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Dörffler-Melly, J.

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CHAPTER 3

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

Janine Dörffler-Melly¹, Maria M.W. Koopman¹, Harry R. Büsser¹, Martin H. Prins²

Departments of Vascular Medicine¹ and Epidemiology & Biostatistics², Academic Medical Center of Amsterdam, Amsterdam, the Netherlands

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

Peripheral vascular disease is frequently treated by implantation of an infrainguinal autologous venous or artificial graft. Occlusion rates vary between 15 and 75%, depending on a number of risk factors. To prevent graft occlusion, patients are usually treated with either an antiplatelet or antithrombotic drug, or a combination of both. It is unknown which regimen is optimal to prevent infrainguinal graft occlusion. The aim of this analysis was to evaluate whether antiplatelet treatment in patients with chronic PVD undergoing infrainguinal bypass surgery improves graft patency, limb salvage and survival by performing a meta-analysis of randomised clinical trials.

A literature search was performed in MEDLINE from 1966-onwards and EMBASE from 1980-onwards. Data was extracted and pooled for an intention to treat analysis. The treatment and control groups were compared for important prognostic factors and differences are described.

The administration of platelet-inhibitors such as acetyl salicylate (ASA), ASA/dipyridamole (DIP), ticlopidine, or pentoxifylline (PTX), results in improved venous and artificial graft patency compared to no treatment. However, subgroup analysis for graft-type, i.e. venous versus artificial shows that patients receiving a prosthetic graft will profit more from ASA or ASA/DIP administration than those receiving a venous graft. Antiplatelet therapy with ASA has an inferior effect on venous graft patency compared with vitamin K antagonists (VKA). The effect of antiplatelet therapy on graft patency and amputation in patients treated with an artificial graft should be evaluated in larger RCTs. For further improvement of antiplatelet therapy in venous grafts, it might be worth, to combine aspirin and a thienopyridine, such as for example clopidogrel.
Introduction

Symptomatic peripheral arterial occlusive disease (PAOD) of the lower extremities may present itself as either intermittent claudication (IC), i.e. as pain on walking, or at a progressive stage, as critical limb ischemia (CLI), i.e. as pain at rest, ulceration and gangrene. The implantation of a femoro-popliteal or femoro-distal bypass graft is one option of treatment for patients, who are jeopardized with limb loss or who are greatly impaired in their walking ability by the disease. Through placement of an infrainguinal graft the occluded arterial segment is bypassed, thereby improving limb perfusion, relieving the symptoms of claudication or rest pain, and avoiding amputation for ulceration and gangrene (limb salvage).

Patency rates for femoro-popliteal and femoro-crunal grafts depend on several risk factors, such as graft material, length of the the bypass, site of the distal anastomosis, outflow-conditions in the calf, presence of diabetes mellitus, and gender. Thus, autologous saphenous vein is superior to artificial materials such as Dacron or PTFE, the distal anastomosis placed above knee represents a lower risk for graft failure, and male gender has a better outcome than female gender. Graft failure occurs for two pathophysiological reasons: most frequently, at the site of the distal or proximal anastomosis smooth muscle cells of the medial layer of the vessel wall grow into the intimal layer (neo-intimal hyperplasia), thus narrowing the diameter of the perfused graft (stenosis). When more than 70% of the perfused diameter is reduced, the stenosis becomes hemodynamically significant, causing IC, and graft occlusion is often followed by the formation of a thrombosis at the stenotic site. 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 thus, the need for surgical reintervention, is of major clinical and economic importance. Occlusion rates vary between 15 and 75 %, depending on the various risk factors described above. In addition, in patients with lower limb atherosclerosis, platelet aggregation is frequently increased. Moreover, the body's physiological stress response to surgery is to cause a prothrombotic state. The intensity of platelet uptake by graft material has been shown to be inversely related to graft patency at one year. In animal experiments, antiplatelet drugs, when started before bypass surgery, have been shown to increase patency in artificial grafts when compared with no treatment.

To prevent graft occlusion, patients are usually treated with either an antiplatelet or antithrombotic drug, or a combination of both. It is unknown which regimen is optimal to prevent infrainguinal graft occlusion. The aim of this analysis was to evaluate whether antiplatelet treatment in patients with chronic PAOD undergoing infrainguinal bypass surgery improves graft patency, limb salvage and survival by performing a meta-analysis of randomized clinical trials.


