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CHAPTER 2

ANTITHROMBOTIC AGENTS FOR PREVENTING THROMBOSIS AFTER PERIPHERAL ARTERIAL BYPASS SURGERY: A META-ANALYSIS

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This chapter summarizes a systematic review, produced for the Cochrane Review Group on Peripheral Vascular Diseases; accepted for publication in the Cochrane Library.
Summary

Chronic peripheral vascular disease (PVD) is frequently treated by implantation of either an infrainguinal autologous vein or artificial graft. To prevent graft occlusion, patients are usually given an antiplatelet or antithrombotic drug, or a combination of both. It is uncertain which drug is optimal to prevent infrainguinal graft occlusion.

To evaluate whether antithrombotic treatment in patients with chronic PVD undergoing infrainguinal bypass surgery improves graft patency, limb salvage and survival we performed a meta-analysis of randomized clinical trials (RCTs).

For each trial, the number of patients originally allocated to each treatment group and the frequency of outcomes were extracted and pooled for an intention-to-treat analysis. Data collection on each trial comprised inclusion and exclusion criteria, patient details, type of graft, type and dose of antithrombotic therapy used, outcome, and side effects.

The combined results of three trials evaluating vitamin K antagonists (VKA) versus no VKA, suggest that oral anticoagulation favours venous, but not artificial, graft patency, as well as limb salvage and survival. Two other studies comparing VKA with aspirin, or aspirin/dipyridamole, supported a superior effect of VKA on the patency of venous but not artificial grafts. Subgroup analysis for artificial grafts as performed in one trial showed a favourable effect of antiplatelet agents on synthetic bypasses. In two trials with a relatively small number of patients low molecular weight heparin treatment was associated with a lower incidence of early postoperative graft thrombosis compared to treatment with unfractionated heparin. In conclusion, patients operated on for an infrainguinal venous graft should be treated with VKA, whereas patients receiving artificial grafts might profit more from platelet inhibitors (aspirin). Randomised controlled trials with larger patient numbers comparing antithrombotic therapies with either placebo or antiplatelet therapies are needed in the future.
Introduction

Lower limb atherosclerosis may manifest as pain on walking (intermittent claudication, IC), and, if more severe, pain while at rest, ulceration and gangrene (critical limb ischaemia, CLI). IC corresponds to Fontaine's classification stage II, and CLI to stages III and IV.

Treatment in selected patients includes placement of a femoro-popliteal or femoro-distal bypass graft to divert blood past the occluded arterial segment, thereby improving perfusion of blood to the limb, relieving the symptoms of claudication or rest pain, and avoiding amputation for ulceration and gangrene (limb salvage). Several different materials may be used for bypass grafting: a section of the patient's own vein (autologous vein graft), artificial graft such as Dacron or polytetrafluoroethylene (PTFE), treated human umbilical vein (taken from a placenta), or a combination of these materials. Graft patency is dependent on many factors including the indication for surgery (IC, CLI), quality of arterial inflow and outflow, type of graft used, surgical technique, progression of atherosclerosis in the proximal or distal arteries, and graft stenosis due to neo-intimal hyperplasia.

The incidence of graft failure (graft occlusion) for above knee femoro-popliteal bypass grafts a year after grafting were described by the European Consensus Document on Critical Limb Ischaemia\(^1\) as 15% when vein is used\(^2\), 20% when PTFE is used\(^3\), and 45%, and 75% respectively, for below knee grafts. Approximately 25% of these failures occur within one month postoperatively (acute phase), of which 10% are due to a consequence of technical error\(^4\) or to thrombogenic graft material\(^5\). The remaining 15% are considered as unexpected early graft failures and might be caused by an increased prothrombotic state. Eighty percent of all graft failures occur between one month and two years postoperatively due to the development of graft stenoses (intermediate and long-term restenosis)\(^6\). Two to three percent fail each year thereafter due to progression of native atherosclerosis in the proximal or distal arteries\(^6\). If blood flow in failed grafts cannot be restored, and further bypass surgery is not possible, then perfusion may be so poor that the limb cannot remain viable and amputation is required. Successful prevention of graft failure, and thus the avoidance of surgical re-intervention is of major clinical and economic importance\(^9\).

