson 2002](#); [Kretschmer 1992](#); [Sarac 1998](#)) only ([Kretschmer 1992](#)) found a statistically significant result in favour of VKA, at 12 and 24 months and at five years. The remaining trials failed to reach statistical significance at any point and the results were heavily weighted by the [Johnson 2002](#) trial. The [Johnson 2002](#) trial appeared to favour no VKA but this result again failed to reach statistical significance; the trialists concluded that there was no difference in the patency of in venous grafts between patients receiving VKA and no VKA. In this study warfarin therapy was withdrawn in most patients with a vein bypass when the data monitoring board found that there was no benefit on patency for vein bypass patients but a probable increase in morbidity. Similar trends were seen for limb loss, limb salvage and death in patients with venous bypasses receiving VKA. It is worth noting that there was considerable heterogeneity between the included trials. In [Sarac 1998](#) and [Johnson 2002](#) all patients received aspirin, but not in [Arfvidsson 1990](#) or [Kretschmer 1992](#). In addition anticoagulation levels were variable and measured differently, and indications for surgery (intermittent claudication versus critical limb ischaemia) varied between trials.

A further meta-analysis demonstrated that VKA has a positive effect on patency compared to ASA and DIP for up to 24 months in patients receiving venous grafts (OR 0.59; 95% CI 0.46 to 0.76) ([Analysis 12.4](#)).

For artificial grafts only two trials compared VKA to no VKA ([Arfvidsson 1990](#); [Johnson 2002](#)) and the meta-analysis was heavily weighted by the [Johnson 2002](#) trial. The data showed no significant difference in patency at three, six, 12 or 24 months. There was however an apparent improvement in patency with VKA at five years (OR 0.43; 95% CI 0.26 to 0.73) ([Analysis 8.5](#)). In the [Johnson 2002](#) trial, patency rates varied between 6 mm and 8 mm bypass subgroups and there was a significant difference in patency in the 6 mm group, 71.4% in the warfarin plus aspirin group compared with 57.9% in the aspirin group. No significant differences in limb loss or death were identified.

Comparison of VKA to ASA and DIP in artificial grafts showed a significant beneficial effect on patency with ASA and DIP at six, 12 and 24 months ([Analysis 13.1](#) to [Analysis 13.4](#)).

Comparing rates of bleeding complications associated with anticoagulation was generally difficult due to differences in reporting. However, VKA was seen to be associated with a higher rate of bleeding complications compared to both no VKA and aspirin ([Arfvidsson 1990](#); [BOA 2000](#); [Kretschmer 1992](#); [Sarac 1998](#)). Both [Arfvidsson 1990](#) and [BOA 2000](#) estimated a major bleeding complication rate of approximately 4% to 5%; this

compares to a rate of 2.5% with aspirin in [BOA 2000](#). The rate of wound haematoma also appears significantly increased with VKA compared with aspirin ([Sarac 1998](#)). Inter-study differences in the therapeutic ranges of anticoagulation clearly have implications on the rate of haemorrhagic complications.

Generally, it should be noted that comparison between the different studies was hampered by the fact that the target international normalised ratio (INR) differed between trials; the ([BOA 2000](#)) trialists aimed at 3.0 to 4.5 whereas the investigators of the [Johnson 2002](#) trial aimed at a value of 1.4 to 2.8. In other studies, a Quick value was used instead of the INR, making direct comparison almost impossible.

The effect of LMWH and UFH on early patency was evaluated in three trials that included a total of 509 patients. Results were largely inconclusive with only one trial ([Samama 1994](#)) showing a positive effect for LMWH above UFH when comparing graft occlusion at day 10 and day 30. Neither [Norgren 2004](#) nor [Swedenborg 1996](#) showed any significant difference. Additionally a per protocol analysis of the [Samama 1994](#) data failed to demonstrate significance. Pooled intention-to-treat data at day 30 did show a marginally positive effect for LMWH over UFH but a much larger cohort of patients receiving venous and artificial bypasses would have to be evaluated for reliable comparison in the future.

One trial comparing LMWH versus ASA and DIP ([Edmondson 1994](#)) found improved graft patency for the LMWH group at six and 12 months but this advantage was only in patients undergoing surgery for limb salvage and not for claudication. Of note, only a quarter of the patients in the study had vein grafts. A larger study is required both to confirm this result and to allow for subgroup analysis comparing graft type.

Overall completeness and applicability of evidence

The evidence for VKA in venous bypasses is weak and at times inconsistent. VKA does appear to be more favourable than antiplatelet therapy in terms of graft patency but there may be an increase in bleeding complications. The evidence for antiplatelet drugs in artificial bypasses is much more consistent and reliable. In order to support these findings and to rule out any divergencies, further large trials with homogeneous, precisely reported patient characteristics of the study participants and study designs are needed. It should be mentioned that extracting data from the included trials was difficult as most publications did not provide raw data, which is ideally needed for an appropriate analysis. Contacting the authors was usually not very successful, either because raw data were no longer available or authors did not reply. Therefore, the numbers of patients and events had to be calculated from the survival curves.

Agreements and disagreements with other studies or reviews

Despite the heterogeneity of the included studies, our findings show a tendency towards agreement between the different trials, which is also biologically plausible. Venous and prosthetic grafts appear to have varying mechanisms of failure. Venous grafts, once they have been incorporated into the high pressure system in the human leg, lose their endothelial layer within days ([Sasaki 2000](#)). Exposure of the subendothelial layers to the blood stream triggers the expression and release of tissue factor ([Channon](#)

1997; Muluk 1998), one of the activators of the coagulation cascade. This process results in locally increased thrombin generation with subsequent thrombus formation that is enhanced by a simultaneous inflammatory process through the release of interleukins (interleukin-1b, interleukin-6, tumour necrosis factor), which attract and activate granulocytes and monocytes. The latter are able to express additional tissue factor, thus enhancing the local thrombogenic process. Vein grafts undergo an active remodelling process over several months following arterialisation, with increases in wall thickness and stiffness and changes to the luminal diameter (Jacot 2004). Venous grafts fail after developing stenosis either at or around anastomotic sites or at points along their length. It is postulated that it is the combination of venous remodeling and intimal hyperplasia (IH) that leads to luminal narrowing and subsequent failure in venous grafts (Owens 2010). Although activated platelets play an important role in thrombus formation and IH, it seems that the activated coagulation system at the graft site of endothelial injury also has a role and thrombin inhibition with VKA may therefore have some benefit. On the other hand, inhibition of platelet deposition on prosthetic grafts might be the more efficient therapy for patients with PTFE and dacron bypasses. IH at the distal anastomosis appears to be the principal cause of prosthetic graft failure. Compliance mismatch between the synthetic graft and the native artery results in altered wall stress and endothelial damage around the anastomosis. Areas of IH develop, particularly at the heel and toe of the anastomosis and on the floor of the recipient artery. Introduction of a vein cuff at the anastomosis reduces the IH response (Kissin 2000) and it is postulated this may be due to a reduction in compliance mismatch (Sarkar 2006). A key step in the initiation of IH is the adherence and aggregation of platelets to the injured endothelium; it may be that this is the main therapeutic target in preventing prosthetic bypass graft failure, where IH has a dominant role. The recently reported CASPAR trial (CASPAR 2010) combined antiplatelet therapy with clopidogrel and aspirin versus aspirin alone and showed significant improvement in graft patency in prosthetic grafts (hazard ratio (HR) 0.65; 95% CI 0.45 to 0.95) but not venous grafts (HR 1.25; 95% CI 0.94 to 1.67), which would seem to support this argument.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence suggests that patients subjected to infrainguinal venous graft surgery are more likely to benefit from VKA than

platelet inhibitors. Patients receiving an artificial graft usually benefit from platelet inhibitors (aspirin).

Implications for research

Evidence-based results suggest VKA may be of more benefit in venous bypasses. The evidence for antiplatelets in prosthetic grafts is stronger and more consistent. Large randomised controlled trials are required to further evaluate the effects of VKA on venous bypasses and to determine the optimal dose (INR value aimed at) and length of treatment. Additionally, the effect of LMWH compared with UFH in perioperative treatment should be evaluated in larger RCTs that include a subgroup analysis of venous and artificial grafts. In view of the new available antithrombotic agents, such as direct thrombin inhibitors (for example dabigatran) or the factor Xa inhibitors (rivaroxaban and apixaban), many new trials should investigate the efficacy and safety of these agents for bypass patency, limb salvage, and survival. At present graft patency is variably assessed between trials (including clinically, the ankle-brachial pressure index, duplex scanning, angiography) and it would be useful to reach a consensus as to how this should be defined, including the degree of stenosis that may indicate a failing graft that requires intervention. This would allow improved comparison between trials. Furthermore, presentation of data should be much more 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 of follow up. Thus, the reader would be enabled 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-knee and below-knee anastomosis, and inflow and outflow conditions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arfvidsson 1990

Study characteristics

Arfvidsson 1990 (Continued)

Methods	An open, randomised clinical trial with patients undergoing infrainguinal revascularisation.
Participants	116 patients suffering from IC or severe arterial insufficiency were included in the study. 92 patients (79%) had critical or severe ischemia (PAOD stages III and IV) and 24 patients suffered from (21%) claudication (stage IIb). There was no significant difference between the treatment and the control group concerning age (71 ± 1 vs 73 ± 1 years), sex (37 m/24 f vs 36 m/19 f), duration of symptoms (26 ± 4 vs 25 ± 4 months), diabetes mellitus (15 vs 15 patients), stage of the disease (46 vs 46 patients with CLI), smoking (35 vs 29 patients), or type of reconstruction (27 vs 22 saphenous vein and 14 vs 19 PTFE grafts). Patients undergoing thrombendarterectomy were excluded from the analysis (20 vs 14).
Interventions	61 patients were assigned to treatment with dicoumarol. 55 patients no anticoagulation. All patients received 10 to 20,000 IU/24 hours iv heparin pre and postoperatively for three to five days. Dicoumarol was started within two days postoperatively; aimed for simplastin levels of 10% to 20%.
Outcomes	Graft occlusion, limb loss and death were primary endpoints at one, two, three, four, five, six, nine, and 12 months, thereafter every 12 months. Assessment of graft patency was performed by Doppler flow measurement and arteriography when in doubt. Bleeding complications requiring hospitalisation were recorded.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Low risk	Patients were randomly allocated to the two different treatment groups by a person not involved in the decision about the admission or non-admission of the patients into the study.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seven patients with occlusions within 2 weeks were excluded in each group, no patients lost to follow up.
Selective reporting (reporting bias)	Unclear risk	No explicit statement on primary/secondary outcomes of study, however there are no obvious omissions.
Other bias	Low risk	Appears to be free of other sources of bias

BOA 2000
Study characteristics

Methods	An open, randomised, multicentre clinical trial of patients undergoing infrainguinal bypass surgery.
Participants	2690 patients undergoing infrainguinal venous or artificial bypass surgery were included. Baseline characteristics did not differ significantly between comparison groups regarding age (69 ± 10 vs 69 ± 10

Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery (Review)

BOA 2000 (Continued)

years), sex (65 vs 63% male), stage of the disease (50% vs 52% claudicants), site of the distal anastomosis (45% vs 48% popliteal above knee, 36% vs 32% popliteal below knee, 18% vs 19% crural, 2% vs 1% pedal), graft material (59% vs 58% vein), and preoperative antithrombotic medication (63% vs 65%). There were 54% smokers, 39% with hypertension, 26% with diabetes mellitus, and 16% with hyperlipidemia in both groups.

Interventions	1339 were assigned to coumarin derivatives (phenprocoumon or acenocoumarol). 1351 to aspirin 80 mg daily, started within five days after surgery. The intended INR range was 3.0 to 4.5, which was achieved in 50% of the observed patient years.
Outcomes	Primary endpoint was graft patency assessed clinically by Doppler flow measurement or duplex sonography or by arteriography if indicated. Secondary endpoints were vascular death, myocardial infarction, stroke, amputation, vascular intervention, and major haemorrhage. Follow up was at three, six, 12, 18, and 24 months, with six monthly visits thereafter. Mean observation time was 21 months.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated blocked sequences of numbers based on different block lengths, stratified by centre.
Allocation concealment (selection bias)	Low risk	Randomisation by telephone at remote location.
Blinding (performance bias and detection bias) All outcomes	High risk	'To avoid the ethical and practical difficulties of sham monitoring of blood coagulation in the aspirin group, treatment assignment was open.' However, those adjudicating/classifying adverse events were 'unaware of treatment status.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small numbers of withdrawals, unlikely to influence result. '13 patients assigned oral anticoagulants were excluded after randomisation because they refused participation (6), did not undergo bypass surgery (3), or were already randomised (4). 27 patients assigned aspirin were withdrawn because they refused participation (7), did not have bypass surgery (17), or were already randomised (3).'
Selective reporting (reporting bias)	Low risk	Planned outcomes discussed, adverse events discussed.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Cole 1993

Study characteristics

Methods	A randomised, open, single centre clinical trial of patients undergoing infrainguinal bypass surgery.
Participants	28 patients considered as 'high risk' for infrainguinal bypass grafting to either the blind popliteal segment or to a single outflow tibial vessel, were assigned to heparin treatment (n = 14; 13 venous bypasses and one PTFE graft) or to treatment with anicrod (n = 14; 12 venous, one PTFE, one composite graft).

Cole 1993 (Continued)

Patient characteristics were not further specified regarding age, sex, diabetes mellitus, arterial hypertension, hyperlipidemia, or smoking.

Interventions	Heparin was administered intravenously during operation at a dose of 100 IU/kg. Ancrod was administered before operation for 12 hours at a dose of 70 IU, until fibrinogen levels were stabilised between 0.2 to 0.5 mg/L. Ancrod was continued postoperatively for 48 hours.
Outcomes	Primary outcomes were fibrinogen depletion and early graft patency. Graft patency was determined clinically by ABI and Doppler flow measurement before hospital discharge and one month postoperatively.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation - generated by Rannor Call routine on Statistical Analysis System (SAS Institute Inc, Cary, NC).
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed but seems unlikely given nature of intervention. Unclear if those assessing patency were blind to treatment group.
Incomplete outcome data (attrition bias) All outcomes	High risk	'One patient in the ancrod group withdrew from the study when surgery had to be delayed because the fibrinogen was found to be less than 0.2gm/L; the prothrombin time indicated that fibrinogen was completely absent and that surgery should be postponed until it was restored to the desired level. This patient was therefore removed from the study and from further analysis.' This is a potentially important side effect of ancrod treatment in a small sample size; exclusion may introduce bias.
Selective reporting (reporting bias)	High risk	No explicit statement on primary or secondary outcomes, no detailed analysis of adverse events.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Edmondson 1994
Study characteristics

Methods	An open, randomised, multicentre clinical trial in patients undergoing femoropopliteal bypass grafting.
Participants	Patients with angiographically proven peripheral vascular disease undergoing venous or prosthetic femoropopliteal bypass surgery were included. Comparison groups were separated for patients with IC (n = 53 receiving LMWH, n = 54 ASA/DIP) and patients suffering from CLI (n = 41 and n = 52, respectively). Basic characteristics did not differ significantly between comparison groups such as age (66.8 vs 68.4 years), sex (65% vs 70% male), smoking (29% vs 31%), diabetes mellitus (15% vs 20%), and hyperlipidemia (5% vs 7%). There were 51% vs 56% claudicants in both groups, respectively. Approximately 20% of the patients had one patent run-off vessel in both groups, 25% - 30% had two patent vessels, and 50% had three patent run-off vessels. The distal anastomosis was located above knee in 68% vs 69% and

Edmondson 1994 (Continued)

below knee in 28% vs 27% of the patients. There were 29% vs 25% vein grafts in the two comparison groups.

Interventions	94 patients were randomised to receive 2500 IU LMWH (Fragmin) sc once daily. 106 patients to receive 300 mg aspirin and 100 mg dipyridamole, both three times per day for three months.
Outcomes	On the seventh postoperative day patients were assessed for primary graft occlusion, wound infection, thrombectomy, bleeding, and death. Total follow up was one year with visits at one, three, six, and 12 months. Graft patency was evaluated clinically and by ABI, and if indicated, supplemented by arteriography or duplex sonography.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Computer generated random numbers.'
Allocation concealment (selection bias)	Low risk	'Central telephone randomisation.'
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	'3 on low molecular weight heparin and 2 on aspirin & dipyridymole were lost to follow up.' Similar numbers between 2 groups, unlikely to introduce bias.
Selective reporting (reporting bias)	Unclear risk	No explicit statement on primary/secondary outcomes, however there are no obvious admissions.
Other bias	Low risk	Appears to be free of other sources of bias.