**Methods**

**Objectives**

To determine the efficacy of pharmacotherapy using antiplatelet drugs in patients with lower limb atherosclerosis undergoing femoro-popliteal and femoro-distal bypass grafting. Outcomes will include the overall success of therapy (graft patency and limb salvage rates) and complications of treatment.

**Criteria for considering studies for this review**

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

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

*Types of interventions* Antiplatelet therapy versus placebo; one antiplatelet regimen versus another, or antiplatelet therapy versus alternative treatment. The type of therapy, dosage, time of starting compared with surgery (pre- or postoperatively), and duration of the therapy were recorded.


**Search strategy for identification of studies**

The search strategy was that adopted by the Cochrane Review Group on Peripheral Vascular Diseases. In addition, the following were reviewed:
1. Reference list of papers resulting from this search.
2. The National Library of Medicine's MEDLINE database systematically searched from 1966 - 1999 using the terms 'antiplatelet' and 'arterial surgery'
3. EMBASE searched from 1980 - 1999 using the same terms.
5. Authors of published trials were contacted to enquire if 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 reviewer 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 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 information by contacting the author. 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 included inclusion and exclusion criteria, patient details (age, gender, co-morbidity), severity of arterial occlusive disease (as determined by ankle brachial pressure index, ABPI, and the European Consensus definition of critical limb ischemia), type of graft (autologous vein, artificial, human umbilical vein, composite graft), level of proximal graft anastomosis (common superficial femoral artery) and distal anastomosis (above knee popliteal, below knee popliteal, distal arteries), type of antiplatelet therapy used (dose, commencement of therapy relative to surgery, duration of therapy, compliance), and outcome (as mentioned in section 'criteria for considering trial for review'). The treatment and control groups were compared for important prognostic factors. If any of the above data were not available further information was sought from the author. If possible, results of individual trials were combined in a common odds ratio, using a fixed effect model. The 95% confidence interval of the effect sizes were calculated.
**Methodological quality of included studies**

Randomisation was clearly concealed (score A) in 10 of 18 (55%) studies, while the potential for bias was lowest (summary score A) in 7 of the 18 (39%) trials. In general, data presentation was not separated for graft types, and number of grafts were frequently different from the number of patients, without appropriate documentation. All data were extracted including those patients that stopped drug administration for adverse effects or because they were lost to follow-up, to allow for an intention-to-treat analysis. Figures for graft failure were calculated from the survival curves, if raw data were not reported or unavailable after contacting the authors.

**Results**

**Description of studies**

Of all eligible trials 181-18 studies could be included in this analysis, while 7 trials26-34 had to be excluded because of one or more of the following reasons: lack of control group, no randomisation, retrospective study or selection or performance bias. Ehersman et al (1977) included a heterogenous cohort of patients treated on either the aorto-iliacal, femoro-popliteal, or both segment with either thrombendarterectomy or with a venous or prosthetic bypass. Results were not presented separately for patients treated with infrainguinal bypass surgery; consequently the study could not be included in our analysis. The studies are described in detail in the appendix.

**ASA (ASA) OR ASA/DIPYRIDAMOL (ASA/DIP) VERSUS NO ASA**

Seven trials could be included (Clyne CA 1987, Donaldson 1985, Franks 1992, Goldman 1984, Green 1982, Kohler 1984, McCollum 1991) to study the effect of ASA or ASA/DIP on infrainguinal bypass patency, with a total of 1094 patients randomised to the treatment (n = 572) or to the control group (n = 522). Odds ratio for primary occlusion at 12 months for all grafts was 0.58 [0.44, 0.77], showing a positive, statistically significant effect of ASA on infrainguinal grafts within one year (Figure 1). When subgroup analysis was performed for venous grafts alone including 3 trials (Clyne CA 1987, Franks 1992, McCollum 1991), this effect was attenuated to OR [95%CI fixed] 0.67 [0.48,0.94]. This attenuated effect of ASA became even more evident, when ORs were calculated for timepoints 1, 3, 6, and 24 months postoperatively with respective values of 0.77 [0.28, 2.10], 0.85 [0.54, 1.34], 0.88 [0.59, 1.31], 0.78 [0.56, 1.09]. Subgroup analysis for prosthetic grafts, however, showed a much stronger positive and statistically significant effect of ASA on primary patency, as calculated from 4 RCTs (Clyne CA 1987, Donaldson 1985, Goldman 1984, Green 1982), at all timepoints, 1, 3, 6, and 12 months (OR 0.22 [0.10, 0.50], 0.33
Amputation could not be evaluated as a secondary outcome, due to missing data.