There is evidence that patients with lower limb atherosclerosis frequently tend to have a prothrombotic state\(^10,11\). Furthermore, the body's physiological stress response to surgery may add to a prothrombotic state. Therefore, it is important to discover whether post-operative treatment following infrainguinal bypass grafting should include long- or short-term anticoagulation in order to counteract the risk of a prothrombotic state, and if so, whether the same treatment is optimal for all kinds of grafts and patients. Although several reviews have been published over the past 10 years\(^12-16\) addressing similar questions, none of these a reviews met current methodological standards. It was the objective of this study to determine the efficacy of
antithrombotic drugs in patients with lower limb atherosclerosis (both IC and CLI) undergoing femoro-popliteal and femoro-distal bypass grafting. Outcomes included the overall success of therapy (graft patency and limb salvage rates) and complications of treatment.

**Methods**

**Criteria for considering studies for this review**

*Types of studies* Trials in which participants have been randomly allocated to receive either antithrombotic therapy versus placebo, or one antithrombotic regimen versus another, or antithrombotic therapy versus an alternative treatment. Trials using alternation were included, and considered as quasi-randomised clinical trials.

*Types of participants* All patients undergoing femoro-popliteal or femoro-distal bypass grafting for the treatment of intermittent claudication and critical limb ischaemia. Patients undergoing bypass surgery for trauma were excluded. Quality control measures to assess the bypass graft (such as doppler- and duplexsonography or angiography), the graft material used, the sites of the proximal and distal anastomosis and the patient's risk factors for graft occlusion were recorded.

*Types of interventions* Either antithrombotic therapy versus placebo, or one antithrombotic regimen versus another, or antithrombotic therapy versus an alternative treatment. The type of therapy, dosage, time of starting in relation to surgery (pre- or post-operatively), and duration of therapy were recorded.

*Types of outcome measures*

1. Primary graft patency: i.e. patency rates after surgery without further intervention, as determined by clinical examination, measurement of ankle brachial pressure index (ABPI), Doppler or duplex sonography, or angiography.

- Limb salvage rate.
- Mortality.
- Side effects of treatment.

**Search strategy for identification of studies**

All publications which might contain reports of RCTs or controlled clinical trials of antithrombotic therapy after peripheral arterial bypass surgery in patients with IC and/or CLI were sought using the search strategy described by the Cochrane Review Group on Peripheral Vascular Diseases. This strategy includes hand searching of relevant medical journals and extensive MEDLINE and EMBASE searches (up to and including December 2000). Additional searches on MEDLINE and EMBASE were made using the terms 'anticoagulant' and 'arterial surgery'.
Additional trial references were sought by: reviewing reference lists of papers resulting from this search; handsearching proceedings from meetings of the Vascular Surgical Society of Great Britain and Ireland, European Vascular Surgical Society, and North American Society of Vascular Surgery; and through contact with authors of published trials to enquire whether they were aware of any unpublished trials.

Methods of the review
The reviewers independently selected which trials were suitable for inclusion in the review. Disagreements were resolved by discussion. The methodological quality of each trial was assessed independently by two reviewers using the checklist provided by the Peripheral Vascular Diseases Collaborative Review Group, with emphasis on concealment of randomisation. Each trial was given an allocation score of A (clearly concealed), B (unclear if concealed), or C (clearly not concealed) and a summary score of A (low risk of bias), B (moderate risk), or C (high risk). Trials scoring A were included and those scoring C were excluded. For a trial scoring B, an attempt was made to obtain more information by contacting the author. If no additional information could be obtained, results of the analysis were considered with caution because of the moderate risk of bias. In the absence of consensus over the inclusion of a trial, a third opinion was sought.

For each trial, the number of patients originally allocated to each treatment group was extracted from the data and an 'intention to treat' analysis was performed. Data collection on each trial comprised inclusion and exclusion criteria, patient details (age, gender, co-morbidity), severity of arterial occlusive disease, as determined by ABPI and the European Consensus definition of CLI, type of graft (autologous vein, artificial), 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, compliance), and outcome (as mentioned in section 'criteria for considering trial for review'). The treatment and control groups were compared for important prognostic factors and differences described. If any of the above data were not available, further information was sought from the author. If possible, results of individual trials were confirmed in a common odds ratio, using a fixed effect model. The 95% confidence intervals of the effect sizes were calculated.