Jivegard 2005
Study characteristics

Methods	Multicentre, placebo controlled, randomised, double blind study of patients with lower limb ischaemia undergoing bypass surgery. Randomisation took place 1-5 days postsurgery.
Participants	284 patients with lower limb ischaemia secondary to peripheral arterial disease with symptoms lasting more than 2 weeks who underwent a bypass procedure were randomised. Characteristics between each group were similar; including re-operation before randomisation (7% vs 6%), female sex (45% in each), present smoker (31% vs 30%), malignancy (2% vs 1%), diabetes (37% vs 36%) and age (73 vs 74 years).
Interventions	141 patients (116 of whom had infrainguinal bypasses) were randomised to receive 5000 iu dalteparin by a subcutaneous injection of 0.2mls once daily for 3 months. 140 patients (113 of whom had infrainguinal bypasses) received a 0.2ml placebo injection for 3 months.

Jivegard 2005 (Continued)

All patients received aspirin.

Outcomes	Primary objective was primary graft patency at three and 12 months postoperatively. Graft was considered patent if fulfilled one of eight specific criteria which defined standards for combinations of pulse palpation, doppler assessment, ankle-brachial pressure index and intraoperative or autopsy findings. Secondary outcomes were healing of ischaemic ulcers and degree of rest pain in operated leg, acceptability of self injections after bypass grafting for lower limb ischaemia, incidence of other vascular events and death.
Notes	Published data includes patients receiving both supra and infrainguinal bypass procedures analysed together. Communication with authors provided patency data for infrainguinal bypasses separately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using a computer algorithm method, taking into account 17 different parameters believed to be potential relevance for the patency of peripheral arterial bypass grafts.
Allocation concealment (selection bias)	Low risk	Randomisation at remote location via fax.
Blinding (performance bias and detection bias) All outcomes	Low risk	All patients, investigators, and study teams blind to intervention until all statistical analysis performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small number of withdrawals, unlikely to introduce bias. '2 patients withdrawn early after randomisation. One further patient with an occluded bypass by the time of randomisation also excluded.'
Selective reporting (reporting bias)	Low risk	Planned outcomes discussed, adverse events discussed.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Johnson 2002
Study characteristics

Methods	An open, randomised multicentre clinical trial in patients with PAD scheduled for elective axillofemoral, femoral-femoral, femoropopliteal or femorodistal bypass surgery. Randomisation was between 1 October 1991 and 30 September 1995.
Participants	A total of 614 patients with either IC or CLI (rest pain and/or tissue loss) undergoing either femoropopliteal above or below knee, or femorocrural prosthetic or venous bypass surgery were included. Those receiving axillofemoral, femoro-femoral or femoropedal bypasses were excluded from comparison in this analysis. Patient characteristics included diabetes (85% to 91%), cholesterol levels (187 to 203 mg/dL), hypertension (85% to 91%), prior stroke (16.6% to 17.8%), prior myocardial infarction (18.6% to 30.0%).
Interventions	325 mg ASA was started one day preoperatively in both groups plus administration of warfarin approximately 5 mg/day in the treatment group on the first or second postoperative day. The low dose target INR was 1.4 to 2.8.

Johnson 2002 (Continued)

Outcomes	Assisted primary graft occlusion, above- or below-knee amputation, and death were clinical endpoints. Monthly monitoring of the INR was performed in the warfarin group. Follow-up visits were every three months to assess bypass patency by ABI measurement and duplexsonography scanning if necessary.
Notes	Randomisation was on the first postoperative day following stratification to prosthetic or venous graft material. Completion of randomisation was performed by a telephone call to the study coordinating center. Patency rates reported in this study were assisted primary patency rates, because bypass revision was permitted for bypasses identified as patient but stenotic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Low risk	Allocated via telephone at remote location.
Blinding (performance bias and detection bias) All outcomes	High risk	'Nonmasked clinical trial'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 patients were lost to follow up - 9 patients on warfarin + aspirin, 5 patients on aspirin alone. Comparable between two groups, unlikely to introduce bias given large sample size.
Selective reporting (reporting bias)	Low risk	Planned outcomes discussed, adverse events discussed.
Other bias	Low risk	Appears to be free of other sources of bias.

Kretschmer 1992

Study characteristics

Methods	An open, randomised, single centre clinical trial of patients receiving femoropopliteal reversed vein grafts.
Participants	130 patients receiving an elective femoropopliteal venous bypass were assigned to treatment with coumarins or to no anticoagulant nor antiplatelet treatment. Patient characteristics such as sex (79% vs 78% male), age (62.5 vs 62.3 years), diabetes mellitus (35% vs 36%), arterial hypertension (27% vs 27%), stage of the disease (49% vs 53% claudicants), distal anastomotic site (42% vs 43% above knee), and poor run-off with 0 to 1 patent vessel (80% vs 77%) did not differ significantly in the two comparison groups.
Interventions	Patients were assigned to treatment with coumarin-derivatives (phenprocoumon) or to no anticoagulation. Phenprocoumon was started in the second postoperative week until death or graft occlusion. Anticoagulant treatment was aimed at 15% to 25% for Quick values, 10% to 20% for Hepatoquick, or 5% to 12% for Thrombotest.
Outcomes	Primary endpoints were graft occlusion, limb loss, and death. Graft patency assessment was performed by evaluation of pulsatile Doppler flow and ABI, which prompted an angiography at an ABI-fall of 30%. Successfully treated stenoses were considered as patent bypasses. Follow-up visits were at three-monthly intervals during the first year and six-monthly thereafter for 10 years.

Kretschmer 1992 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned to the two treatment groups by adaptive randomisation allowing optimum balancing of prognostic factors between groups according to Pocock (see Additional references).
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Reviewers were not blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow up.
Selective reporting (reporting bias)	Unclear risk	Stated primary outcomes discussed, adverse events discussed in limited detail. No obvious admissions.
Other bias	Low risk	Appears to be free of other sources of bias.

Logason 2001
Study characteristics

Methods	An open, randomised, multicentre clinical trial of patients undergoing femorodistal bypass.
Participants	314 patients from 16 centres undergoing femoro-distal bypass were randomised to receive either dextran or LMWH in the perioperative period. Patient characteristics such as age (74 vs 73 years), diabetes (32% vs 37%), hypertension (46% vs 34%), cardiac problems (42% vs 46%), pulmonary problems (10% vs 8%) smoking (49% vs 46%), indication for surgery (acute ischaemia 1% vs 3%, intermittent claudication 15% vs 18%, rest pain 34% vs 26%, ulcer or gangrene 50% vs 53%) and type of graft (54% vs 50% vein) were similar between the two groups. 28 patients were excluded postrandomisation.
Interventions	<p>Patients were assigned treatment with dextran or LMWH in the perioperative period.</p> <p>The dextran group received a total dose of 2500mls Dextran 70; 500mls at anaesthetic induction and again immediately post-operatively and a further 500mls on the morning of post-operative days one, two and three. These patients received 5000 iu heparin at cross-clamping.</p> <p>The LMWH group received 40mg enoxaparin sc the day before surgery and every evening for seven days postoperatively. At cross clamping this group received 20mg enoxaparin iv.</p>
Outcomes	Graft patency was assessed at day one, days five to seven, day 30 and three months. Patency was determined using pulse palpation, ABPI and clinical judgement. Duplex scanning and angiography were used for cases of uncertainty. Patency was assessed blindly. Groups were also compared for blood loss, transfusion rates, and complications such as allergy, haemorrhage, myocardial infarction, heart failure and death. Haemoglobin, platelet count, serum creatinine and APTT were compared at days five to seven.

Notes

Logason 2001 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random list.
Allocation concealment (selection bias)	Low risk	Randomisation occurred separately at each participating centre with sequentially numbered sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	'For practical reasons the study was not blind, but the surgeon assessing patency was blinded to the group.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total of 28 patients excluded after randomisation; five from each group had anticoagulation before or after surgery, five had improper randomisation (two from dextran group, three from enoxaparin group), five did not have the planned operation performed (three from the dextran group, two from the enoxaparin group), five had the incorrect treatment (one from the dextran group, four from the enoxaparin treatment) and three had a creatinine of >200µmol/l (one from the dextran group, two from the enoxaparin group). Exclusions are generally comparable between each group. Missing data for eight patients when comparing graft patency at three months.
Selective reporting (reporting bias)	Low risk	All planned outcomes discussed, no omissions apparent.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Norgren 2004
Study characteristics

Methods	An open, multicentre (20 centres), randomised trial of 849 patients undergoing vascular surgery between November 2000 and December 2002.
Participants	Inclusion criteria: patients undergoing surgery for critical limb ischemia (464), intermittent claudication (201), abdominal aortic aneurysm (118), other aneurysm (43), other indication (35). This included 313 patients who underwent femoropopliteal bypass with either autologous or synthetic grafts who could be included in this Cochrane review. Exclusion criteria: carotid surgery Age: 40-96 years (median, 74 years) Sex: 507 men, 342 women.
Interventions	40mg of enoxaparin iv immediately before arterial clamping with a corresponding heparin solution used to irrigate the vessels locally. 5000 IU UFH iv intraoperatively immediately before arterial clamping with a corresponding heparin solution used to irrigate the vessels locally. Preoperative use of other antithrombotics aspirin, LMWH, UFH, clopidogrel, dextran was similar in both groups.

Norgren 2004 (Continued)

Postoperative treatment was given at the discretion of the individual hospital, mostly aspirin 75 mg/d or 160 mg/d but dextran or LMWH was allowed.

313 patients underwent femoropopliteal reconstructions 176 received LMWH and 137 received UFH.

Outcomes Patency of arterial reconstruction at days 1 and 30 was recorded as was perioperative blood loss and protamine use to stop bleeding.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of 20 patients per hospital.
Allocation concealment (selection bias)	Low risk	'Sealed envelope principle.'
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	23 patients died and that 9 were not followed up 'for other reasons' but no information regarding which groups they belonged to or reasons for dropouts.
Selective reporting (reporting bias)	Low risk	Stated primary outcomes discussed, adverse events discussed, no obvious admissions.
Other bias	Unclear risk	Pharmaceutical company supported trial.

Nydahl 1992
Study characteristics

Methods	An open, randomised clinical trial in patients undergoing infrainguinal bypass surgery.
Participants	13 patients admitted for infrainguinal bypass surgery were assigned to the two treatment groups. Mean age was 62 vs 74 years in the heparin and antithrombin group, respectively, while 71% vs 83% suffered from claudication. All patients but one had below-knee popliteal distal anastomosis, 57% vs 50% had diabetes mellitus. The number of smokers was higher in the antithrombin group (14% vs 50%).
Interventions	Seven patients were randomised to perioperative treatment with a single intravenous dose of 5000 IU UFH. Six patients to treatment with 1500 IU antithrombin into the femoral artery.
Outcomes	Patency assessment of the graft was performed by ABI evaluation and Doppler flow measurement one month after surgery.
Notes	The study was planned to include 20 patients, but was stopped after inclusion of 13 patients, because all patients receiving antithrombin presented intraoperative graft thrombosis. Randomisation procedure was not specified.

Nydahl 1992 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or withdrawals postrandomisation apparent.
Selective reporting (reporting bias)	Unclear risk	Stated outcomes and adverse events discussed.
Other bias	High risk	Small sample size - the study was planned to include 20 patients, but was stopped after inclusion of 13 patients because all patients receiving antithrombin developed intraoperative graft thrombosis.

Samama 1994
Study characteristics

Methods	An open, randomised multicentre study conducted between 1990 and 1992 in patients undergoing elective femorodistal reconstructive surgery.
Participants	All patients scheduled for femorodistal reconstructive surgery under general anesthesia were eligible for the study. Patient characteristics such as age (72.4 vs 71.4 years), sex (2.3 vs. 2.0 m/f ratio), BMI (24.7 vs 24.1), diabetes mellitus (32.3% vs 33 %), dyslipidemia (28.3% vs. 23%), arterial hypertension (61.6% vs 63%), smoking (47.5% vs 49%), graft material (67.7% vs 68% autologous vein), and site of the distal anastomosis (8.1% vs 11% above-knee; 39.4% vs 31% below-knee femoropopliteal) did not significantly differ between comparison groups.
Interventions	100 patients were randomly assigned to treatment with UFH. 99 patients were randomly assigned to treatment with LMWH (Enoxaparin). Treatment was started intraoperatively with an intravenous bolus, followed by flushing the saphenous vein or prosthetic graft and subcutaneous injections twice daily for 10 days.
Outcomes	Primary endpoint was graft thrombosis at 10 days postoperatively, which was assessed by angiography on day 10 ± 2 or before if indicated and clinically on day 30. Bleeding complications were recorded, defining major hemorrhage as a loss of > 2 g/dl of hemoglobin or transfusion of more than 2 packed red cell units.
Notes	Data was analysed with intention to treat for drug efficacy. In an additional intra-protocol analysis 67 angiographically assessed grafts (LMWH-group) were compared to 64 grafts (UFH-group). Eligible patients were randomly allocated to either of the two treatment groups. Randomisation procedure was not specified, nor was any clarification given by the authors.

Samama 1994 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization was balanced by blocks of four patients, which were separate for each centre.'
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis carried out. 'Two patients (allocated to the enoxaparin group) never received any treatment and were excluded from analysis.'
Selective reporting (reporting bias)	Unclear risk	Stated outcomes discussed, adverse events discussed, no omissions apparent.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Sarac 1998
Study characteristics

Methods	An open, randomised, two centre clinical trial with patients scheduled for venous infrainguinal bypass surgery.
Participants	Country: USA. Sex: 44 male, 12 female. 56 patients were scheduled for venous infrainguinal bypass surgery and were defined as high risk patients for graft occlusion, meaning that there was only a marginal venous conduit and/or poor arterial run-off, prior graft failure. Patient characteristics differed in a higher percentage of diabetes mellitus in the aspirin group (53% vs 79%), but not for mean age (69.4 vs 66.2 years), sex (81% vs 75%), arterial hypertension (84% vs 100%), smoking (97% vs 75%).
Interventions	32 patients (37 grafts) were randomised to warfarin and aspirin 325 mg/d. Warfarin therapy was started on postoperative days two or three with a target INR of two to three. 24 patients (27 grafts) to only aspirin 325 mg/d postoperatively
Outcomes	Primary endpoints were graft patency and limb loss. Graft patency was assessed by evaluation of ABI and duplexsonography. A decrease of 0.15 in ABI and graft velocity of more than 150 cm/sec or less than 30 cm/sec were defined as a failing graft requiring arteriography. Follow up was at two and four weeks, three and six months and every six months thereafter for three years. Occurrence of death, bleeding complications, and evacuation of wound haematoma were recorded.
Notes	Postoperative morbidity rates were similar between groups but a higher incidence of wound haematomas in the warfarin group.

Risk of bias

Sarac 1998 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-assisted random number generator.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Large numbers of patients withdrawn over course of study in both groups in tables assessing patency; no explanation whether this reflects censorship due to shorter follow-up period only or withdrawals for other reasons.
Selective reporting (reporting bias)	Unclear risk	Stated outcomes discussed, adverse events discussed, no omissions apparent.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Schneider 1979
Study characteristics

Methods	An open, randomised, single centre clinical trial performed between 1974 and 1978.
Participants	Patients underwent either thrombendarterectomy or femoropopliteal venous bypass surgery. Among 213 eligible patients 91 were randomised to receive a femoropopliteal venous bypass. Patient characteristics did not differ significantly regarding age, sex, diabetes mellitus, arterial hypertension, smoking, and hyperlipidemia.
Interventions	All patients were treated with therapeutic doses of heparin and coumarins in the first one to two post-operative weeks and were then randomly allocated to either coumarins (Quick, aim 25% to 30%) or aspirin, or aspirin/dipyridamole. Coumarin-derivate versus ASA 1g or ASA 1g and dipyridamole 225 mg in infrainguinal venous bypasses and TEA.
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 mmHg. Signs of occlusions were measured angiographically. Follow-up period was two years with three-monthly visits during the first year and six-monthly contacts 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 patients, including those undergoing TEA.
Notes	After contacting the authors, analysis of two additional publications of the same data was enabled. Allocation concealment remained unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.

Schneider 1979 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Coumarins vs antiplatelet was treated as open trial. Aspirin vs Aspirin + dipyridamole was double blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	13 patients in the antiplatelet groups discontinued therapy, 2 patients in the coumarin group discontinued therapy - no clear explanation for these dropouts given but postulates that may in part be related to side effects.
Selective reporting (reporting bias)	High risk	Stated outcomes discussed, limited discussion on adverse events.
Other bias	Low risk	Appears to be free of other potential sources of bias.