**Figure 1. ASA or ASA/DIP versus no ASA: Primary occlusion in all grafts at 12 months reported in the publication**

| Study      | ASA/DIP | Nothing | OR (95% CI) OR (95% CI) |
|------------|---------|---------|-------------------------|-------------------------|
|            | n/N     | n/N     |                         |                         |
| Clyne ASA/DIP | 11/69   | 22/62   | 0.36 [0.16, 0.79]       |                         |
| Donaldson ASA/DIP | 4/32   | 15/33   | 0.21 [0.07, 0.60]       |                         |
| Franks ASA/DIP  | 6/80   | 9/65    | 0.51 [0.17, 1.48]       |                         |
| Goldman ASA/DIP  | 8/22   | 18/31   | 0.43 [0.14, 1.26]       |                         |
| Green ASA/DIP   | 6/32   | 10/17   | 0.17 [0.05, 0.58]       |                         |
| Kohler ASA      | 22/51  | 17/51   | 1.51 [0.68, 3.34]       |                         |
| McCollum ASA    | 63/286 | 74/263  | 0.72 [0.49, 1.06]       |                         |
| Total           | 120/572| 165/522 | 0.58 [0.44, 0.77]       |                         |

Analysis for cardiovascular events, was possible for 4 trials (Clyne CA 1987, Donaldson 1985, Green 1982, McCollum 1991) including 811 patients; thereby, ASA or ASA/DIP had a slight, statistically non-significant protective effect on postoperative myocardial infarction or stroke (OR 0.74 [95% CI 0.49, 1.13]). Gastrointestinal side effects as evaluated in 966 patients (Clyne CA 1987, Donaldson 1985, Goldman 1984, Green 1982, Kohler 1984, McCollum 1991) were increased, but not statistically significantly, in patients receiving aspirin (OR 1.44 [95% CI 0.92, 2.24]). OR for postoperative mortality was 0.82 [95% CI 0.52, 1.23], showing a slight tendency in favour of ASA or ASA/DIP. Major bleeding was not statistically significantly increased, as evaluated in 2 trials (Green 1982, McCollum 1991, OR 1.88 [95% CI 0.85, 4.16].
2. ASPIRIN (ASA) OR ASPIRIN/DIPYRIDAMOL (ASA/DIP) VERSUS PENTOXIFYLLINE (PTX)

The effect of PTX on graft patency compared to ASA or ASA/DIP treatment could only be evaluated in a formal analysis from two RCTs (Lucas 1984, Raithel 1987) at 6 months postoperatively. Thereby, 78 patients were assigned to ASA or ASA/DIP treatment and 73 to PTX with an OR of 1.40 [0.63, 3.11], showing an equal or slightly favouring, non-significant effect of PTX on primary graft patency. At other timepoints, only the study of Raithel provided raw data, showing a similar effect on graft patency of both drugs (OR 1.00 and 0.92).

3. ASPIRIN/DIPYRIDAMOL (ASA/DIP) VERSUS INDOMETHACIN (IND)

The single eligible RCT (D'Addato 1992) comparing ASA/DIP versus IND in 113 infrainguinal PTFE grafts (57 randomised to ASA/DIP and 56 to IND), showed a favourable effect of IND at 3 months postoperatively on graft patency, which did not reach statistical significance (OR 1.64 [0.52, 5.20]). This effect was attenuated within one year postoperatively to OR 1.33 [0.62, 2.90].

4. ASPIRIN/DIPYRIDAMOL VERSUS VKA

In the two studies (BOA 2000, Schneider 1979), primary patency for all grafts including 1356 patients in the coumarin group and 1385 in the ASA group 3, 6, 12, and 24 months postoperatively showed almost no difference for coumarin versus ASA (OR 0.89 [95% CI 0.69, 1.15], OR 0.99 [95% CI 0.81, 1.22], OR 0.92 [95% CI 0.77, 1.11], OR 0.91 [95% CI 0.77, 1.08]).

