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CHAPTER 4

PREVENTION OF REOCCLUSION IN SYMPTOMATIC PAOD PATIENTS UNDERGOING PERIPHERAL CATHETER INTERVENTION

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

Patients with peripheral arterial occlusive disease are frequently treated by balloon angioplasty. However, 30 to 40% of those treated for femoropopliteal obstructions will suffer from reocclusion within one to three years. The risk for reocclusion depends on various factors, such as the length of the occlusion (>10 cm), lower leg outflow, the stage of the disease (intermittent claudication versus critical limb ischemia), presence of diabetes mellitus, or smoking. In order to prevent reocclusion, patients are given antiplatelet or antithrombotic agents according to the treating doctor’s preference.

We performed a meta-analysis including all randomized clinical trials meeting current methodological standards, that compared one antiplatelet agent versus a placebo, or versus another antiplatelet or an antithrombotic agent, or versus another therapy strategy. The literature search was performed in MEDLINE and EMBASE data bases starting in 1966 until 12/2000. In addition, a list of handsearched journals, as delivered by the PVD group of the Cochrane Collaboration, was included in the search, and companies producing antiplatelet or antithrombotic agents were contacted for further information on ongoing or unpublished trials.

An approximately 30% reduction of reocclusion was found after the administration of aspirin at doses 50 to 100 mg combined with dipyridamole as compared to placebo at 6 months of follow-up. This effect was not statistically significant and evaluated in only a small group of 356 patients. Four further trials comparing high doses of aspirin with low doses, were pooled to evaluate the efficacy and safety in patients with PAOD who had undergone femoropopliteal angioplasty. Analysis of these data revealed that higher doses of aspirin (300 to 1000 mg) do not improve patency rates following angioplasty compared with low doses of ASA (50 to 300 mg), at any timepoint of follow-up. In contrast, side effects, mainly gastrointestinal, were clearly more frequent in the high dose groups.
Introduction

Peripheral arterial occlusive disease (PAOD) leads to ischemic pain on walking (intermittent claudication) or, if more severe, to rest pain and gangrene. Based on the severity of symptoms the stages of the disease are defined as Fontaine stages I to IV: stage I representing an asymptomatic stage, stage IIa the occurrence of claudication after a walking distance of more than 200 m, stage IIb claudication after less than 200 m, stage III rest pain, and stage IV presence of ischemic ulcers.

Percutaneous transluminal angioplasty (PTA) is a well established endovascular procedure for lower limb atherosclerosis. First invented by Dotter and Judkins in 1964 and technically improved by Grünzig in 1979 the method is used in the treatment of arteries of the lower limbs, and as a modified procedure in upper limbs, coronary, carotid, mesenteric and renal arteries. In PTA an arterial obstruction is treated either by dilatation of a stenosis or recanalization of a total vessel occlusion, using a wire-guided inflatable balloon-catheter. For treatment of the lower limbs, usually the femoral artery in the groin is cannulated and a deflated balloon-catheter is inserted and pushed forward along the guide-wire to the sites of obstruction. The method can be combined with local thrombolysis (LTL) and percutaneous transluminal thrombus extraction (PTEE) in cases of acute-on-chronic disease. By these procedures the thrombi or emboli, respectively, are soaked with thrombolytic agents, such as recombinant tissue plasminogen activator (rtPA), streptokinase or urokinase by local administration through modified catheters. The pretreated thrombi are then removed through the catheter by suction. Any residual stenosis, i.e. a remaining obstruction due to atherosclerotic plaques, can be dilated by PTA in the same session. Another method is to leave an infusion catheter at the occluded site for six to eight hours, constantly administering thrombolytics and to assess patency later by angiography. If necessary, this procedure can be repeated, but patients may require intensive care for several days thereafter.

In cases complicated by major endothelial damage or non-satisfactory dilatation, i.e. > 50% of rest-stenosis, wall stents can be implanted in an attempt to reduce the risk for reocclusion. Stents are mainly applied at the aortic bifurcation or iliac segments and only exceptionally at the femoropopliteal level, because of the significantly higher risk for reocclusion in the smaller distal arteries due to their reduced caliber.