Swedenborg 1996
Study characteristics

Methods	An open, randomised clinical trial of patients undergoing elective infrainguinal bypass surgery.
Participants	18 patients were investigated receiving 18 autologous saphenous vein grafts. Patient characteristics regarding age, sex, preoperative ABI, stage of the disease (claudication), smoking, site of the distal anastomosis did not differ significantly in the two comparison groups.
Interventions	LMWH (Fragmin) or UFH in a dose of 70 anti-Xa activity U/kg of UFH or LMWH (Fragmin) was administered intravenously once during surgery.
Outcomes	The main focus of this study was to evaluate hypercoagulability as a risk factor, whereas early graft occlusion was only of secondary interest. Follow-up duration was not specified, but the term 'postoperatively' implied occlusion shortly after operation but no longer than 24 hours. No further information was accessible for follow-up evaluations of graft patency, limb salvage or survival.
Notes	Patients scheduled for saphenous vein infrainguinal bypass were randomised to either treatment strategy. Randomisation procedure was not specified and attempts to contact the authors were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or dropouts apparent.

Swedenborg 1996 (Continued)

Selective reporting (re-reporting bias)	High risk	Stated outcomes discussed, no discussion of adverse events.
Other bias	High risk	Small sample size.

ABI: ankle-brachial pressure index
 ASA: acetylsalicylic acid (aspirin)
 BMI: body mass index
 CLI: critical limb ischaemia
 DIP: dipyridamole
 IC: intermittent claudication
 INR: international normalised ratio
 iv: intravenous
 LMWH: low molecular weight heparin
 PAD: peripheral arterial disease
 PTA: peripheral percutaneous angioplasty
 PTFE: polytetrafluoroethylene
 Simplastin: a reagent used to measure thrombin time
 TEA: thrombendarterectomy
 UFH: unfractionated heparin
 vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alja-Kulju 1990	Retrospective study.
Benedetti 1988	Not an RCT. No control group investigated. Heterogeneous cohort of different operations (aortofemoral, femoropopliteal, femorotibial, extraanatomical) and different graft materials such as Dacron, PTFE, composite, saphenous vein. Insufficient presentation of data.
Evans 1966	No control group was used.
Fietze-Fischer 1987	Prostaglandin treatment
Gruss 1991	Prostaglandin treatment
Kretschmer 1987	Retrospective study.
Kretschmer 1988	Retrospective study.
Kujath 2002	Pilot study to identify optimal dosing regimen of LMWH, no control group, heterogenic group of operations.
McMillan 1997	Patients were not randomised.
Ohtake 1997	Retrospective study of a platelet inhibitor compared to warfarin as antithrombotic therapy after femoro-popliteal bypass surgery in PTFE grafts.
Ray 1997	No control group was used.
Rosenthal 1987	Retrospective study.
Waibel 1981	Heterogenic group of operations containing only small number of femoral bypasses. Insufficient information.

PTFE: polytetrafluoroethylene
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Occlusion in all bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Occlusion in all bypasses, 3 months	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.30, 1.40]
1.2 Occlusion in all bypasses, 6 months	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.28, 1.03]
1.3 Occlusion in all bypasses, 12 months	4	890	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.49, 0.99]
1.4 Occlusion in all bypasses, 24 months	4	890	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.56, 1.05]
1.5 Occlusion in all bypasses, 5 years	3	833	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.61, 1.07]

Analysis 1.1. Comparison 1: Occlusion in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Occlusion in all bypasses, 3 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	9	41	10	41	56.6%	0.87 [0.32, 2.42]	
Kretschmer 1992	2	66	1	64	11.3%	1.91 [0.19, 18.68]	
Sarac 1998	3	37	7	27	32.0%	0.26 [0.07, 1.03]	
Total (95% CI)		144		132	100.0%	0.65 [0.30, 1.40]	
Total events:	14		18				
Heterogeneity: Chi ² = 2.87, df = 2 (P = 0.24); I ² = 30%							
Test for overall effect: Z = 1.10 (P = 0.27)							
Test for subgroup differences: Not applicable							

Analysis 1.2. Comparison 1: Occlusion in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Occlusion in all bypasses, 6 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Arfvidsson 1990	13	41	14	41	49.9%	0.90 [0.36 , 2.24]			
Kretschmer 1992	2	66	6	64	20.6%	0.34 [0.08 , 1.40]			
Sarac 1998	5	37	9	27	29.5%	0.32 [0.10 , 1.05]			
Total (95% CI)		144		132	100.0%	0.54 [0.28 , 1.03]			
Total events:	20		29						
Heterogeneity: Chi ² = 2.35, df = 2 (P = 0.31); I ² = 15%									
Test for overall effect: Z = 1.87 (P = 0.06)									
Test for subgroup differences: Not applicable									

Analysis 1.3. Comparison 1: Occlusion in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Occlusion in all bypasses, 12 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Sarac 1998	8	37	10	27	10.3%	0.47 [0.16 , 1.41]			
Kretschmer 1992	3	66	16	64	13.2%	0.20 [0.07 , 0.52]			
Arfvidsson 1990	17	41	18	41	16.3%	0.91 [0.38 , 2.16]			
Johnson 2002	42	308	45	306	60.2%	0.92 [0.58 , 1.44]			
Total (95% CI)		452		438	100.0%	0.70 [0.49 , 0.99]			
Total events:	70		89						
Heterogeneity: Chi ² = 8.78, df = 3 (P = 0.03); I ² = 66%									
Test for overall effect: Z = 2.01 (P = 0.04)									
Test for subgroup differences: Not applicable									

Analysis 1.4. Comparison 1: Occlusion in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Occlusion in all bypasses, 24 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Arfvidsson 1990	22	41	25	41	13.3%	0.74 [0.31 , 1.78]			
Johnson 2002	59	308	61	306	63.2%	0.95 [0.64 , 1.42]			
Kretschmer 1992	10	66	20	64	15.2%	0.41 [0.18 , 0.92]			
Sarac 1998	8	37	10	27	8.4%	0.47 [0.16 , 1.41]			
Total (95% CI)		452		438	100.0%	0.76 [0.56 , 1.05]			
Total events:	99		116						
Heterogeneity: Chi ² = 4.23, df = 3 (P = 0.24); I ² = 29%									
Test for overall effect: Z = 1.67 (P = 0.09)									
Test for subgroup differences: Not applicable									

Analysis 1.5. Comparison 1: Occlusion in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Occlusion in all bypasses, 5 years

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	27	41	29	48	10.8%	1.26 [0.53 , 2.97]	
Johnson 2002	109	308	119	306	74.1%	0.86 [0.62 , 1.19]	
Kretschmer 1992	16	66	28	64	15.1%	0.42 [0.20 , 0.87]	
Total (95% CI)		415		418	100.0%	0.80 [0.61 , 1.07]	
Total events:	152		176				
Heterogeneity: Chi ² = 4.28, df = 2 (P = 0.12); I ² = 53%							
Test for overall effect: Z = 1.51 (P = 0.13)							
Test for subgroup differences: Not applicable							

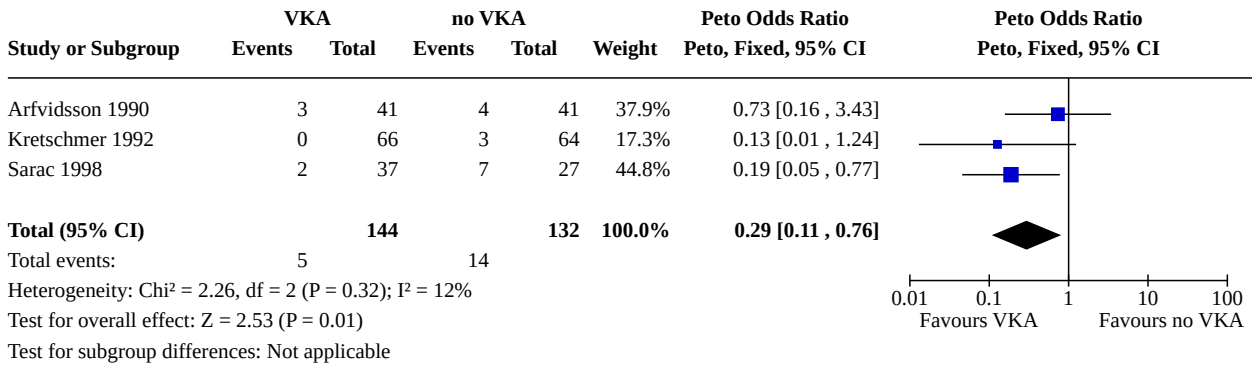
Comparison 2. Limb loss in all bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Limb loss in all bypasses, 3 months	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.10, 0.72]
2.2 Limb loss in all bypasses, 6 months	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.11, 0.76]
2.3 Limb loss in all bypasses, 12 months	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.21, 1.11]
2.4 Limb loss in all bypasses, 24 months	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.26, 0.96]
2.5 Limb loss in all bypasses, 5 years	2	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.19, 0.69]

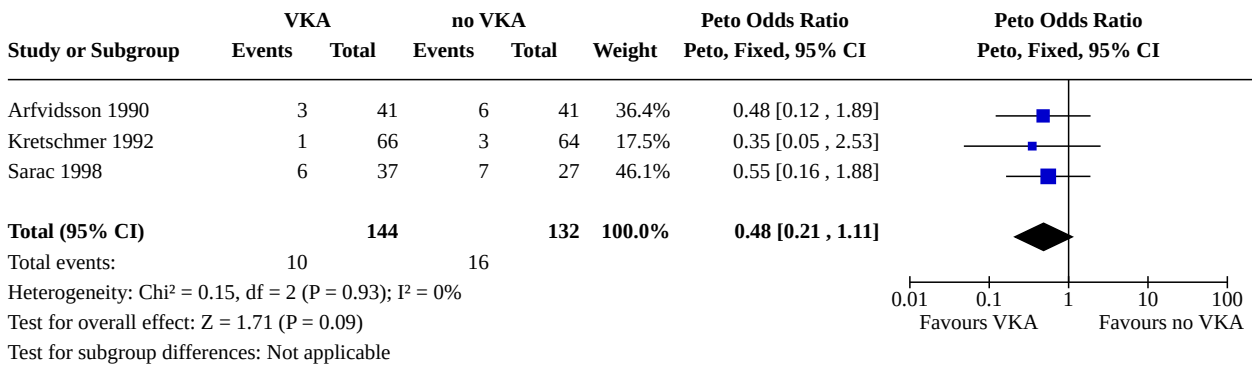
Analysis 2.1. Comparison 2: Limb loss in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Limb loss in all bypasses, 3 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	3	41	3	41	36.3%	1.00 [0.19 , 5.22]	
Kretschmer 1992	0	66	3	64	19.0%	0.13 [0.01 , 1.24]	
Sarac 1998	1	37	7	27	44.7%	0.12 [0.03 , 0.55]	
Total (95% CI)		144		132	100.0%	0.27 [0.10 , 0.72]	
Total events:	4		13				
Heterogeneity: Chi ² = 3.89, df = 2 (P = 0.14); I ² = 49%							
Test for overall effect: Z = 2.61 (P = 0.009)							
Test for subgroup differences: Not applicable							

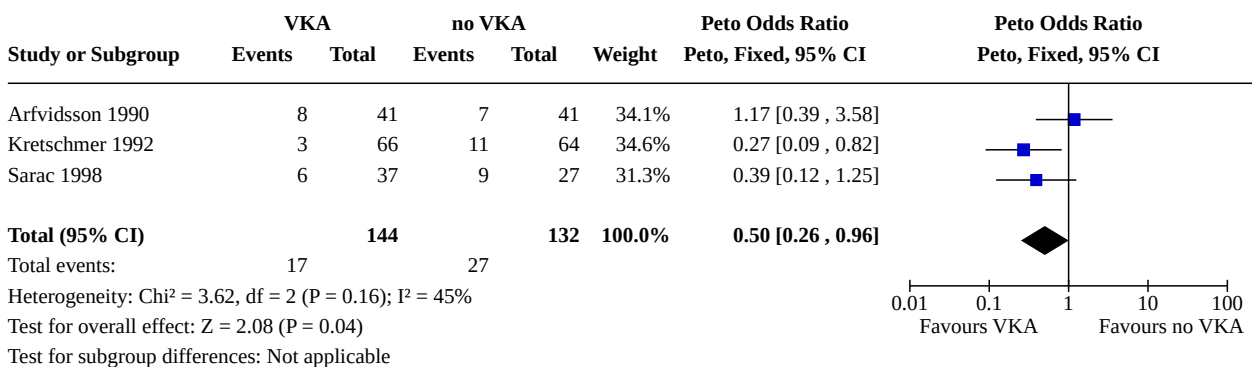
Analysis 2.2. Comparison 2: Limb loss in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Limb loss in all bypasses, 6 months



Analysis 2.3. Comparison 2: Limb loss in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Limb loss in all bypasses, 12 months



Analysis 2.4. Comparison 2: Limb loss in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Limb loss in all bypasses, 24 months



Analysis 2.5. Comparison 2: Limb loss in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Limb loss in all bypasses, 5 years

Study or Subgroup	Favours VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	11	41	13	41	48.3%	0.79 [0.31 , 2.04]	
Kretschmer 1992	3	66	19	64	51.7%	0.17 [0.07 , 0.42]	
Total (95% CI)		107		105	100.0%	0.36 [0.19 , 0.69]	
Total events:	14		32				
Heterogeneity: Chi ² = 5.28, df = 1 (P = 0.02); I ² = 81%							
Test for overall effect: Z = 3.07 (P = 0.002)							
Test for subgroup differences: Not applicable							

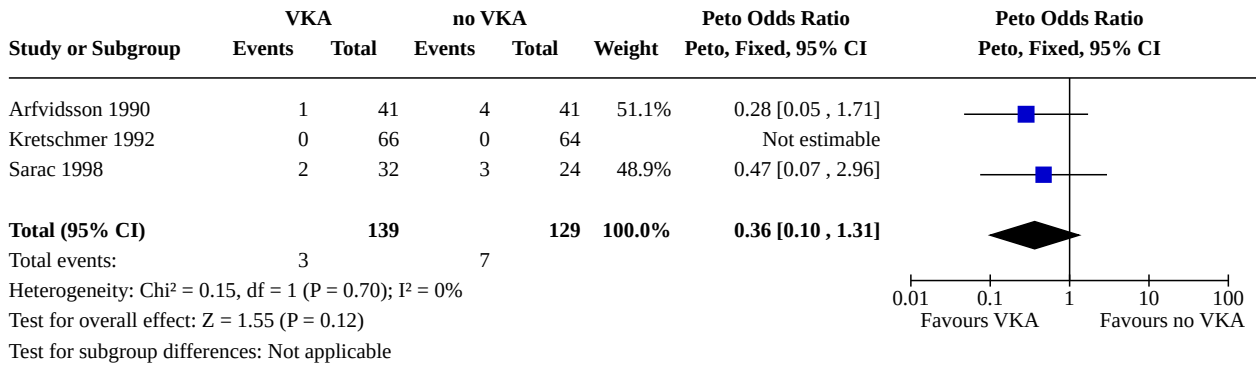
Comparison 3. Deaths in all bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Deaths in all bypasses, 3 months	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.04, 1.04]
3.2 Deaths in all bypasses, 6 months	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.10, 1.31]
3.3 Deaths in all bypasses, 12 months	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.21, 0.97]
3.4 Deaths in all bypasses, 24 months	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.38, 1.15]
3.5 Deaths in all bypasses, 5 years	2	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.35, 1.05]