Intention-to-treat analysis for venous grafts included 814 patients randomised to coumarin treatment versus 823 to ASA. The effect of ASA alone or with a combination of ASA and DIP on patency rates was statistically significantly inferior to VKA (OR 95% at 3 months 0.66 [0.46, 0.93], 6 months 0.71 [0.53,0.95], 12 months 0.65 [0.49, 0.85], 24 months 0.59 [0.46-0.76]). For patients treated with an artificial conduit, a group that has been analysed only by the BOA trialists (542 in coumarin group versus 562 in ASA group), a statistically significantly stronger effect of ASA was found in comparison to VKA (OR 95% at 3 months 1.32 [0.89,1.95], 6 months 1.47 [1.08,1.99], 12 months 1.33 [1.02,1.74], 24 months 1.41 [1.11,1.80]).

The two trials did not report data on limb salvage and survival suitable for a formal meta-analysis. However, in the BOA 2000 trial limb amputation had to be performed in 100 (7.5%) coumarin treated and 110 (8.3%) ASA 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 2 patients (0.6%) stopping coumarin treatment for bleeding complications, and 13 patients (21%) stopping aspirin for different reasons. Three patients of each group died within 2 years. Major haemorrhage requiring hospital attendance in the BOA 2000 trial was reported with 119 (9%) in the oral anticoagulant
group versus 59 (4.5%) in the aspirin group. No data were reported for assisted primary patency or secondary patency rates.

5. **ASA/DIPYRIDAMOL (ASA/DIP) Versus Low Molecular Weight Heparin (LMWH)**

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, respectively, in the ASA group. Thus, odds ratios at 6 and 12 months were 0.60 [0.29, 1.27] and 0.84 [0.47, 1.51], showing a statistically non-significant positive effect for LMWH. Nine patients in the LMWH group (4 with patent grafts) and 2 in the aspirin group died during follow-up. No major bleedings or adverse events occurred.

6. **PENTOXIFILLYNE (PTX) Versus Nothing**

Data extracted from the one included trial refers to 50 patients, showing a strong positive effect of PTX on primary patency in venous femoropopliteal graft at 6, 12, and 24 months postoperatively with OR 0.18, 0.18, 0.09 [0.01, 0.40]. However, this effect was not statistically significant, probably due to the small number of patients.

7. **TICLOPIDINE (TIC) Versus Nothing**

Intention-to-treat analysis of the two trials (Becquemin 1997, Shionoya 1990) including 285 patients delivered evidence for a strong significant effect of TIC on venous bypass patency at 6, 12, and 24 months postoperatively with OR 0.32 [95% CI 0.14, 0.70], 0.41, [0.22, 0.79] and 0.37 [0.21, 0.64]. This effect was mainly due to the data from the Becquemin trial that contributed 243 of the 285 patients, whereas the Shionoya trial (42 patients) showed equal effects for TIC and placebo at 1, 6, and 12 months; however, a positive effect was also seen in this trial 24 months postoperatively.

8. **ILOPROST Versus Nothing**

Intention-to-treat analysis for primary graft patency for all grafts showed a protective effect of Iloprost at 3 days and 3 months postoperatively, but no longer at 12 months (OR 0.66 [95% CI 0.40, 1.07], 0.58 [0.40, 0.85], 0.97 [0.69, 1.37]). Subgroup analysis for venous and prosthetic grafts showed a strong positive effect early postoperatively in prosthetic grafts (3 days OR 0.16 [0.04, 0.64]), which was not present any more after one year (0.94 [0.40, 2.18]; this effect was not seen in venous grafts (OR 0.85 [0.50, 1.46], 0.52 [0.34, 0.81], 0.95 [0.65, 1.39].
9. SULFINPYRAZON VERSUS NOTHING

We included all 46 patients receiving a venous femoropopliteal bypass in an intention to treat analysis. In both groups 4 graft failures were observed. All occlusions occurred within the first 3 months postoperatively. Consequently, the OR for primary patency at 3 months postoperatively was 1.0 [0.22, 4.59].