Methodological quality of included studies
All trials were open studies, and allocation was randomised, although concealment of randomisation was often not clearly reported. Contacting the authors did not provide any additional data, as raw data was no longer accessible or because authors did not respond to our inquiries. A formal meta-analysis was performed in three comparison categories, including two or three trials each: 1) coumarin-derivatives compared to no coumarins, 2) coumarin-
derivatives compared to aspirin or aspirin/dipyriramol\textsuperscript{17,18}, and 3) low molecular weight heparin versus unfractionated heparin for early occlusion\textsuperscript{22,24}.

Results

Studies identified

Our search yielded 15 eligible studies which investigated the efficacy of anticoagulant treatment in infrainguinal bypass surgery\textsuperscript{17-25}. Six of these studies could not be included for the following reasons: studies were retrospective\textsuperscript{20-26}, identical cohorts of patients were reported in interim analyses\textsuperscript{20,25}, treatment groups were not compared to a control group\textsuperscript{15}, or other levels than the femoro-popliteal or femoro-distal were investigated. The studies are described in detail in the appendix.


The number of events in these three studies was calculated from the survival curves, unless reported otherwise. Intention-to-treat analysis could be performed for bypass patency rates, limb salvage, and survival (Arfvidsson et al 1990; 68 randomised, of whom 20 underwent TEA versus 62 randomised, of whom 14 underwent TEA). The three trials yielded a total of 146 grafts and patients in the treatment group versus 136 grafts and patients in the control group for inclusion.

Three months postoperatively, antithrombotic treatment for all grafts, including venous and PTFE, compared to no anticoagulant treatment had a statistically non-significant effect (OR 0.66, CI 95\% [0.31,1.40]) on primary patency. At timepoints 6, 12, 24 months, and 5 years a positive effect of coumarins on graft patency was evident for all grafts with the following odds ratios: six months OR 0.55, CI 95\% [0.29,1.06], 12 months OR 0.47, CI 95\% [0.27,0.83], 24 months OR 0.54, CI 95\% [0.32,0.91], five years OR 0.57, 95\% [0.33,0.99].

Subgroup analysis defined for graft type with 125 included patients treated with VKA versus 110 control patients showed a positive effect for venous grafts (three months OR 0.46, CI 95\% [0.14,1.48], six months OR 0.40, CI 95\% [0.16,0.97], 12 months OR 0.34, CI 95\% [0.17,0.68], 24 months OR 0.48, CI 95\% [0.26,0.87], and five years OR 0.51, CI 95\% [0.27,0.94]), whereas no effect for artificial conduits at the same timepoints was found (six months OR 0.87, CI 95\% [0.19,3.92], 12 months OR 1.20, CI 95\% [0.28,5.18], 24 months OR 0.97, CI 95\% [0.24,3.92], five years OR 1.05, CI 95\% [0.25,4.42]).

The effect of coumarins on limb salvage, and survival could be calculated for 139 patients in the treatment group and 129 controls, since for seven patients with early occlusion in each group of the Arfvidsson study no follow-up data were provided. There was a tendency for coumarins to reduce limb loss during the whole observation time (three months OR 0.24, CI 95\% [0.08,0.73], six months OR 0.30, CI 95\% [0.11,0.83], 12 months OR 0.47, CI 95\% [0.20,1.13],
24 months OR 0.50, CI 95% [0.25, 0.98], and five years OR 0.34, CI 95% [0.17, 0.70]). For survival, a non-significant trend was observed (six months OR 0.34, CI 95% [0.08, 1.39], 24 months OR 0.66, CI 95% [0.38, 1.15]).

The effect of coumarins on patency, limb salvage, and survival was similar in the two trials by Kretschmer and Arfvidsson, in which patients did not receive aspirin. In the trial of Sarac 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. 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.

Bleeding complications requiring hospitalisation occurred in eight patients in the treatment group and in none in the control group in Arfvidsson's trial; one patient in the treatment group in Kretschmer's trial had a lethal bleeding complication. In Sarac's study four (14.4%) patients of the treatment group required operative evacuation of wound hematoma compared to only one in the control group. Furthermore, in the warfarin/aspirin group one gastrointestinal bleeding occurred and three in the aspirin group, and analogously, one, resp. one, central nervous system and three, resp. genitourinary bleedings were recorded.