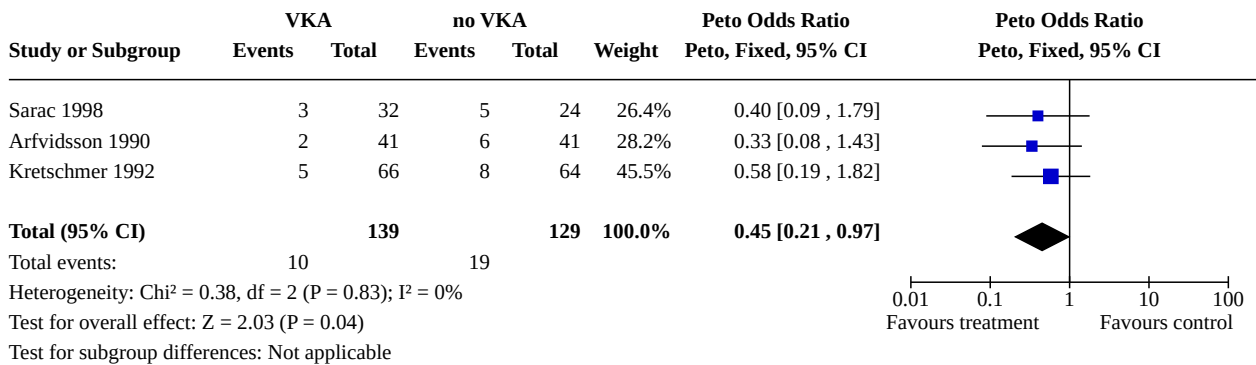
Analysis 3.1. Comparison 3: Deaths in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Deaths in all bypasses, 3 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	0	41	2	41	34.8%	0.13 [0.01 , 2.15]	
Kretschmer 1992	0	66	0	64		Not estimable	
Sarac 1998	1	32	3	24	65.2%	0.25 [0.03 , 1.91]	
Total (95% CI)		139		129	100.0%	0.20 [0.04 , 1.04]	
Total events:	1		5				
Heterogeneity: Chi ² = 0.13, df = 1 (P = 0.72); I ² = 0%							
Test for overall effect: Z = 1.92 (P = 0.06)							
Test for subgroup differences: Not applicable							

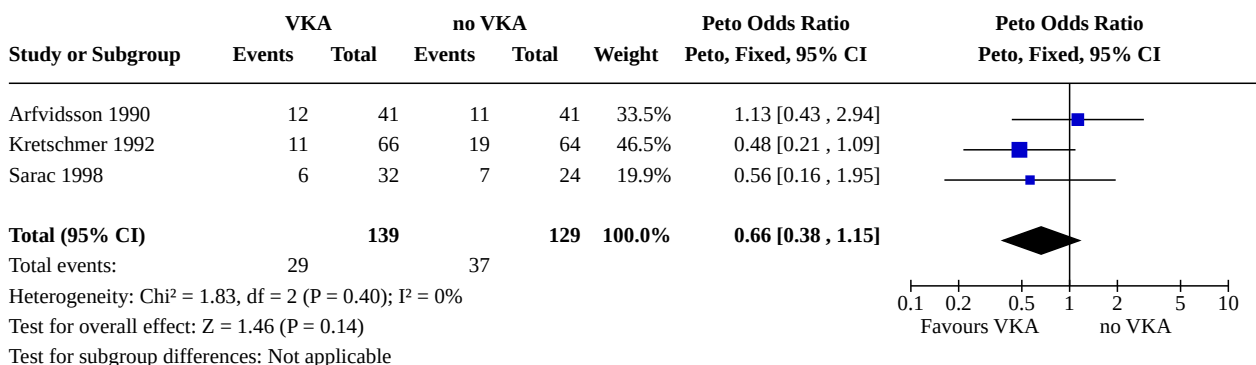
Analysis 3.2. Comparison 3: Deaths in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Deaths in all bypasses, 6 months



Analysis 3.3. Comparison 3: Deaths in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Deaths in all bypasses, 12 months



Analysis 3.4. Comparison 3: Deaths in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Deaths in all bypasses, 24 months



Analysis 3.5. Comparison 3: Deaths in all bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Deaths in all bypasses, 5 years

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Arfvidsson 1990	24	41	24	41	39.8%	1.00 [0.42, 2.39]			
Kretschmer 1992	18	66	30	64	60.2%	0.43 [0.21, 0.88]			
Total (95% CI)		107		105	100.0%	0.60 [0.35, 1.05]			
Total events:	42		54						
Heterogeneity: Chi ² = 2.12, df = 1 (P = 0.15); I ² = 53%									
Test for overall effect: Z = 1.79 (P = 0.07)									
Test for subgroup differences: Not applicable									

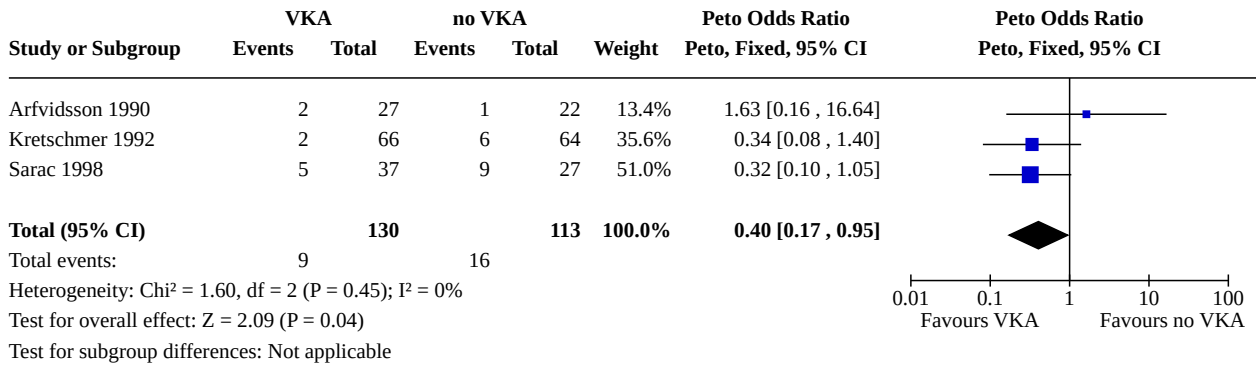
Comparison 4. Occlusion in venous bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Occlusion in venous bypasses, 3 months	3	243	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.14, 1.42]
4.2 Occlusion in venous bypasses, 6 months	3	243	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.17, 0.95]
4.3 Occlusion in venous bypasses, 12 months	4	650	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.49, 1.14]
4.4 Occlusion in venous bypasses, 24 months	4	650	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.55, 1.17]
4.5 Occlusion in venous bypasses, 5 years	3	586	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.71, 1.40]

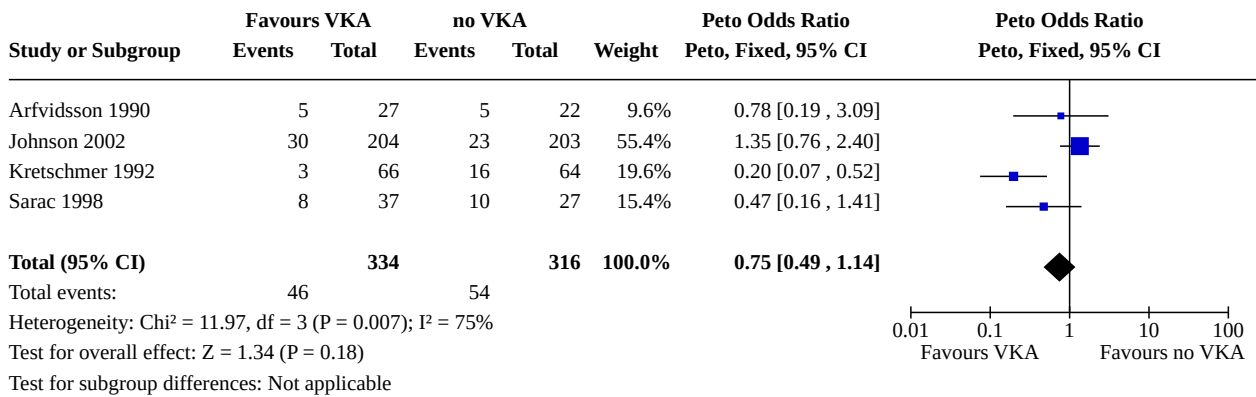
Analysis 4.1. Comparison 4: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Occlusion in venous bypasses, 3 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Arfvidsson 1990	0	27	0	22		Not estimable			
Kretschmer 1992	2	66	1	64	26.1%	1.91 [0.19, 18.68]			
Sarac 1998	3	37	7	27	73.9%	0.26 [0.07, 1.03]			
Total (95% CI)		130		113	100.0%	0.44 [0.14, 1.42]			
Total events:	5		8						
Heterogeneity: Chi ² = 2.13, df = 1 (P = 0.14); I ² = 53%									
Test for overall effect: Z = 1.37 (P = 0.17)									
Test for subgroup differences: Not applicable									

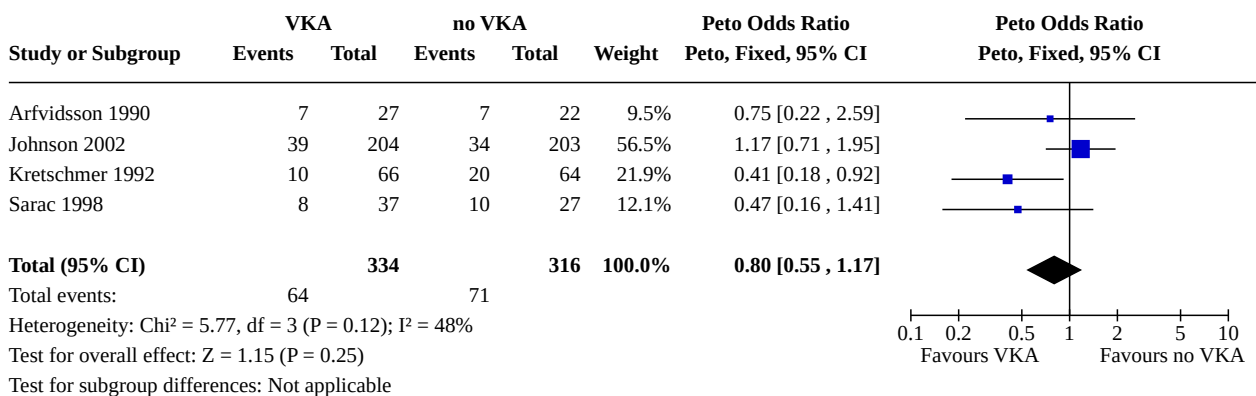
Analysis 4.2. Comparison 4: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Occlusion in venous bypasses, 6 months



Analysis 4.3. Comparison 4: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Occlusion in venous bypasses, 12 months

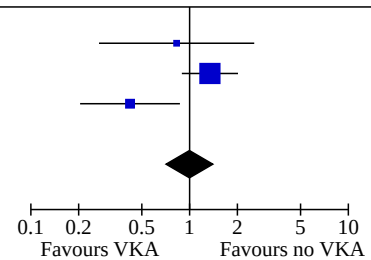


Analysis 4.4. Comparison 4: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Occlusion in venous bypasses, 24 months



Analysis 4.5. Comparison 4: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Occlusion in venous bypasses, 5 years

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Arfvidsson 1990	11	27	10	22	9.0%	0.83 [0.27, 2.55]			
Johnson 2002	78	204	64	203	69.1%	1.34 [0.89, 2.02]			
Kretschmer 1992	16	66	28	64	21.9%	0.42 [0.20, 0.87]			
Total (95% CI)		297		289	100.0%	1.00 [0.71, 1.40]			
Total events:	105		102						
Heterogeneity: Chi ² = 7.60, df = 2 (P = 0.02); I ² = 74%									
Test for overall effect: Z = 0.01 (P = 0.99)									
Test for subgroup differences: Not applicable									

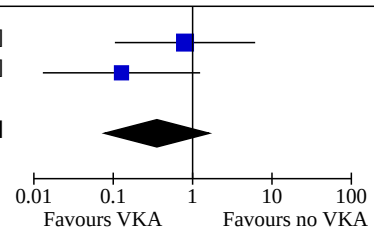


Comparison 5. Limb loss in venous bypasses, vitamin K antagonist (VKA) versus no VKA

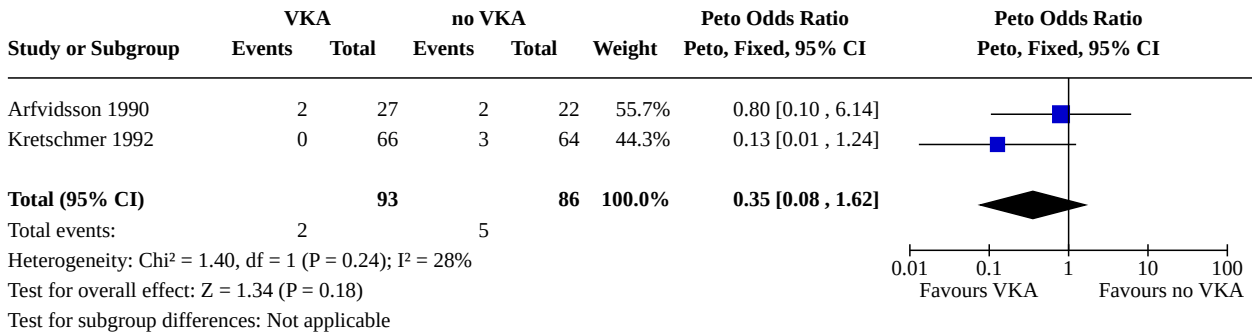
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Limb loss in venous bypasses, 3 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.08, 1.62]
5.2 Limb loss in venous bypasses, 6 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.08, 1.62]
5.3 Limb loss in venous bypasses, 12 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.11, 1.65]
5.4 Limb loss in venous bypasses, 24 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.18, 1.07]
5.5 Limb loss in venous bypasses, 5 years	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.14, 0.60]

Analysis 5.1. Comparison 5: Limb loss in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Limb loss in venous bypasses, 3 months

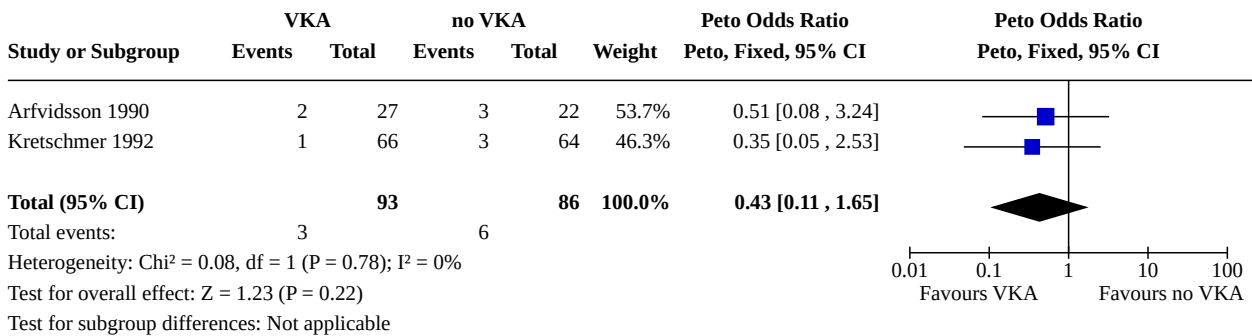
Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Arfvidsson 1990	2	27	2	22	55.7%	0.80 [0.10, 6.14]			
Kretschmer 1992	0	66	3	64	44.3%	0.13 [0.01, 1.24]			
Total (95% CI)		93		86	100.0%	0.35 [0.08, 1.62]			
Total events:	2		5						
Heterogeneity: Chi ² = 1.40, df = 1 (P = 0.24); I ² = 28%									
Test for overall effect: Z = 1.34 (P = 0.18)									
Test for subgroup differences: Not applicable									



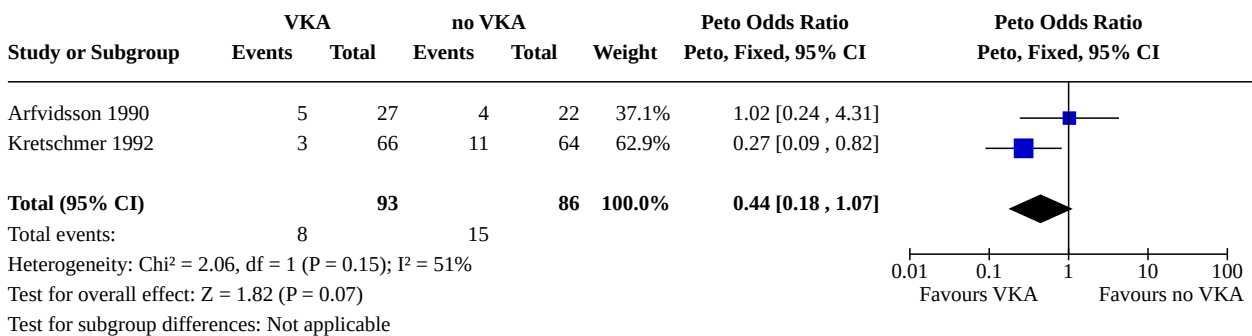
Analysis 5.2. Comparison 5: Limb loss in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Limb loss in venous bypasses, 6 months



Analysis 5.3. Comparison 5: Limb loss in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Limb loss in venous bypasses, 12 months



Analysis 5.4. Comparison 5: Limb loss in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Limb loss in venous bypasses, 24 months



Analysis 5.5. Comparison 5: Limb loss in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Limb loss in venous bypasses, 5 years