Discussion

In the present meta-analysis the effect of postoperatively administered antiplatelet treatment was evaluated in PAOD patients receiving infrainguinal bypasses. Thereby, it was shown that antiplatelet treatment with aspirin (ASA) or a combination of ASA and dipyridamole (ASA/DIP) has an overall positive effect on primary patency 12 months postoperatively (OR 0.58 [95% CI 0.44, 0.77]). Interestingly, the size of the effect differed between patients receiving either artificial or venous grafts. Thus, when analysis was limited to the subgroups receiving artificial (PTFE or Dacron) grafts, this effect was statistically significant at timepoints 1, 3, 6, and 12 months postoperatively with OR 0.22 [95% CI 0.10, 0.50], 0.33 [0.17, 0.68], 0.23 [0.13, 0.42], 0.22 [0.12, 0.38], respectively. In contrast, the effect of ASA/DIP in patients receiving venous bypasses was clearly less (OR 0.77 [95% CI 0.28, 2.10], 0.85 [0.54, 1.34], 0.88 [0.59, 1.31], 0.78 [0.56, 1.09]). The effect on cardiovascular events including myocardial infarction and stroke as performed in 4 trials (811 patients) showed a slight, statistically non-significant protective effect for patients treated with ASA or ASA/DIP. Gastrointestinal side-effects and bleeding were not increased in the ASA or ASA/DIP group. Ticlopidine (TIC), another agent preventing platelet aggregation, was evaluated in two trials including 285 patients undergoing venous bypass surgery (Becquemin 1997, Shionoya 1990). Primary patency was significantly improved at 6, 12, and 24 months postoperatively with an OR of 0.32 [0.14, 0.70], 0.41, [0.22, 0.79] and 0.37 [0.21, 0.64]. Thus, TIC seems to be the only antiplatelet agent achieving as favourable an effect on venous graft patency, as it was found for the treatment with vitamin K antagonists (VKA) (BOA 2000, Schneider 1979). Unfortunately, the trials did not include a subgroup for artificial grafts. For other agents (Pentoxifylline, Indobufen, and Iloprost) data are inconclusive.

ASA/DIP was compared with pentoxifylline (PTX) in 151 patients treated with a venous or artificial bypass, but the number of patients included in these trials was too small to provide conclusive evidence. However, a comparison of ASA/DIP with VKA was possible in a large group of patients. Results indicated that overall there was no difference between the drugs. But, in accordance with the effects size of ASA/DIP on graft patency, there was a difference in relative effect of ASA alone or ASA/DIP on patency rates, which was statistically significantly inferior to VKA (OR 95% CI from 3 to 24 months 0.66 [0.46, 0.93], 0.59 [0.46-0.76]). The effect
on patients treated with an artificial conduit showed a statistically significantly stronger effect of ASA in comparison to VKA (OR 95% at 3 months 1.32 [0.89,1.95], 6 months 1.47 [1.08,1.99], 12 months 1.33 [1.02,1.74], 24 months 1.41 [1.11,1.80]).

A possible pathophysiological mechanism explaining these results could be, that tissue factor (TF) expression, is enhanced in a saphenous vein segment that is placed into a high pressure arterial system. Consequently, as TF is the strongest activator of the extrinsic coagulation cascade, local thrombin generation on the vulnerated graft endothelium is increased. Thus, VKA could be more potent in keeping the venous graft patent. On the other hand, prosthetic grafts are known to induce platelet deposition to a higher extent than venous grafts; this effect is inhibited by ASA or DIP. However, one exception has to be noted, i.e. that TIC reached a good effect on venous graft patency, which is comparable to that achieved by VKA. One reason for this stronger effect could be, that TIC as a thienopyridine functions differently than ASA, since its metabolites are noncompetitive antagonists of the platelet ADP receptor. Thus, by inhibiting the ADP induced platelet activation, TIC might not only attenuate platelet aggregation and activation, but also platelet induced coagulation.

In conclusion, according to the results of our meta-analysis, the administration of platelet-inhibitors such as ASA, ASA/DIP, Ticlopidine, or PTX, will result in improved venous and artificial graft patency compared to no treatment. However, subgroup analysis for graft-type, i.e. venous versus PTFE or Daflon, shows that patients receiving a prosthetic graft will benefit more from ASA or ASA/DIP administration than those treated with a venous graft. For further improvement of antiplatelet therapy in venous grafts, it might be worth, to combine aspirin and a thienopyridine, such as for example clopidogrel, which has already been shown to be effective in patients suffering from myocardial infarction or being submitted to coronary stenting. Thus, combined antiplatelet therapy of clopidogrel and aspirin in secondary prevention of venous infrainguinal bypass surgery might be the most promising strategy in the future.
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Appendix