2. **VKA VERSUS ASPIRIN OR ASPIRIN/DIPYRIDAMOLE** (BOA 2000; Schneider 1979)

Patency for all grafts, including 1356 patients in the coumarin group and 1385 in the aspirin group, postoperatively showed almost no difference for coumarin versus aspirin (at three months postoperatively OR 0.89, CI 95% [0.69, 1.15]; six months OR 0.99, CI 95% [0.81, 1.22]; 12 months OR 0.92, CI 95% [0.77, 1.11]; 24 months OR 0.91, CI 95% [0.77, 1.08]).

Intention-to-treat analysis for venous grafts included 814 patients randomised to coumarin treatment versus 823 to aspirin. Coumarins had a statistically significant favourable effect on patency rates compared to antiplatelet treatment either with aspirin alone or with a combination of aspirin and dipyridamole (at three months OR 0.66, CI 95% [0.46, 0.93]; six months OR 0.71, CI 95% [0.53,0.95]; 12 months OR 0.65, CI 95% [0.49, 0.85]; 24 months OR 0.59, CI 95% [0.46-0.76]).

For patients treated with an artificial conduit - a group that had been analysed only by the BOA trialists (542 in coumarin group versus 562 in aspirin group) - no statistically significant positive effect was found for coumarins (at three months OR 1.32, CI 95% [0.89,1.95]; six months OR 1.47, CI 95% [1.08,1.99]; 12 months OR 1.33, CI 95% [1.02,1.74]; 24 months OR 1.41, CI 95% [1.11,1.80]).

The trials did not report data on limb salvage and survival suitable for a formal meta-analysis. However, in the BOA trial limb amputation had to be performed in 100 (7.5%) coumarin treated...
and 110 (8.3%) aspirin treated patients, whereas haemorrhage necessitating hospital admittance was reported for 108 (8.1%) and 56 (4.2%) patients, respectively, in these groups. In the Schneider 1979 trial adverse effects were reported for two patients (0.6%) stopping coumarin treatment for bleeding complications, and 13 patients (21%) stopping aspirin for different reasons. Three patients from each group died within two years. Major haemorrhage requiring hospital attendance in the BOA 2000 trial was reported as 119 (9%) in the oral anticoagulant group versus 59 (4.5%) in the aspirin group. No distinct data were reported for assisted primary patency or secondary patency rates.

**A. Heparin Versus LMWH (Samama 1994; Swedenborg 1996)**

An intention-to-treat-analysis performed by the trialists yielded eight of 99 (7.9%) versus 22 of 100 (22%) occlusions on day 10, and 11 of 99 (10.9%) versus 24 of 100 (24%) on day 30, respectively. A separate intra-protocol analysis was performed in addition, 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. This difference did not reach statistical significance.

In Swedenborg's trial, early graft occlusion occurred in two cases of each group. Analysis of both trials regarding primary graft patency showed an OR 0.38, CI 95% [0.18,0.80] for 10 days postoperatively and an OR 0.41, CI 95% [0.20, 0.85] for 30 days postoperatively, favouring LMWH versus UFH for early graft thrombosis.

**4. LMWH VERSUS ASPIRIN/DIPYRIDAMOLE** (Edmondson 1994)

In the 94 patients randomised to LMWH and the 106 patients to ASA/DIP, there were 12 and 21 occlusions at six and 12 months, respectively, in the LMWH group, and 30 and 38 occlusions at the same timepoints in the aspirin group. Thus, odds ratios at six and 12 months were 0.60, CI 95% [0.29, 1.27] and 0.84, CI 95% [0.47, 1.51] respectively, showing no significantly positive effect for LMWH. Nine patients in the LMWH group (four with patent grafts) and two in the aspirin group died during follow-up. No major bleedings or adverse events occurred.

**5. HEPARIN VERSUS ANCROD (Cole 1993)**

Among the 14 patients randomised to either heparin or ancrod, one graft in each group occluded within 24 h postoperatively. One patient suffered from postoperative bleeding and graft failure in the ancrod group. No further events occurred during one month follow-up. Primary patency at one month was 12/13 and 13/14 with an OR 1.08, CI 95% [0.06,18.18]. Ancrod was as efficient as unfractionated heparin. No data on limb salvage, survival, or primary assisted patency were reported.
Graft thrombosis occurred intraoperatively in five out of six patients in the AT group, whereas no occlusion occurred in the heparin group. One patient in the heparin group suffered from major bleeding and another died from myocardial infarction on the second postoperative day.