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Arfvidsson 1990	7	27	7	22	35.4%	0.75 [0.22, 2.59]		
Kretschmer 1992	3	66	19	64	64.6%	0.17 [0.07, 0.42]		
Total (95% CI)		93		86	100.0%	0.29 [0.14, 0.60]		
Total events:	10		26					
Heterogeneity: Chi ² = 3.63, df = 1 (P = 0.06); I ² = 72%								
Test for overall effect: Z = 3.33 (P = 0.0009)								
Test for subgroup differences: Not applicable								

Comparison 6. Limb salvage venous grafts, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Limb salvage 6 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Limb salvage venous grafts, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Limb salvage 6 months

Study or Subgroup	VKA		no VKA		Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Sarac 1998	35	37	20	27	5.32 [1.29, 21.92]			

Comparison 7. Deaths in venous bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Deaths in venous bypasses, 3 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.00, 5.55]
7.2 Deaths in venous bypasses, 6 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.04, 4.08]
7.3 Deaths in venous bypasses, 12 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.18, 1.31]
7.4 Deaths in venous bypasses, 24 months	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.32, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 Deaths in venous bypasses, 5 years	2	179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.30, 1.00]

Analysis 7.1. Comparison 7: Deaths in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Deaths in venous bypasses, 3 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	0	27	1	22	100.0%	0.11 [0.00, 5.55]	
Kretschmer 1992	0	66	0	64		Not estimable	
Total (95% CI)		93		86	100.0%	0.11 [0.00, 5.55]	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
Test for subgroup differences: Not applicable							

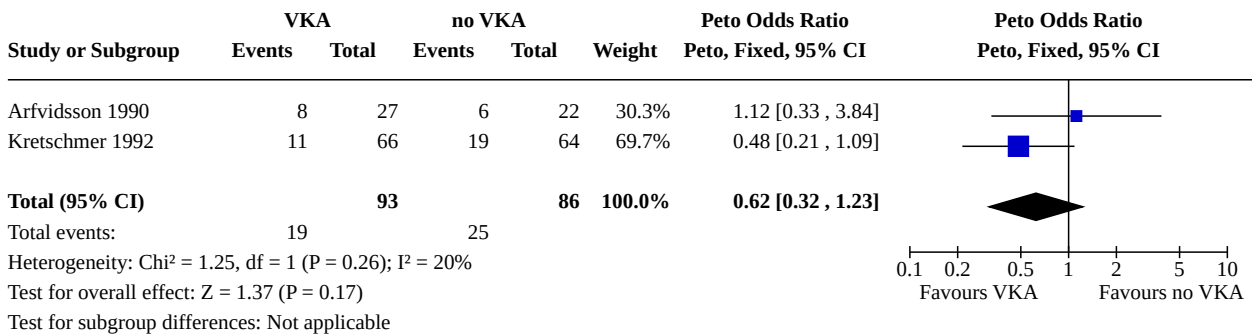
Analysis 7.2. Comparison 7: Deaths in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Deaths in venous bypasses, 6 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	1	27	2	22	100.0%	0.40 [0.04, 4.08]	
Kretschmer 1992	0	66	0	64		Not estimable	
Total (95% CI)		93		86	100.0%	0.40 [0.04, 4.08]	
Total events:	1		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							
Test for subgroup differences: Not applicable							

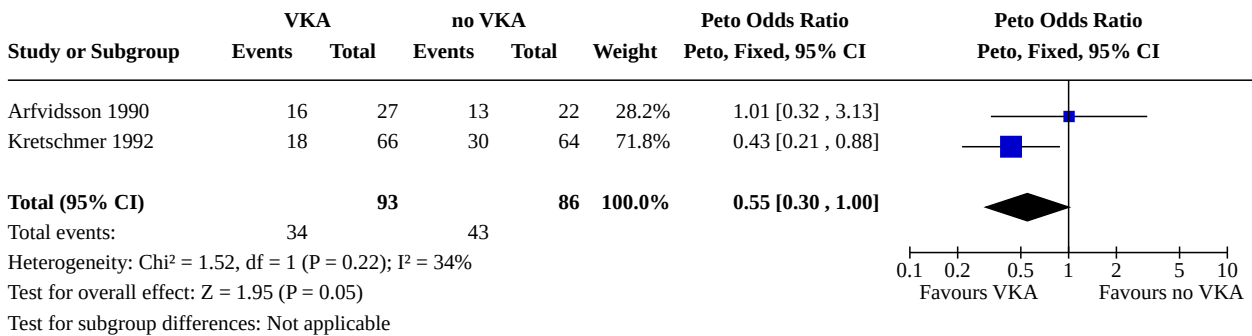
Analysis 7.3. Comparison 7: Deaths in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Deaths in venous bypasses, 12 months

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	1	27	3	22	23.9%	0.27 [0.04, 2.09]	
Kretschmer 1992	5	66	8	64	76.1%	0.58 [0.19, 1.82]	
Total (95% CI)		93		86	100.0%	0.48 [0.18, 1.31]	
Total events:	6		11				
Heterogeneity: Chi ² = 0.40, df = 1 (P = 0.53); I ² = 0%							
Test for overall effect: Z = 1.42 (P = 0.15)							
Test for subgroup differences: Not applicable							

Analysis 7.4. Comparison 7: Deaths in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Deaths in venous bypasses, 24 months



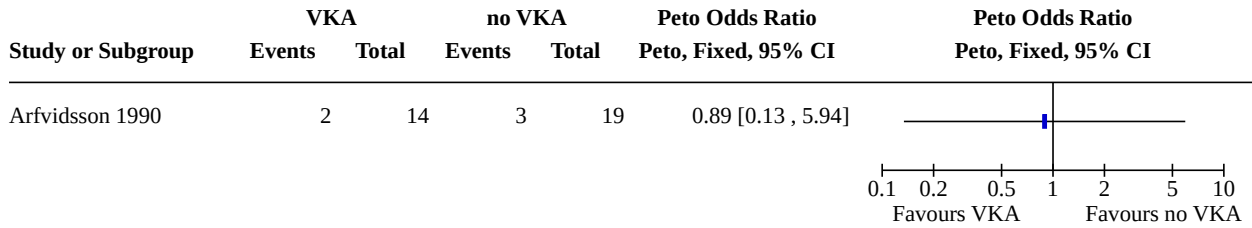
Analysis 7.5. Comparison 7: Deaths in venous bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Deaths in venous bypasses, 5 years



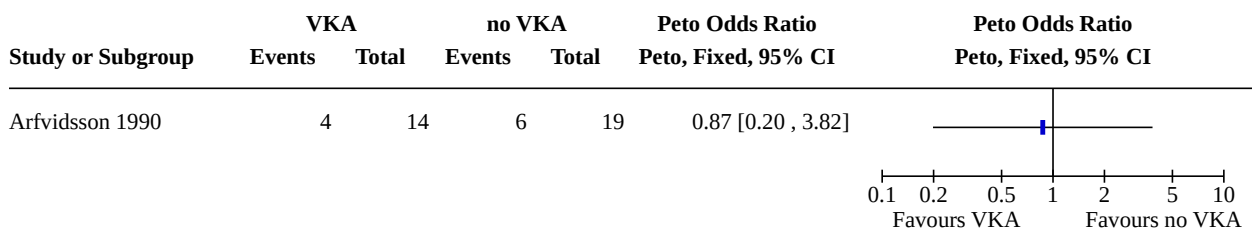
Comparison 8. Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Occlusion in artificial bypasses, 3 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
8.2 Occlusion in artificial bypasses, 6 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
8.3 Occlusion in artificial bypasses, 12 months	2	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.31, 1.13]
8.4 Occlusion in artificial bypasses, 24 months	2	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.40, 1.29]
8.5 Occlusion in artificial bypasses, 5 years	2	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.26, 0.73]

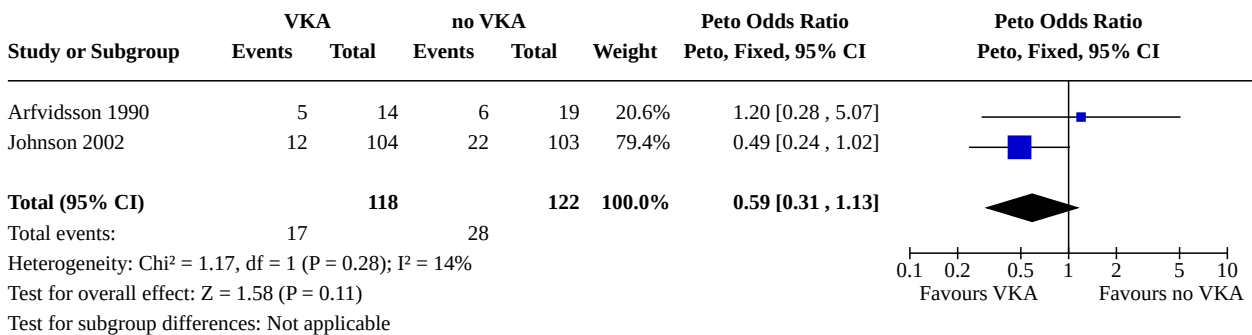
Analysis 8.1. Comparison 8: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Occlusion in artificial bypasses, 3 months



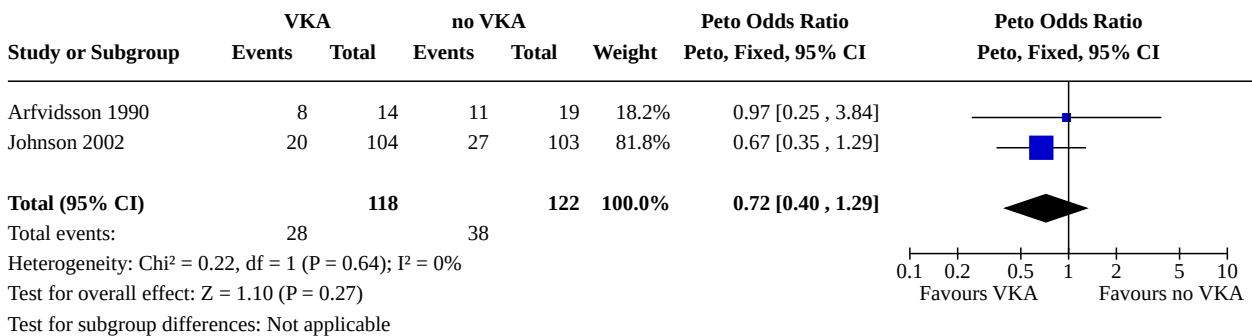
Analysis 8.2. Comparison 8: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Occlusion in artificial bypasses, 6 months



Analysis 8.3. Comparison 8: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Occlusion in artificial bypasses, 12 months



Analysis 8.4. Comparison 8: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Occlusion in artificial bypasses, 24 months



Analysis 8.5. Comparison 8: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Occlusion in artificial bypasses, 5 years

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Arfvidsson 1990	9	14	12	19	13.2%	1.05 [0.26 , 4.31]	
Johnson 2002	31	104	55	103	86.8%	0.38 [0.22 , 0.66]	
Total (95% CI)		118		122	100.0%	0.43 [0.26 , 0.73]	
Total events:	40		67				
Heterogeneity: Chi ² = 1.72, df = 1 (P = 0.19); I ² = 42%							
Test for overall effect: Z = 3.18 (P = 0.001)							
Test for subgroup differences: Not applicable							

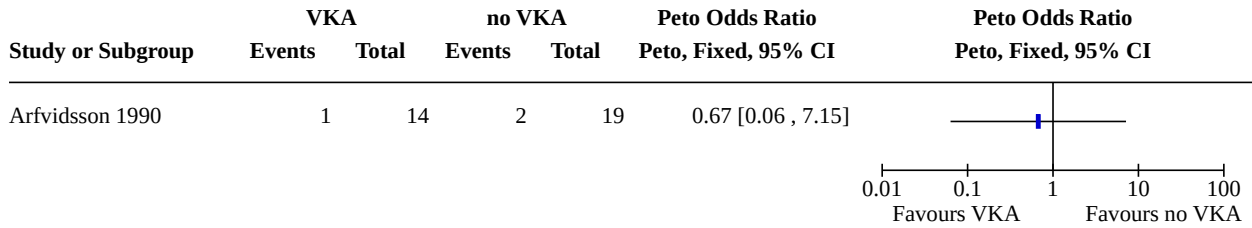
Comparison 9. Limb loss in artificial bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Limb loss in artificial bypasses, 3 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9.2 Limb loss in artificial bypasses, 6 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9.3 Limb loss in artificial bypasses, 12 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9.4 Limb loss in artificial bypasses, 24 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9.5 Limb loss in artificial bypasses, 5 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

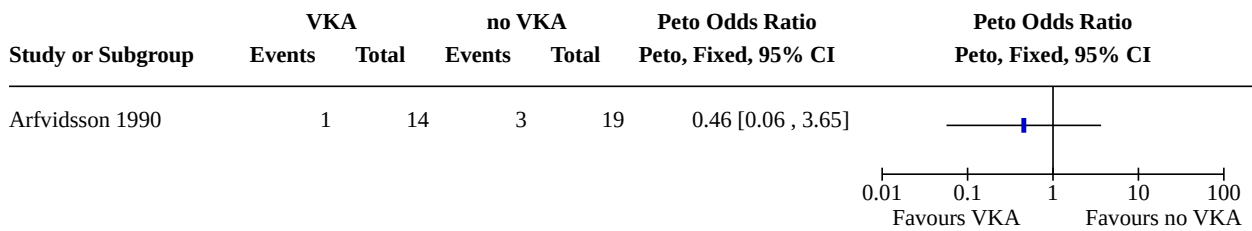
Analysis 9.1. Comparison 9: Limb loss in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Limb loss in artificial bypasses, 3 months

Study or Subgroup	VKA		no VKA		Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total		
Arfvidsson 1990	1	14	1	19	1.38 [0.08 , 23.79]	

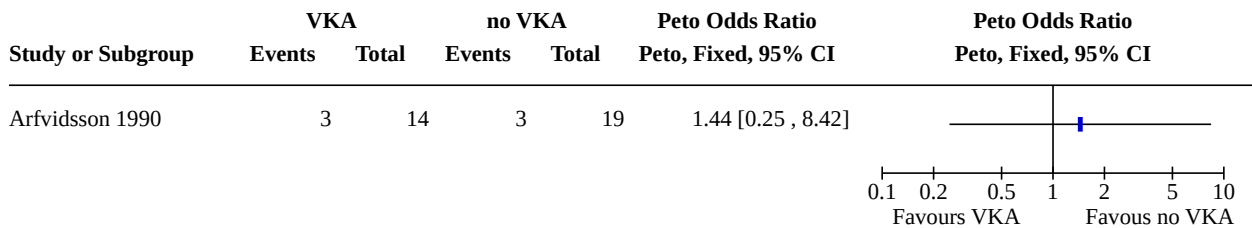
Analysis 9.2. Comparison 9: Limb loss in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Limb loss in artificial bypasses, 6 months



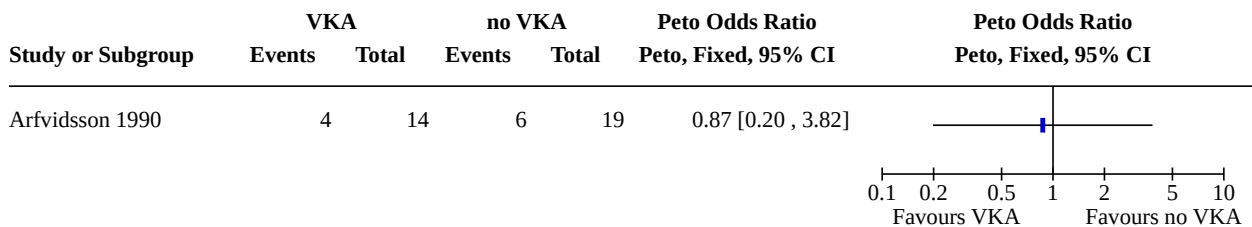
Analysis 9.3. Comparison 9: Limb loss in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Limb loss in artificial bypasses, 12 months



Analysis 9.4. Comparison 9: Limb loss in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Limb loss in artificial bypasses, 24 months