1. **ASPIRIN (ASA) OR ASPIRIN/DIPYRIDAMOL (ASA/DIP) VERSUS NO ASPIRIN**

Clyne

Randomized clinical trial including 148 femorodistal bypasses. Unfortunately, all data are reported on a bypass rather than patient level. Since it was considered a minor source of bias (8 of 140 received two grafts) the data were used as reported. Of the 148 grafts 70 were randomized to the control group receiving no antiplatelet or anticoagulant therapy and 78 to the treatment group. 98 of the patients were operated for rest pain, 42 for claudication. Active treatment consisted of 300 mg ASA and 200 mg DIP b.d for 48 hours preoperatively and was continued for six weeks after surgery. All patients received heparin perioperatively. Among the bypasses were 93 autogenous vein (44 controls and 49 treated) and 55 prosthetic including PTFE, Dacron and umbilical vein (26 controls and 29 treated). Primary endpoints were graft failure, limb loss, death, and 12 months follow-up. Graft patency was assessed clinically and by Doppler ankle blood pressure before discharge, at 1, 3, 6, and 12 months postoperatively. Arteriography was performed when further operative treatment was considered. Allocation Score B, summary score B.

Donaldson

Randomized double blind clinical trial of 65 patients (52 males, 13 females) receiving 73 femoro-popliteal Dacron bypass grafts (38 placebo versus 35 treatment). Patients in the treatment group (n = 33) received three times daily 330 mg ASA and 75 mg DIP, whereas those in the control group (n = 32) received placebos. Therapy was started preoperatively and continued for 12 months postoperatively. All patients received heparin intraoperatively. Ten distal anastomoses were implanted. Assessment of graft patency was performed by a standardised treadmill test, ankle/brachial systolic pressure index (ABPI), Doppler ultrasound and by palpation at 3, 6, 9, and 12 months postoperatively. Plasma drug levels were measured for ASA and DIP. Patients were excluded from the study if they had a history of dyspepsia, peptic ulceration or hypersensitivity to ASA or DIP. For the formal meta-analysis, the number of patients was included (not the number of grafts), and graft failures counted as reported for each group at the different time-points. Allocation score B, summary score B.

Franks

Multicenter randomized placebo-controlled trial including 80 patients allocated to ASA/DIP and 65 to placebo. All patients underwent venous femoro-popliteal bypass surgery. A dose of 300 mg ASA and 150 mg DIP twice daily was administered in the treatment group. Only patients with a patent graft at 6 months postoperatively were included into the study. Graft patency was assessed three monthly in the first year and six monthly from the second to the fifth year by clinical investigation, doppler or duplex ultrasound and if indicated by angiography. Allocation score A, summary score A.
Goldman

Randomized placebo-controlled clinical trial including 53 patients (43 male, 10 female) for femoropopliteal Dacron or PTFE grafts, 31 patients were allocated to placebo and 22 patients were allocated to ASA/DIP in a regime of 300 mg ASA once and 75 mg DIP 3 times daily on 31 to matching placebo. Therapy was started 48 h before surgery and continued for 12 months. Graft patency was assessed in monthly follow-up visits up to one year based on reported symptoms, palpation, directional Doppler, and isotope angiography. Allocation score A, summary score A.

Green

Randomized double-blind clinical trial including 49 patients undergoing infrainguinal PTFE bypass surgery. Patients were randomized to either placebo (n = 17), to ASA alone (n = 16), or to ASA/DIP (n =16). Treatment was with 325 mg ASA once daily, or 325mg ASA once daily combined with 75 mg DIP three times per day. Most of the patients (88 and 87%) underwent surgery for critical limb ischemia. Exclusion criteria were a pre-existing infrainguinal autogenous saphenous vein bypass, concomitant inflow disease, hypersensitivity to ASA or DIP, platelet or clotting abnormalities, gastrointestinal disturbances, bleeding tendencies, required medication with ASA for other reasons. Medication was started 48 hours preoperatively and continued for one year. Follow-up visits were every 3 months, or when problems arose, until death or withdrawal or for at least one year. Primary graft occlusion, withdrawal, and death were considered as treatment failures. Graft patency was assessed by clinical examination and ABI change. Allocation score A, summary score A.

Kohler

Randomized double-blind clinical study performed from 1978 to 1982. In total 88 patients, 34 males and 10 females in each group, scheduled for infrainguinal saphenous vein or PTFE bypass surgery, received 102 grafts (51 grafts in each group) and were randomised to either treatment with ASA or placebo. Mean age was 66 years in both groups. Exclusion criteria were concomitant inflow disease, hypersensitivity to ASA or DIP, gastrointestinal bleeding, recently taken platelet-active drugs or anticoagulants for any reason, or geographical inaccessibility. Two thirds of the patients were operated for critical limb ischemia. Treatment consisted of ASA 325 mg 1x/day and DIP 75 mg 3x/day or matching placebos. Medication was started on the first postoperative day and continued for two years. Graft patency, the primary endpoint, was assessed at three and six weeks, further at 3, 6, 12, 18, 24 months postoperatively by evaluation of clinical symptoms, palpation of the graft, ABI assessment, and if indicated by angiography. Allocation score A, summary score B.
McCollum