Discussion

Our meta-analysis shows that in infrainguinal venous bypasses vitamin K antagonists (VKA) have a favourable effect on patency rates, limb salvage, and survival, whereas patients undergoing artificial bypass surgery seem to benefit from antiplatelet therapy regarding primary patency and limb salvage. This conclusion could be drawn from the comparison performed between patients treated with coumarins versus patients receiving no vitamin K antagonists, both in the presence and in the absence of aspirin, and is consistent with the findings of the study by Schneider 1979 and the BOA trialists who compared coumarin-derivatives to aspirin both in venous and artificial grafts. Moreover, there are indications for low molecular weight heparin to improve early patency in comparison to unfractionated heparin.

However, it should be noted that these results are based on a relatively small number of clinical trials including a total of 3240 patients undergoing infrainguinal bypass surgery who were randomised to one of four different drugs, i.e. to coumarin-derivatives, aspirin with or without dipyridamol, unfractionated heparin, low molecular weight heparin, or to no drug.

For the effect of oral VKA and aspirin (ASA) on patency, some interesting observations were made by performing subgroup analysis defining the type of graft. Thereby, comparison of VKA versus no VKA had a significant and strong positive effect favouring VKA on the 235 patients extracted from three trials (Arfvidsson 1990; Kretschmer 1992; Sarae 1998) receiving a venous graft, with odds ratios ranging from 0.36 to 0.51 within two to five years follow-up. Similarly, comparison of VKA versus ASA in 1637 patients (BOA 2000; Schneider 1979) showed no effect on venous grafts for ASA, but significant effect of VKA (OR 0.59, CI 95% [0.46, 0.76]). In contrast, in the 1104 patients receiving artificial grafts, VKA could not improve patency, whereas ASA was favouring the outcome within two to five years (OR 1.32 95% CI, CI 95% [0.89, 1.94]).

The effect of LMWH and UFH on early patency was evaluated in two trials including only 217 patients. However, the stronger effect of LMWH demonstrated in all grafts is consistent with trials comparing the two drugs in recurrent venous thromboembolism, where LMWH has also been more potent and safer. However, much larger cohorts of patients receiving venous and artificial bypasses will have to be evaluated in the future to obtain a reliable comparison between LMWH and UFH.

The presented findings are not only consistent within the different trials described and analysed herein, but are also biologically plausible. Venous grafts, once they have been
incorporated into the high pressure system in the human leg, lose their endothelial layer within days, being literally denuded. Exposure of the subendothelial layers to the blood stream triggers the expression and release of tissue factor, the initiator of the coagulation cascade. This process results in locally increased thrombin generation, and subsequent thrombus formation. It is enhanced by a simultaneous inflammatory process caused by the release of interleukins (IL-1b, IL-6, TNF) that attract and activate granulocytes and monocytes. The latter are able to express additional tissue factor, thus enhancing the local thrombogenic process. Although activated platelets play an important role in thrombus formation, it seems that the activated coagulation system at the graft site of endothelial injury has a stronger impact, initially necessitating some kind of thrombin inhibition, which is achieved by VKA. On the other hand, inhibition of platelet deposition on prosthetic grafts might be the more efficient therapy for patients with PTFE and dacron bypasses.

Finally, it should be mentioned that extracting data from the described trials was difficult, as most publications did not provide the raw data needed for an appropriate analysis. Subgroup analysis, in particular, in which more detailed patient characteristics such as levels of the distal anastomosis, distal outflow, or secondary graft patency could have been taken into account, could not be performed. Contacting the authors was usually not very successful, as raw data was no longer available or authors did not reply. Therefore, numbers of patients and events had to be calculated from the survival curves. However, we do think that our conclusions are valid and reliable, because of their impressive consistency on the effect of VKA on venous bypasses and, likewise, the favourable effect of aspirin on artificial conduits found in all the trials. Consequently, it is unlikely that there is a publication bias. In addition, companies that provide antithrombotic and antiplatelet drugs were contacted, and so far no unpublished or ongoing trials have been detected.