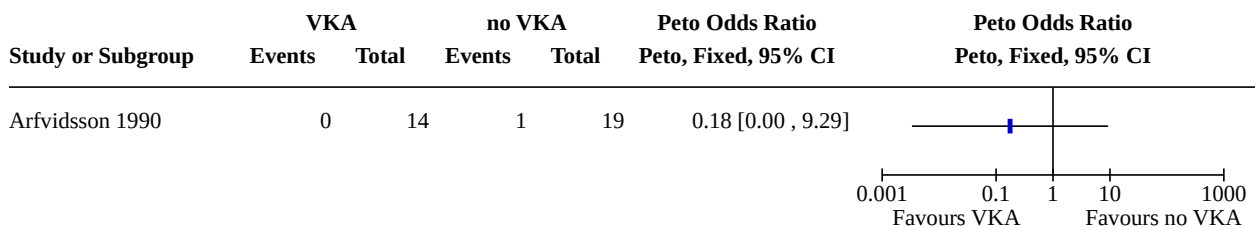
Analysis 9.5. Comparison 9: Limb loss in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Limb loss in artificial bypasses, 5 years



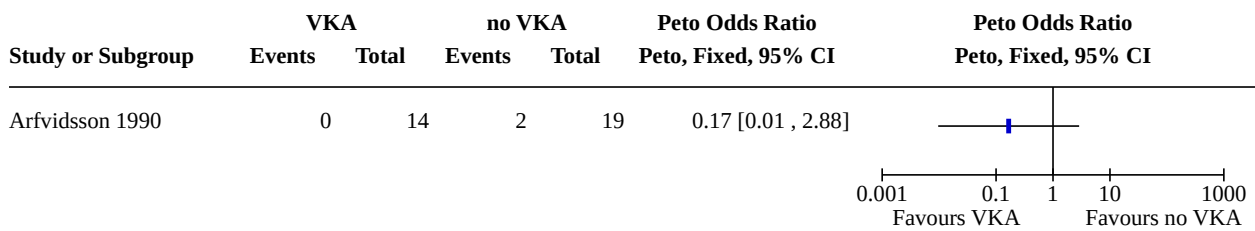
Comparison 10. Deaths in artificial bypasses, vitamin K antagonist (VKA) versus no VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Deaths in artificial bypasses, 3 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
10.2 Deaths in artificial bypasses, 6 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
10.3 Deaths in artificial bypasses, 12 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
10.4 Deaths in artificial bypasses, 24 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
10.5 Deaths in artificial bypasses, 5 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

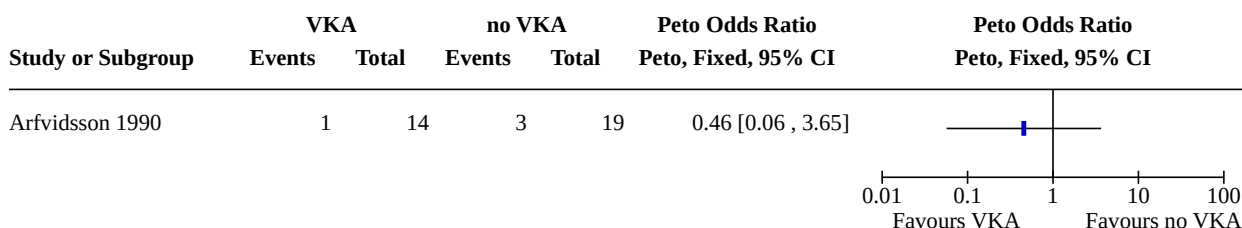
Analysis 10.1. Comparison 10: Deaths in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 1: Deaths in artificial bypasses, 3 months



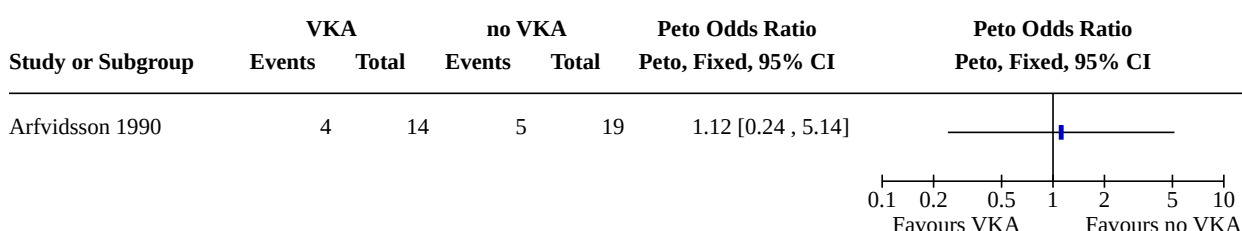
Analysis 10.2. Comparison 10: Deaths in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 2: Deaths in artificial bypasses, 6 months



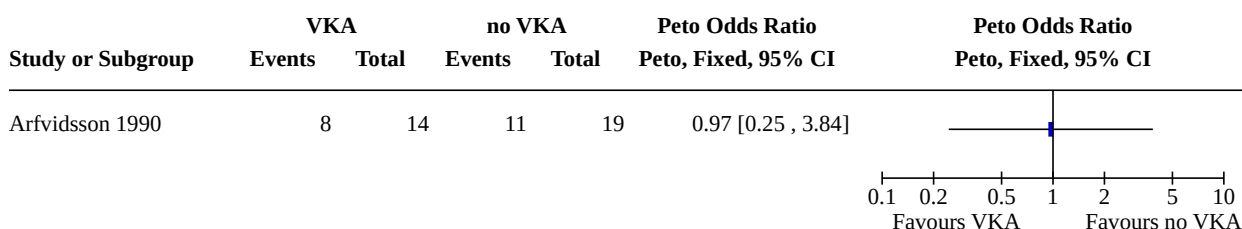
Analysis 10.3. Comparison 10: Deaths in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 3: Deaths in artificial bypasses, 12 months



Analysis 10.4. Comparison 10: Deaths in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 4: Deaths in artificial bypasses, 24 months



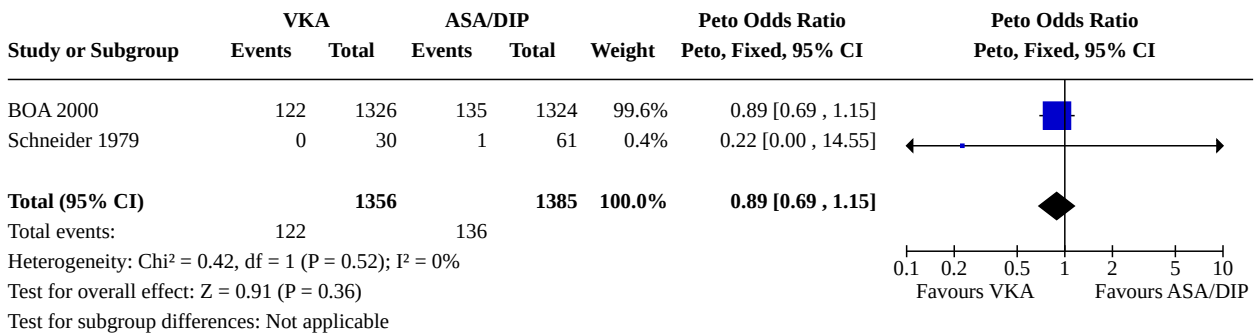
Analysis 10.5. Comparison 10: Deaths in artificial bypasses, vitamin K antagonist (VKA) versus no VKA, Outcome 5: Deaths in artificial bypasses, 5 years



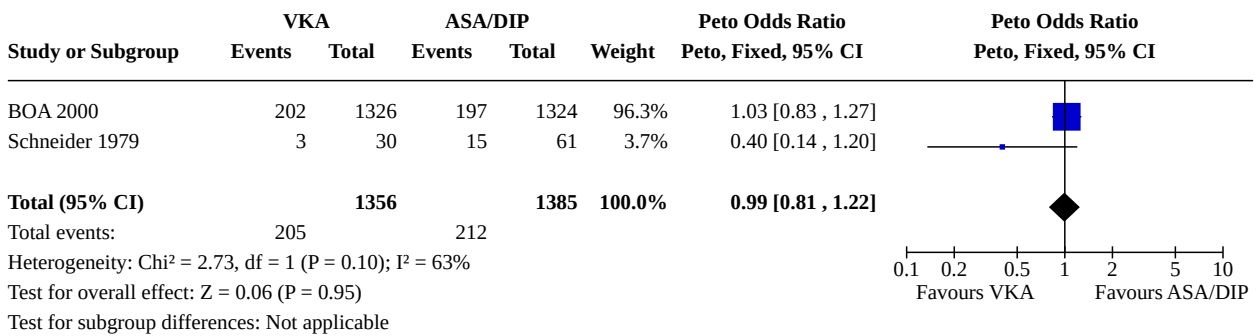
Comparison 11. Occlusion in all bypasses, vitamin K antagonist (VKA) versus ASA/DIP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Occlusion in all bypasses, 3 months	2	2741	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.69, 1.15]
11.2 Occlusion in all bypasses, 6 months	2	2741	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.81, 1.22]
11.3 Occlusion in all bypasses, 12 months	2	2741	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.77, 1.11]
11.4 Occlusion in all bypasses, 24 months	2	2741	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.77, 1.08]

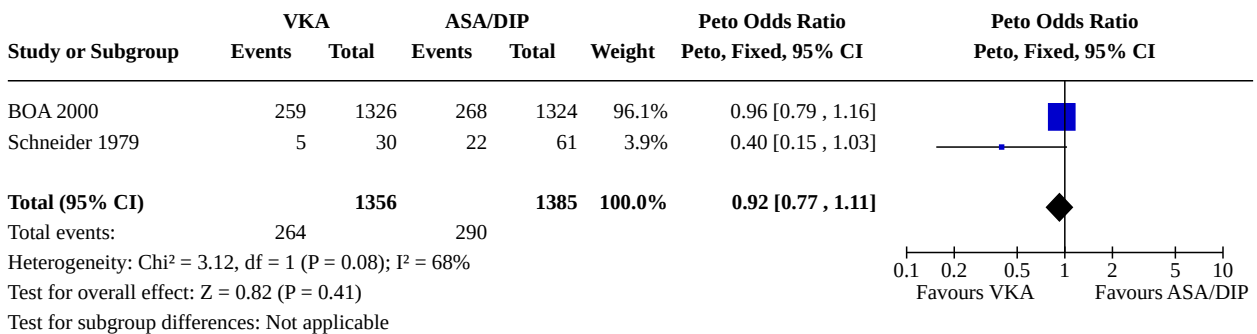
Analysis 11.1. Comparison 11: Occlusion in all bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 1: Occlusion in all bypasses, 3 months



Analysis 11.2. Comparison 11: Occlusion in all bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 2: Occlusion in all bypasses, 6 months



Analysis 11.3. Comparison 11: Occlusion in all bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 3: Occlusion in all bypasses, 12 months



Analysis 11.4. Comparison 11: Occlusion in all bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 4: Occlusion in all bypasses, 24 months

Study or Subgroup	VKA		ASA/DIP		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
BOA 2000	334	1326	348	1324	96.2%	0.94 [0.79, 1.12]	
Schneider 1979	8	30	31	61	3.8%	0.38 [0.16, 0.91]	
Total (95% CI)		1356		1385	100.0%	0.91 [0.77, 1.08]	
Total events:	342		379				
Heterogeneity: Chi ² = 4.04, df = 1 (P = 0.04); I ² = 75%							
Test for overall effect: Z = 1.06 (P = 0.29)							
Test for subgroup differences: Not applicable							

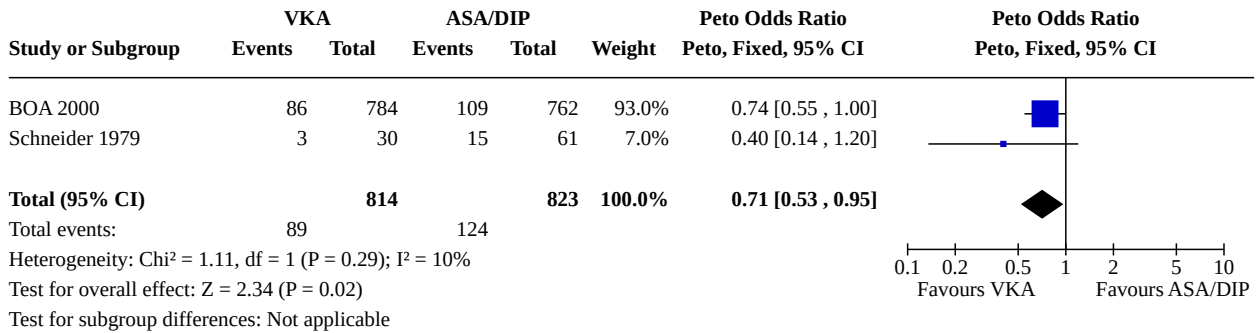
Comparison 12. Occlusion in venous bypasses, vitamin K antagonist (VKA) versus ASA/DIP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Occlusion in venous bypasses, 3 months	2	1637	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.46, 0.92]
12.2 Occlusion in venous bypasses, 6 months	2	1637	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.53, 0.95]
12.3 Occlusion in venous bypasses, 12 months	2	1637	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.49, 0.85]
12.4 Occlusion in venous bypasses, 24 months	2	1637	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.46, 0.76]

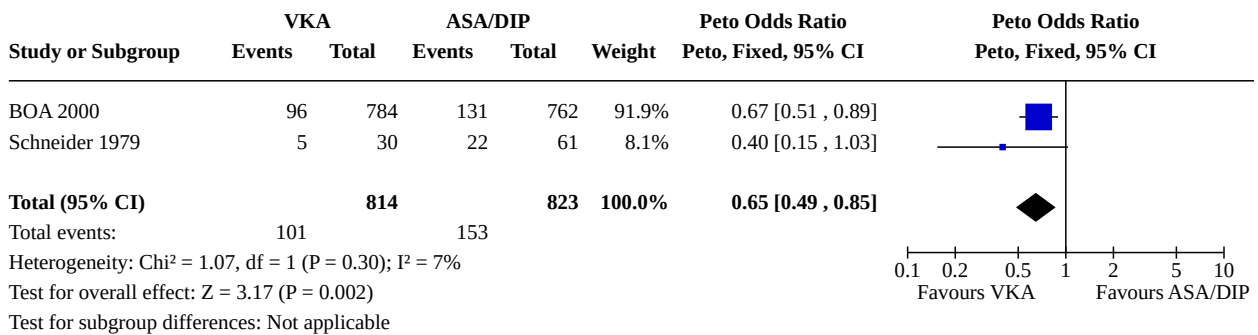
Analysis 12.1. Comparison 12: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 1: Occlusion in venous bypasses, 3 months

Study or Subgroup	VKA		ASA/DIP		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
BOA 2000	59	784	84	762	99.3%	0.66 [0.47, 0.93]	
Schneider 1979	0	30	1	61	0.7%	0.22 [0.00, 14.55]	
Total (95% CI)		814		823	100.0%	0.65 [0.46, 0.92]	
Total events:	59		85				
Heterogeneity: Chi ² = 0.25, df = 1 (P = 0.61); I ² = 0%							
Test for overall effect: Z = 2.42 (P = 0.02)							
Test for subgroup differences: Not applicable							

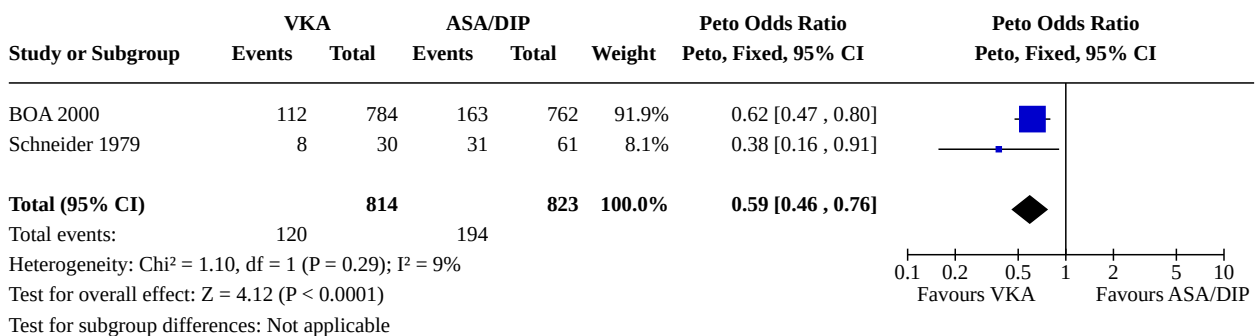
Analysis 12.2. Comparison 12: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 2: Occlusion in venous bypasses, 6 months



Analysis 12.3. Comparison 12: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 3: Occlusion in venous bypasses, 12 months



Analysis 12.4. Comparison 12: Occlusion in venous bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 4: Occlusion in venous bypasses, 24 months