Multicenter randomized double-blind clinical study performed between 1984 and 1989, in which 286 patients undergoing infrainguinal venous bypass surgery were randomised to receive ASA/DIP and 263 placebo. Randomisation was performed by identical looking medication and placebo capsules in badges of 10, with numbered containers. Mean age of the patients was 66 years, 75 percent of all were males in both groups, and 60 percent of the patients were operated for limb ischemia. Treatment with ASA/DIP was at a dose of 300 mg and 150 mg 2x/d, respectively, starting 48 h before surgery until indefinitely. Primary endpoints were graft occlusion, myocardial infarction and stroke. Patency assessment was performed by pulse palpation, Doppler signal or duplexsonography, DSA, isotope angiography at 3-monthly intervals during the first year, and 6-monthly for 5 years. Allocation score A, summary score A.

2. ASPIRIN (ASA) OR ASPIRIN/DIPYRIDAMOL (ASA/DIP) VERSUS PENTOXIFYLLINE (PTX)

Lucas

Randomized clinical trial including 97 patients undergoing vascular surgery on either the aortoiliac or femoropopliteal level. 49 patients were randomized to ASA/DIP therapy (1050 mg + 150 mg daily) and 48 patients to PTX (1200 mg/d) using a random number table. Data were extracted of those patients undergoing femoro-popliteal venous or artificial bypass surgery. Thus, in our analysis, 14 patients (4 with IC and 10 patients with CLI) were included, who were randomised to ASA/DIP and 19 patients (9 with IC and 10 with CLI), who were randomized to PTX. Mean age was 66 ± 10 y and 69 ± 8 years for both groups with 71% and 80% males. ABI values were 0.46 ± 0.27 and 0.33 ± 0.33, reflecting the higher proportion of critical limb ischemia in the PTX group. Graft occlusion within 6 months was the primary endpoint, evaluated by clinical examination, ABPI, treadmill assessment of walking distance, and angiography. Follow-up visits were at 1, 3, 4, and 6 months. Subgroup analysis for graft-type could not be performed. Allocation procedure was concealed: score A, summary score B.

Raithel

Randomised clinical trial of 118 consecutively treated patients undergoing prosthetic femoropopliteal bypass surgery, randomised to either ASA (59 patients) or PTX (59 patients). Most patients underwent surgery for critical ischemia (95 % and 97 %). Mean age was comparable in both groups with an average of 67 years. Length of graft or run-off was not different in both groups. Treatment consisted of either three times 400 mg PTX daily or three times 500 mg ASA per day, started two days before surgery and continued for 12 months. Graft patency was assessed by clinical examination, pulses, Doppler pressure, and arteriography when indicated, before and 3, 6, 9, and 12 months postoperatively. Allocation score B, summary score B.
3. **ASPIRIN/DIPYRIDAMOL (ASA/DIP) VERSUS INDOBUFEN (IND)**

D'Addato\textsuperscript{1}

Multicenter double-blind randomized clinical trial including 113 patients receiving a PTFE femoropopliteal graft. Among these, 56 patients were randomized to IND and 57 patients to ASA/DIP. Mean age was 67 and 66 years, respectively. 66% and 75% underwent surgery for critical limb ischemia. The administered doses were 400 mg IND daily or 900 mg ASA combined with 225 mg DIP, started two days before surgery and continued for 12 months. Graft-patency was assessed by angiography six days and 12 months postoperatively, and every three months by physical examination, Doppler ultrasound measurements on the graft, followed by angiography if indicated. Allocation score A, summary score A.