Patients submitted to infrainguinal venous graft surgery should be treated with VKA. Patients receiving an artificial graft might profit more from platelet inhibitors (aspirin). Prevention of early occlusion in infrainguinal bypass surgery by perioperative treatment with low molecular weight heparins seems to be more successful than administration of unfractionated heparin.

Randomised clinical trials performed with appropriate concealment of allocation, are called for to evaluate the efficacy at the lowest possible effective dose of aspirin in infrainguinal venous and artificial grafts. With regard to vitamin K antagonists, the studies presented did not investigate how long therapy should be continued; consequently, RCTs designed to determine optimal therapy duration are needed. In addition, the effect of LMWH compared to UFH in perioperative treatment should be evaluated in larger RCTs including subgroup analysis of venous and artificial grafts. Furthermore, presentation of data should be much more detailed and not show only survival curves for overall patency. Tables showing raw data would improve the transparency of the trial performance, and allow comparison of endpoints at consecutive
timepoints of follow-up. Thus, readers would be able to identify the number of occlusions or other endpoints at different timepoints in each comparison group, as well as in subgroups defined by bypass material, above and below knee anastomosis, and in- and outflow conditions.

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References


Appendix

1. VITAMIN K ANTAGONISTS (VKA) VERSUS NO VKA
Kretschmer 1992
Open, randomized clinical trial of 130 patients with chronic arterial occlusive disease of the femoropopliteal level, undergoing elective infrainguinal venous bypass surgery. Sixty-six patients were randomly assigned to treatment with coumarin-derivatives and 64 to no anticoagulation. Randomisation was adapted using sex, age, diabetes mellitus, blood pressure, and clinical status as stratifying variables. In patients randomised to coumarin-derivatives, phenprocoumon was started in the first or second postoperative week, aiming at 15-25% for Quick values, 10-20% for Hepatoquick, or five to 12% for Thrombotest. Patency assessment was performed by evaluation of pulsatile Doppler flow and ABPI which prompted an angiography at an ABPI-fall of 30%. Primary graft occlusion, limb loss and death were assessed at three, six, nine, and 12 months, and every six months thereafter for 10 years. Serious drug related complication was recorded in respect to causes of death. Non-fatal bleeding complications were not reported. Successfully treated stenoses were considered as patent bypasses. Allocation score A, summary score B.

Arvidsson 1990
Open randomized clinical trial with 130 patients undergoing infrainguinal revascularisation. Thirty-four patients underwent thrombendarterectomy (TEA) and were therefore not considered for the current analysis. Thus, 96 patients, who underwent venous or artificial bypass surgery, were included, and heparin was administered postoperatively as an infusion of 10-20 000 IU/24 hours for three to five days. In those randomised to coumarin therapy, dicoumarol was started within two days postoperatively, aiming at Simplastin levels of 10-20%. Graft-occlusion, limb loss and death were primary endpoints. Bleeding complications requiring hospitalisation were recorded. Assessment of graft patency was performed by Doppler flow measurement and arteriography when in doubt. Follow-up was once monthly for six months, thereafter at nine and 12 months, further by yearly contacts. Allocation score B, summary score B.

Sarac 1998
Open randomized clinical trial with 56 patients scheduled for venous infrainguinal bypass surgery. All patients were defined as high risk patients for graft occlusion (marginal venous conduit, poor arterial runoff, prior graft failure). Thirty-two patients were randomized to warfarin and aspirin and 24 to only aspirin postoperatively. Anticoagulant therapy was started immediately after surgery with a target INR of 2-3. Primary endpoints were graft patency and limb loss. Graft patency was assessed by evaluation of ABPI and duplexsonography. A decrease of 0.15 in ABPI and a graft velocity of more than 150 cm/sec or less than 30 cm/sec prompted 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. Allocation score B, summary score B.

2. VKA VERSUS ASPIRIN/DIPYRIDAMOL

Schneider 1979

Open, randomized clinical trial performed from 1974 to 1978. Patients underwent either femoro-popliteal thrombendarterectomy or femoro-popliteal venous bypass surgery. Of a total of 213 patients 91 were randomised to a femoro-popliteal venous bypass. All patients were treated with therapeutic doses of heparin and coumarins in the first one to two weeks postoperatively, and were then randomly allocated to either coumarins (Quick, aim 25-30%) or aspirin, or aspirin/dipyridamol. Follow-up period was two years with three monthly visits during the first year and six monthly contacts in the second year. 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 objectively assessed by angiography. Drug assessment was performed by measurement of prothrombin time for coumarins and ASA levels in urine. Death and bleeding complications were recorded. Allocation score B, summary score B.