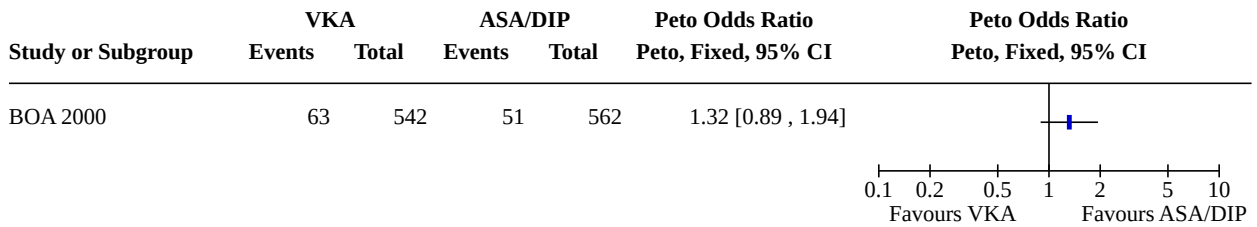


Comparison 13. Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus ASA/DIP

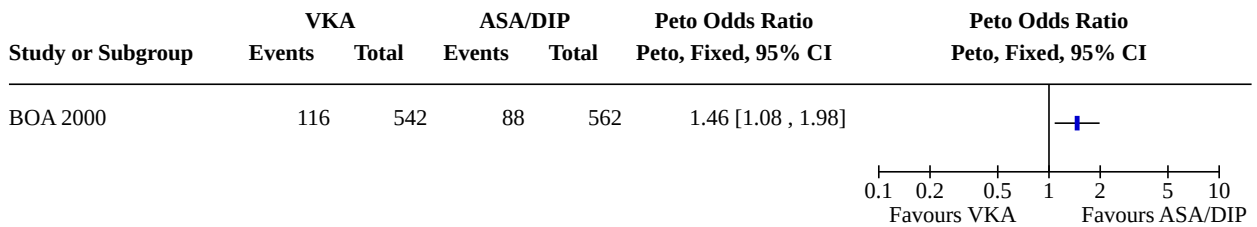
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Occlusion in non-venous bypasses, 3 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Occlusion in non-venous bypasses, 6 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
13.3 Occlusion in non-venous bypasses, 12 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
13.4 Occlusion in non-venous bypasses, 24 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

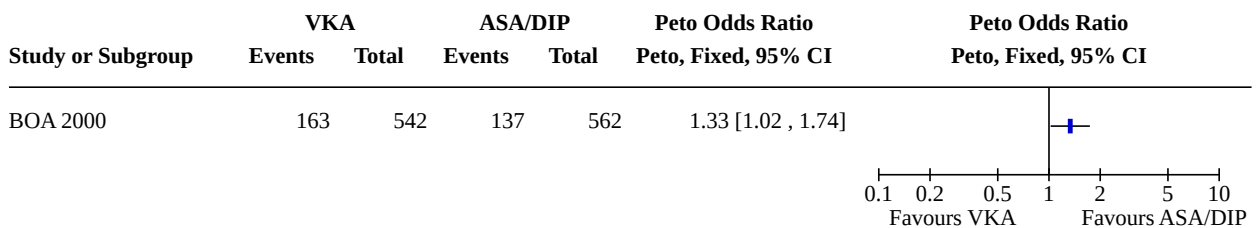
Analysis 13.1. Comparison 13: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 1: Occlusion in non-venous bypasses, 3 months



Analysis 13.2. Comparison 13: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 2: Occlusion in non-venous bypasses, 6 months



Analysis 13.3. Comparison 13: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 3: Occlusion in non-venous bypasses, 12 months



Analysis 13.4. Comparison 13: Occlusion in artificial bypasses, vitamin K antagonist (VKA) versus ASA/DIP, Outcome 4: Occlusion in non-venous bypasses, 24 months

Study or Subgroup	VKA		ASA/DIP		Peto Odds Ratio	Peto Odds Ratio
	Events	Total	Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
BOA 2000	222	542	185	562	1.41 [1.11, 1.80]	

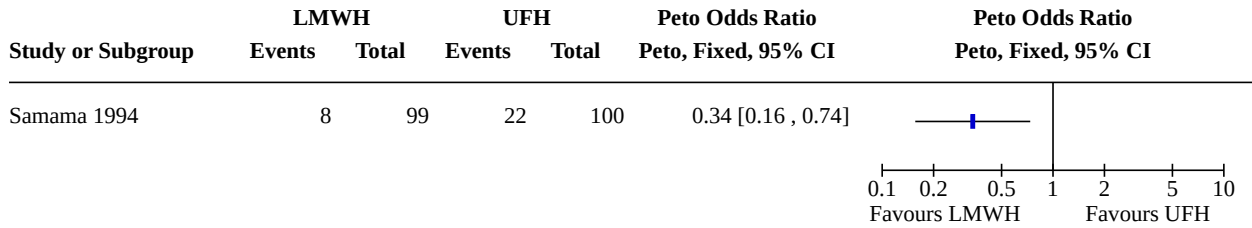
Comparison 14. Occlusion in all bypasses, low molecular weight heparin (LMWH) versus unfractionated heparin (UFH)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Occlusion in all bypasses, 24 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.2 Occlusion in all bypasses, day 10	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
14.3 Occlusion, in all bypasses, day 30	2	507	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.33, 0.90]
14.4 Per protocol	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

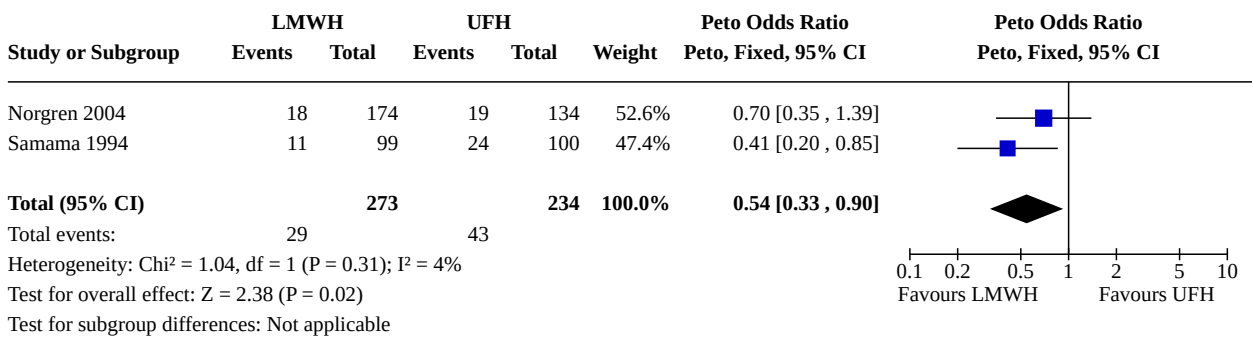
Analysis 14.1. Comparison 14: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 1: Occlusion in all bypasses, 24 hours

Study or Subgroup	LMWH		UFH		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Norgren 2004	7	176	4	137	1.38 [0.39, 4.80]	

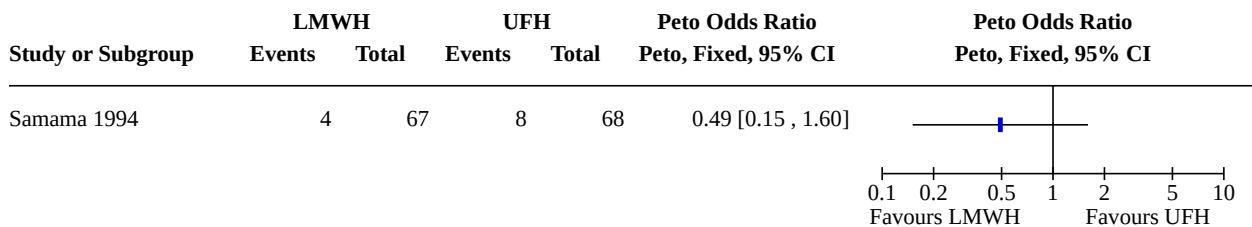
Analysis 14.2. Comparison 14: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 2: Occlusion in all bypasses, day 10



Analysis 14.3. Comparison 14: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 3: Occlusion, in all bypasses, day 30



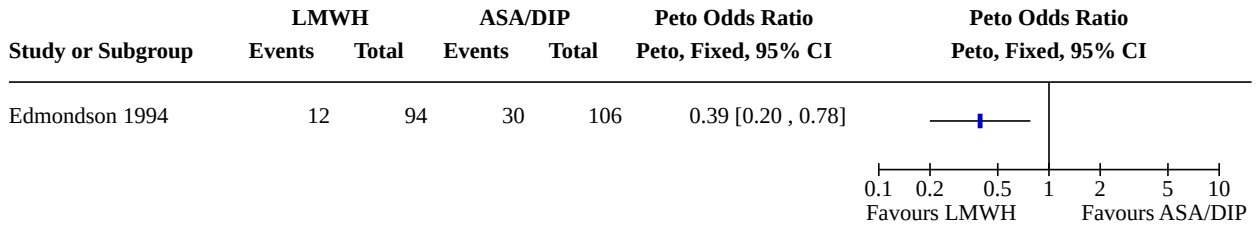
Analysis 14.4. Comparison 14: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 4: Per protocol



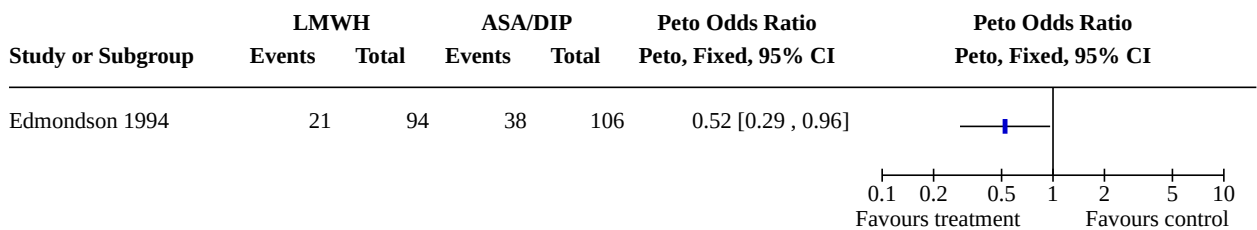
Comparison 15. Occlusion in all bypasses, low molecular weight heparin (LMWH) versus ASA/DIP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Occlusion in all bypasses, 6 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
15.2 Occlusion in all bypasses, 12 months	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Analysis 15.1. Comparison 15: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus ASA/DIP, Outcome 1: Occlusion in all bypasses, 6 months



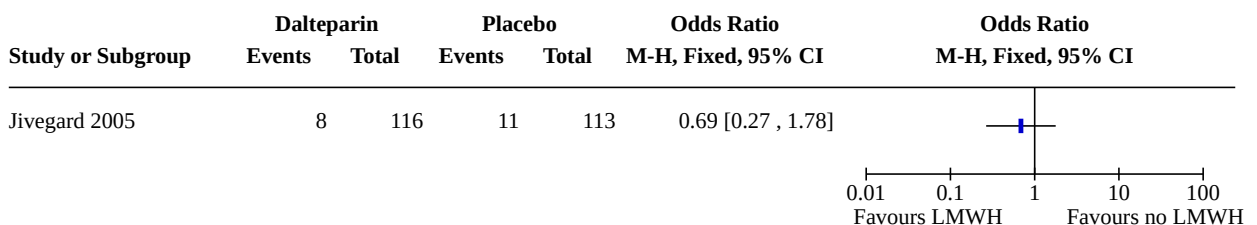
Analysis 15.2. Comparison 15: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus ASA/DIP, Outcome 2: Occlusion in all bypasses, 12 months



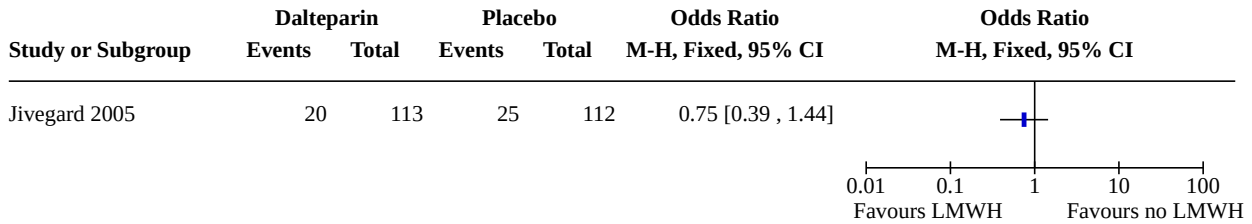
Comparison 16. Occlusion in all bypasses, low molecular weight heparin (LMWH) versus no LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Occlusion in all bypasses, 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.2 Occlusion in all bypasses, 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.3 Occlusion in all bypasses, 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

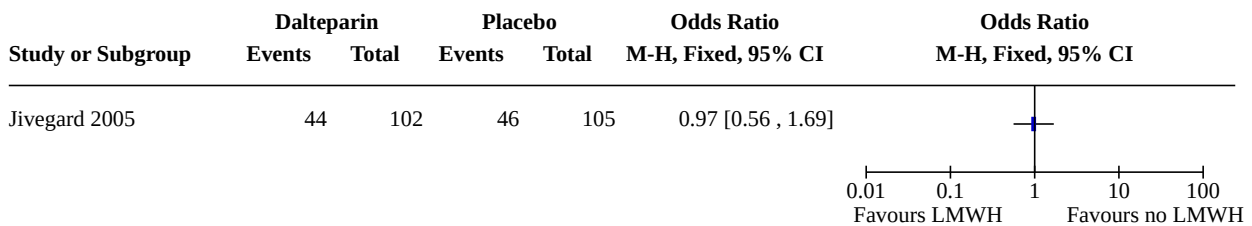
Analysis 16.1. Comparison 16: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus no LMWH, Outcome 1: Occlusion in all bypasses, 1 month



Analysis 16.2. Comparison 16: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus no LMWH, Outcome 2: Occlusion in all bypasses, 3 months



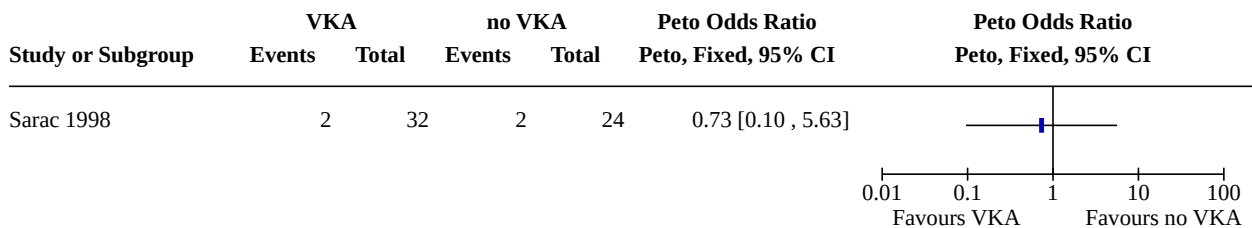
Analysis 16.3. Comparison 16: Occlusion in all bypasses, low molecular weight heparin (LMWH) versus no LMWH, Outcome 3: Occlusion in all bypasses, 12 months



Comparison 17. Survival venous grafts, Sarac study

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Survival 6 months, intention to treat	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
17.2 Survival 2 years, intention to treat	2	147	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.22, 2.21]

Analysis 17.1. Comparison 17: Survival venous grafts, Sarac study, Outcome 1: Survival 6 months, intention to treat



Analysis 17.2. Comparison 17: Survival venous grafts, Sarac study, Outcome 2: Survival 2 years, intention to treat

Study or Subgroup	VKA		no VKA		Weight	Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Sarac 1998	4	32	6	24	70.6%	0.43 [0.11 , 1.70]			
Schneider 1979	2	30	2	61	29.4%	2.22 [0.27 , 18.50]			
Total (95% CI)		62		85	100.0%	0.70 [0.22 , 2.21]			
Total events:	6		8						
Heterogeneity: Chi ² = 1.61, df = 1 (P = 0.20); I ² = 38%									
Test for overall effect: Z = 0.61 (P = 0.54)									
Test for subgroup differences: Not applicable									

Comparison 18. Early graft thrombosis, ancrod versus heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Early graft thrombosis, 24 h and 1 month	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

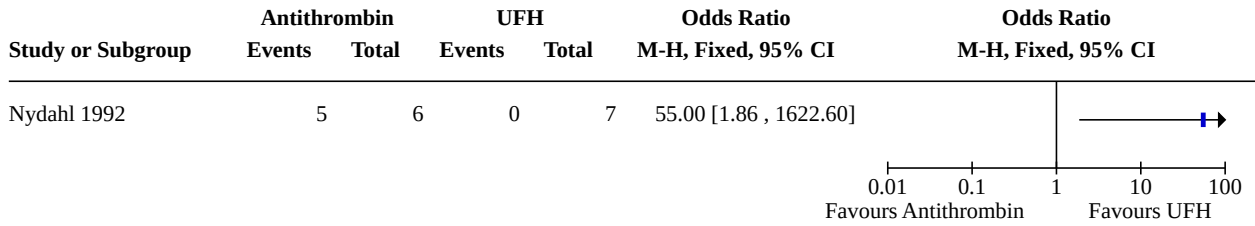
Analysis 18.1. Comparison 18: Early graft thrombosis, ancrod versus heparin, Outcome 1: Early graft thrombosis, 24 h and 1 month