4. **VKA VERSUS ASPIRIN/DIPYRIDAMOL**

Schneider 1979\textsuperscript{2}

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 randomized to a femoro-popliteal venous bypass. All patients were treated with therapeutic doses of heparin and coumarins in the first 1-2 postoperative weeks and were then randomly allocated to either coumarins (Quick, aim 25-30%) or ASA, or ASA/DIP. 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 discharge, and hereafter by evaluation of segmental oscillography. A fall of the systolic pressure of at least 20 mmHg required an 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\textsuperscript{3}

Multicenter, open randomized clinical trial including 2690 patients undergoing infrapinguinal bypass surgery, of whom 1339 were assigned to coumarin derivatives (phenprocoumon or acenocoumarol) and 1351 to ASA 80 mg daily started within five days after surgery. Intended INR (international normalized ratio) range was 3.0-4.5. Follow-up was at 3 and 6 months, and hereafter every six months for 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 A.
5. ASPIRIN/DIPYRIDAMOL (ASA/DIP) VERSUS LOW MOLECULAR WEIGHT HEPARIN (LMWH)
Edmondson

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 ASA and 100 mg DIP, both three times per day for three months. On the 7th postoperative day patients were assessed for graft occlusion, wound infection, bleeding, and death. Total follow-up was one year with, visits at 1, 3, 6, and 12 months. Graft patency was evaluated clinically and by ABI, if indicated supplemented by arteriography or duplexsonography. Allocation score B, summary score B.

6. PENTOXIFYLLINE (PTX) VERSUS NOTHING
Angelides

Double-blind randomized clinical trial including 92 patients undergoing peripheral venous bypass surgery assigned to either PTX (n = 45) or placebo (n = 47). The randomisation procedure was not specified. A daily dose of 400 mg PTX was administered, initially during surgery through an artery, followed by oral administration for 2 years. Mean age was 62 years in both groups. Graft patency was assessed clinically by exercise test, Doppler ultrasound for flow detection and pressure measurement, followed by an angiography if indicated at 1 and 6 months and at 1 and 2 years postoperatively. Allocation score B, summary score B.

7. TICLOPIDINE (TIC) VERSUS NOTHING
Shionoya

Multicenter, randomized clinical trial including PVD patients undergoing elective reconstructive lower limb surgery, randomized to either TIC (112) or to no antithrombotic or antiplatelet therapy (108). Among these, 42 infrainguinal autogenous vein bypasses were randomly allocated to the TIC (n =41) and the control group (n =41), without specification of the randomisation procedure. Another subgroup consisted of 69 and 63 prosthetic grafts of which results were, however, not presented separately and therefore could not be included in our analysis. Data were reported as numbers of operated segments and not as numbers of patients. Mean age was 65 (treatment group) and 66 (controls) years. Patients mainly underwent surgery for claudication, and only in 26% and 19% for limb ischemia. Patients in the treatment group received 3 times daily 100 mg TIC, whereas patients in the control group received no medication affecting the coagulation or fibrinolytic system. Duration of therapy was 2 years starting on day one to 3 postoperatively. Graft patency was evaluated every 3 months by ABI and arteriography if indicated for a total of three years. Allocation score B, summary score B.
Becquemin

Multicenter, randomized clinical trial including patients undergoing femoropopliteal or femorotibial saphenous vein bypass surgery. 122 patients were randomly allocated to 250 mg TIC and 121 to placebo. Mean age was 67 (TIC) and 68 (control group) years. More than 70% of the patients suffered from critical limb ischemia in both groups. Patient characteristics did not differ between the treatment and placebo group, except for a larger rate of tibial grafts in the TIC group. Randomisation took place between the 3rd and 14th postoperative day and continued for two years. Primary endpoint was primary patency at two years postoperatively. Secondary endpoints were secondary graft patency, death from any cause, nonfatal myocardial infarction, nonfatal stroke, limb ischemia, mesenteric infarct, amputation of leg or thigh. Allocation was concealed. Allocation score A, summary score B.

8. ILOPROST VERSUS NOTHING
Iloprost Bypass
Multicenter randomized clinical trial including 517 patients in 21 centers, who underwent femoro-distal venous or prosthetic bypass surgery from 1990 to 1992. Patients were randomised to either intravenous administration of Iloprost or placebo (267 and 250, respectively) for 3 days postoperatively. All patients were suffering from critical limb ischemia. Patency, surgical interventions, and clinical outcome were recorded 2, 3, and 14 days, 6 weeks, 3, 6 and 12 months postoperatively. Allocation score A, summary score A.

9. SULFINPYRAZON (SP) VERSUS NOTHING
Comberg
Randomized clinical trial including 27 patients randomised to SP and 27 to placebo. 23 patients in each group received a venous graft, 1 and 2, respectively, a Goretex graft and 3 and 2, respectively, underwent thrombendarterectomy. Therapy was started on the 14th postoperative day and continued for 6 months. The dose administered was 4 x 200 mg/day. Graft patency was evaluated by clinical examination, including ABI measurement and arterial plethysmography. Allocation score B, summary score B.