BOA 2000

Multicenter, open randomized clinical trial including 2690 patients undergoing infrainguinal bypass surgery, of whom 1339 were assigned to coumarin-derivatives (phenprocoumon or acenocoumarol) and 1351 to aspirin 80 mg daily started within five days after surgery. Intended international normalised ratio (INR) range was 3.0-4.5. Follow-up was at three and six months, thereafter every six months with a mean observation time of 21 months. Both venous and artificial bypasses were employed. Primary endpoint was graft patency, assessed clinically and with doppler or duplex sonography and by arteriography if indicated. Secondary endpoints were vascular death, myocardial infarction, stroke, amputation, vascular intervention, major haemorrhage. Allocation score A, summary score B.

3. UNFRACTIONATED HEPARIN VERSUS LOW MOLECULAR WEIGHT HEPARIN

Early infrainguinal graft failure has been evaluated after intra- and postoperative administration of unfractionated heparin versus low molecular weight heparin in two trials by Samama et al in 1994 and Swedenborg et al in 1996.

Samama 1994

Open randomized multicenter study conducted between 1990 and 1992 in patients undergoing elective femoro-distal reconstructive surgery. 100 patients were randomly assigned to treatment with unfractionated heparin (UFH) and 99 to low molecular weight heparin (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. 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. Heparin induced thrombocytopenia was defined as a decrease of > 50% from the initial platelet count. Data was analysed on an intention-to-treat basis for drug efficacy. In an additional per-protocol analysis 67 angiographically assessed grafts (LWMH-group) were compared to 64 grafts (UH-group). Allocation score B, summary score B.

Swedenborg 1996

Open randomized clinical trial of 18 patients undergoing infrainguinal bypass surgery, comparing the effect of low molecular weight heparin (LMWH, Fragmin) with unfractionated heparin (UFH) on early graft patency. However, the main focus of this study was to evaluate hypercoagulability as a risk factor in these patient groups, and early graft occlusion was only of secondary interest. Therefore, the data on assessment of patency is limited. An attempt to contact the authors was unsuccessful. Eighteen saphenous vein grafts were investigated in 18 patients, nine patients per group were treated with a dose of 70 anti-Xa activity U/kg of UFH or LMWH (Fragmin) iv once during surgery. 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. Allocation score B, summary score B.

4. LOW MOLECULAR WEIGHT HEPARIN VERSUS ASPIRIN/DIPYRIDAMOLE
Edmondson 1994

Open randomized clinical trial in patients undergoing femoropopliteal bypass grafting, of whom 94 were randomised to 2500 IU LMWH (Fragmin) once daily subcutaneously and 106 to 300 mg aspirin and 100 mg dipyridamole, both three times per day for three months. On the seventh postoperative day patients were assessed for 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, if indicated supplemented by arteriography or duplexsonography. Allocation score B, summary score B.
5. ANCROD VERSUS HEPARIN
Cole 1993
Open randomized clinical trial evaluating the effect of intra- and perioperative administration of heparin versus ancrod in patients undergoing infrainguinal bypass surgery (venous and artificial) on fibrinogen depletion and early graft patency. Fourteen patients were randomised 100 IU/kg heparin intravenously during surgery and 14 patients to 70 IU ancrod over 12 hours preoperatively until fibrinogen levels were stabilised between 0.2-0.5 mg/l. There was one withdrawal from the ancrod group. Ancrod was continued postoperatively for 48 h. Graft patency was determined clinically by ABI and doppler flow measurement before hospital discharge and at one month. Allocation score B, summary score B.

6. HEPARIN VERSUS ANTITHROMBIN
Nydahl 1992
Open randomized clinical trial, with six patients randomised to perioperative treatment with a single iv dose of 5000 IU unfractionated heparin and six patients to 1500 IU antithrombin into the femoral artery. Patency assessment of the graft was performed by ABI evaluation and doppler flow measurement one month after surgery. Allocation score B, summary score B.