Study or Subgroup	Ancrod		UFH		Peto Odds Ratio		Peto Odds Ratio	
	Events	Total	Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Cole 1993	1	13	1	14	1.08 [0.06 , 18.28]			

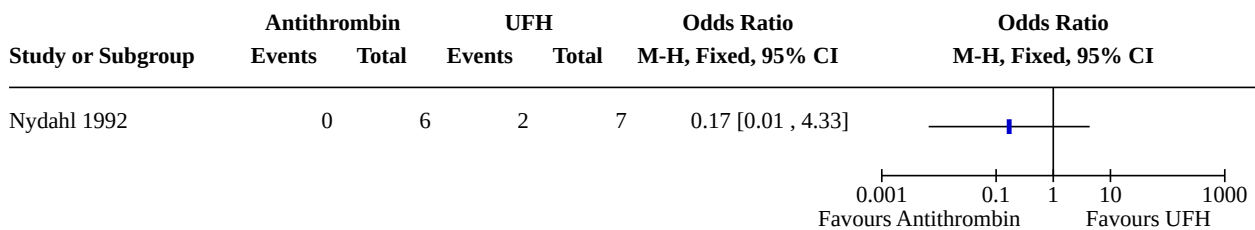
Comparison 19. Early graft thrombosis, unfractionated heparin (UFH) versus antithrombin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Antithrombin versus UFH, intraoperative graft thrombosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
19.2 Antithrombin versus UFH, 1 month occlusion (following thrombendarterectomy)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 19.1. Comparison 19: Early graft thrombosis, unfractionated heparin (UFH) versus antithrombin, Outcome 1: Antithrombin versus UFH, intraoperative graft thrombosis



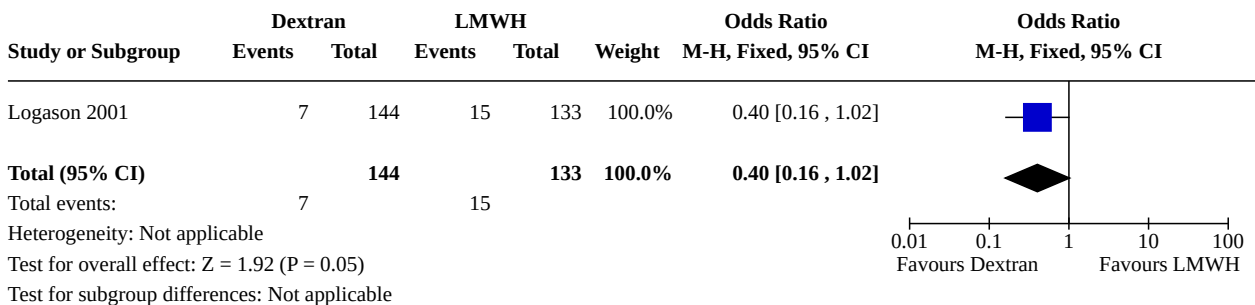
Analysis 19.2. Comparison 19: Early graft thrombosis, unfractionated heparin (UFH) versus antithrombin, Outcome 2: Antithrombin versus UFH, 1 month occlusion (following thrombendarterectomy)



Comparison 20. Early graft occlusion, low molecular weight heparin (LMWH) versus dextran

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Early graft occlusion, 30 days	1	277	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.16, 1.02]

Analysis 20.1. Comparison 20: Early graft occlusion, low molecular weight heparin (LMWH) versus dextran, Outcome 1: Early graft occlusion, 30 days



APPENDICES

Appendix 1. 2010 CENTRAL search strategy

#1	MeSH descriptor Anticoagulants explode all trees	7204
#2	anticoagul* or warfarin or (vitamin near3 antagonist*) or VKA or Nicoumalone or phenindione or acenocoumarol* or Sinthrome or dicoumarol* or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or bishydroxycoumarin* or coumarin* or phenprocoumon* or Xime-lagatran or Exanta or Exarta or H 376/95 or dabigatran or rivaroxaban or BAY59-7939 or odiparcil or LY517717 or YM150 or DU-176b or apixa-ban or betrixaban	6313
#3	MeSH descriptor Platelet Aggregation Inhibitors explode all trees	7255
#4	antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* or (platelet* adj5 inhibit*) or (thrombocyt* adj5 inhibit*)	1825
#5	aspirin* or ASA or dipyridamol* or epoprostenol* or iloprost* or ketanserin* or milrinone* or mopidamol* or pentoxifyllin* or ticlopidine* or trapidil or "eicosapentaenoic Acid" or tirofiban or Aggrastat or eptifibatide or Integrilin or SCH 530348 or "acetyl salicylic acid*" or "acetylsalicylic acid" or "acetyl-salicylic acid" or clopidogrel* or picotamide* or suloctidil* or defibrotide* or cilostazol or Pletal or satigrel or sarpolgrelete or kbt3022 or kbt-3022 or isbo-grel or cv4151 or cv-4151 or triflusal or Dispril or Albyl* or Ticlid* or Persantin* or Plavix or Aggrenox or Plasugrel or Ticagrelor or Cangrelor or Portola	18149
#6	((glycoprotein iib* or gp iib*) near3 (antagonist* or inhibitor*)) or GR144053 or GR-144053 or abciximab or tirofiban* or eptifibatid or eptifibatide or ReoPro or Integrilin* or Aggrastat of indobufen)	1039
#7	antithrombotic*	1132
#8	UFH or bivalirudin*	508
#9	(LMWH OR UH or heparin or nadroparin* OR fraxiparin* OR enoxaparin OR Clexane OR klexane OR lovenox OR dalteparin OR Fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR Innohep OR certoparin OR sandoparin OR reviparin OR clivarin* OR danaproid OR danaparoid or antixarin OR arde-parin* OR bemiparin* OR Zibor OR cy 222 OR embolex OR monoembolex OR parnaparin* OR "rd 11885" Or tedelparin OR Kabi-2165 OR Kabi 2165 or emt-966 or emt-967 or "pk-10 169" or pk-10169 or pk10169 or cy-216 or cy216 or seleparin* or tedegliparin or seleparin* or tedegliparin* or wy90493 or "wy 90493" or "kb 101" or kb101 or lomoparan or orgaran or parnaparin or fluxum or lohepa or lowhepa or "op 2123" or parvoparin or AVE5026)	7691
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	30182
#11	MeSH descriptor Femoral Artery explode all trees	660
#12	MeSH descriptor Popliteal Artery explode all trees	228
#13	MeSH descriptor Saphenous Vein explode all trees	455
#14	MeSH descriptor Peripheral Vascular Diseases explode all trees	2055
#15	MeSH descriptor Arterial Occlusive Diseases, this term only	727
#16	MeSH descriptor Arteriolosclerosis, this term only	0

(Continued)

#17	MeSH descriptor Arteriosclerosis Obliterans explode all trees	67
#18	MeSH descriptor Atherosclerosis explode all trees	265
#19	MeSH descriptor Intermittent Claudication explode all trees	658
#20	MeSH descriptor Ischemia, this term only	678
#21	(peripheral near (arter* or vasc*)) or atherosclerosis or arteriosclerosis or PVD or PAOD or PAD	16435
#22	claudic* or (peripher* or leg or (lower next extremit*))	25982
#23	isch* or CLI	14891
#24	infrainguinal or (infra near inguin*)	149
#25	femoropopliteal or (fem* near pop*)	1782
#26	femorodistal or (femoro* near distal)	53
#27	infrapopliteal or (infra near poplite*)	54
#28	(#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)	51978
#29	bypass or surgery or construct* or reconstruct* or graft*	97587
#30	occlu* or reocclu* or re-occlu*	8491
#31	MeSH descriptor Blood Vessel Prosthesis explode all trees	407
#32	MeSH descriptor Blood Vessel Prosthesis Implantation explode all trees	412
#33	(#29 OR #30 OR #31 OR #32)	103185
#34	(#28 AND #33)	14362
#35	(#34 AND #10)	2700

Appendix 2. 2003 CENTRAL search strategy

- #1 ARTERIAL OCCLUSIVE DISEASES single term (MeSH)
- #2 (peripheral next arterial next occlusive next dis*)
- #3 (arterial next occlusive next dis*)
- #4 (#1 or #2 or #3)
- #5 INTERMITTENT CLAUDICATION single term (MeSH)
- #6 (intermittent next claudication)
- #7 (#5 or #6)
- #8 (critical next limb next isch*)
- #9 (#4 or #7 or #8)
- #10 (femoropopliteal next bypass)
- #11 (bypass next surgery)
- #12 (peripheral next arterial next bypass*)
- #13 femorodistal*
- #14 (femoro next distal*)

- #15 (#10 or #11 or #12 or #13 or #14)
- #16 ANTICOAGULANTS explode all trees (MeSH)
- #17 anticoagulant*
- #18 antithrombotic*
- #19 (#16 or #17 or #18)
- #20 (#9 and #15 and #19)

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>.

CAPPA feedback, 10 April 2014

Summary

First of all we like to compliment authors with their extensive work¹ on the topic of antithrombotics and infrainguinal arterial bypass surgery. Periprocedural prophylactic antithrombotics (PPAT) involves every day practice around the world during arterial interventions in the vascular patient, but is subject to much discussion and evidence based consensus is lacking.

To increase insight in periprocedural prophylactic anticoagulation and to develop evidence based guidelines on this topic for vascular surgery and interventional radiology, a study group was instituted in the Netherlands: CAPPA: Consensus on Arterial PeriProcedural Anticoagulation. This group consists of Dutch vascular surgeons and interventional radiologists and is supported by the Dutch Boards of Vascular Surgery and Interventional Radiology. In our effort to elucidate PPAT we have found two misinterpretations of study data in your review. Correction of this data alters the interpretation and outcome of part of the meta-analysis in your review.

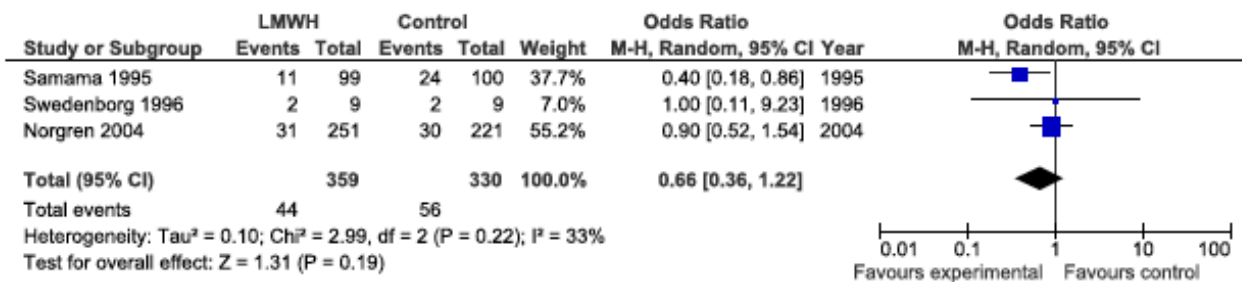
After 2 extensive surveys on daily practice of antithrombotics amongst vascular surgeons² and interventional radiologists³, we performed a systematic review⁴ on the subject of "prophylactic periprocedural antithrombotics in open and endovascular abdominal aortic (AAA) repair". Another systematic review was performed on the subject of "prophylactic intraoperative antithrombotics in open infrainguinal bypass surgery (IABS)". This review has recently been accepted for publication by the Journal of Cardiovascular Surgery (Torino).

While performing this systematic review, we thoroughly studied the manuscripts of the Cochrane review on antithrombotics administered during surgical procedure, especially the sub-heading "Unfractionated heparin (UFH) versus low molecular weight heparin (LMWH)", on page 6, 10 and 12. For accurate interpretation of the data we have contacted authors of included studies. The work by Norgren et al⁵ is one of the key studies of the review and the exact definition of distal reconstructions depicted in his study was not completely clear for us. Dr Norgren clarified to us by mail:

"Distal reconstructions imply a distal anastomosis below the BK popliteal artery (mainly crural arteries or ADP). Proximal reconstructions mean aorto-iliac, aorto-femoral and iliaco-femoral". This means that the numbers depicted in the meta-analysis in the Cochrane review should be corrected for the patency and mortality at day 30: included patients for infrainguinal reconstructions should be: 174 +77 for the LMWH group and 221 for the UFH group. This alteration of data affects the outcome of the meta-analysis, since now no significant difference between the two groups can be found.

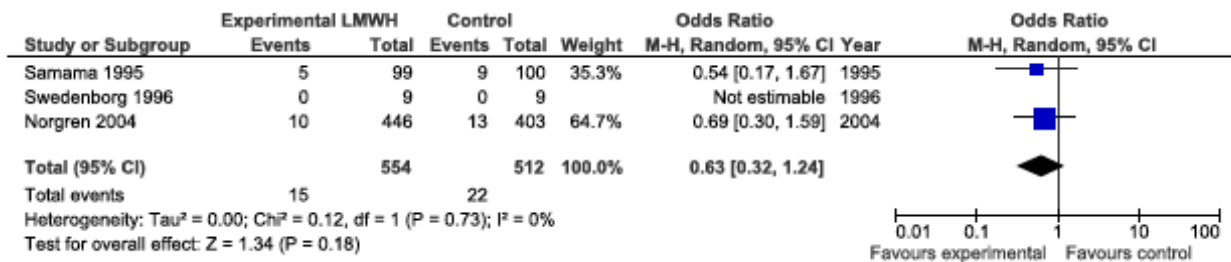
Patency at day 30, see [Figure 3](#)

Figure 3. CAPPA feedback April 2014: Patency at day 30



Mortality at day 30, see [Figure 4](#)

Figure 4. CAPPA feedback April 2014: Mortality at day 30



On the study of Swedenborg et al⁷, it was stated on page 10 of the Cochrane review, that "No time points were included and so the data could not be included in the meta-analysis". After additionally contacting prof. Swedenborg by mail, it was established that the follow up in his study⁷ was 30 days. Therefore we included the data from that study in our meta-analysis.⁵⁻⁷

Stated by the authors of the Cochrane in the discussion on page 12 is that "Pooled intention-to-treat data at day 30 did show a marginally positive effect for LMWH over UFH but a much larger cohort of patients receiving venous and artificial bypasses would have to be evaluated for reliable comparison in the future". From our forest plot it can be deducted that not even this marginal effect is present.

We realize that our remarks are of only very minor importance and we agree with the conclusion of authors that more RCTs should be executed on this topic before any reliable conclusion can be drawn on the topic of LMWH versus UFH as periprocedural prophylactic antithrombotic. We would be obliged if our, small, additions to the Cochrane Review will be published in your Journal.

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Reply

This review has been taken on by new authors who are currently updating the review. The review authors will respond to this feedback as part of the updated review.

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Feedback: On behalf of the CAPPA study group

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WHAT'S NEW

Date	Event	Description
23 January 2023	Amended	This review has been superseded by Cochrane Reviews: 'Antithrombotics after infra-inguinal bypass grafting' (doi.org/10.1002/14651858.CD015141) and 'Antithrombotics after infra-inguinal peripheral endovascular treatment' (doi.org/10.1002/14651858.CD015142) and will no longer be updated.

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 4, 2003

Date	Event	Description
21 April 2014	Feedback has been incorporated	Feedback submitted and added to review.
23 March 2011	New search has been performed	Searches were re-run and the review updated. Three additional studies were included and two additional studies were excluded.
23 March 2011	New citation required but conclusions have not changed	The review was updated by new authors.
14 February 2011	Amended	Link to anticoagulant feedback added

CONTRIBUTIONS OF AUTHORS

For this update Alistair Geraghty (AG) and Karen Welch (KW) independently selected trials, extracted data and carried out data analyses. AG updated the text of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

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

INDEX TERMS**Medical Subject Headings (MeSH)**

Arteriosclerosis [surgery]; Fibrinolytic Agents [*therapeutic use]; Graft Occlusion, Vascular [*prevention & control]; Intermittent Claudication [surgery]; Ischemia [surgery]; Leg [blood supply]; Peripheral Vascular Diseases [*surgery]; Randomized Controlled Trials as Topic; Thrombosis [*prevention & control]; Vitamin K [*antagonists & inhibitors]

MeSH check words

Humans