PTA is a relatively minor procedure, performed under local anesthesia and allowing for full mobilization within 24 hours, if continuous thrombolysis is not applied. However, as a result of this intervention, atherosclerotic plaques are ruptured, and platelets adhere and aggregate at the site of injury. In the initial phase after catheter intervention a hypercoagulable state prevails as parameters of activated coagulation, including thrombin-antithrombin complexes (TAT), D-Dimer and Fibrinopeptide A (Fa), become elevated in the plasma. This activated coagulation
system produces conditions favourable for early thrombotic occlusion, where 'early' is usually defined as a period covering the first four weeks after the intervention.\(^1\)

Subsequently, a condition called intimal hyperplasia, responsible for late complications including restenosis and reocclusion, prevails. Stenosis of the arterial lumen occurs as a result of denudation of the endothelium caused by manipulation of the vessel wall with the catheter, which stimulates media smooth muscle cells to grow into the intimal layer followed by the inclusion of foam cells and calcifications.\(^2\)

Reported rates of early arterial occlusion following PTA vary from 5 to 25\(^%\)\(^3\)-\(^4\), while patients submitted to LTL-treatment have even higher incidences\(^5\)-\(^7\). Thus, either a second PTA intervention, or even bypass surgery, is frequently required. Therefore, prophylactic treatment to prevent reocclusion would make an important contribution to the sustained success of PTA. Current post-interventional treatment strategies mostly include initial administration of heparins\(^8\)-\(^9\) either unfractionated or low molecular weight - followed by antiplatelet drugs or anticoagulants\(^10\) on a long-term basis. Heparins are known to inhibit generation of thrombin and to have an inhibiting effect on smooth muscle cell growth.\(^22\) However, it has been shown that a considerable number of patients do not respond to heparin, thus, other anticoagulants might be more effective. Additionally, acetylsaliclyc acid is well-known for its inhibition of platelet aggregation, thus reducing the likelihood of thrombus-formation.\(^23\) Some patients present with arterial reocclusion despite prophylactic treatment. Peri-interventional management presently depends on the subjective preferences and experience of the treating physicians.

The aim was to determine, whether the administration of any antiplatelet or antithrombotic prophylactic drug is more effective in preventing early and/or late reocclusion after PTA, implantation of a stent, PTA/LTL, LTL or PTA/LTL/PTEE, compared to no treatment or placebo. Also a comparison was made for other antiplatelet or anticoagulant drugs, or any other vasoactive drug management.

**Methods**

**Criteria for considering studies for this review**

*Types of studies* Summary score level A defined trials as randomized trials with double or single blinding or with blind assessment of the outcome. Summary score B studies were randomized trials without blinding. The methodological approach of summary score A studies means that results of these trials are less likely to be subject to bias than results in summary score B studies. However, since a considerable amount of data from unblinded trials was published, these summary score B studies were considered in the review. Additionally, concealment of randomization allocation was defined as allocation score A, if a clear concealment procedure was
described, and as allocation score B, if randomization was mentioned without specification of the procedure.

*Types of participants* Patients with symptomatic chronic or acute-on-chronic peripheral arterial disease, PAOD stages I to IV. Patients were included if they had undergone PTA (alone, or combined with stent-implantation) and/or PTEE and/or LTL and/or laser-assisted PTA or subintimal angioplasty on either the aortoiliac, femoropopliteal or femorocrural segment.

*Types of interventions* Trials were included that compare anticoagulant therapy, antiplatelet therapy, or other pharmacological measures after angioplasty with no treatment, placebo, or any other vasoactive drug.

*Types of outcome measures* Primary outcome measures were reocclusion or restenosis (shown by duplex sonography or angiography) Amputation and death within four weeks after catheter intervention was intended to be used as an outcome, but could not be evaluated, as reports did not include data on these outcomes. This was also the case for secondary outcomes such as myocardial infarction, stroke, and major bleeding (i.e. requiring blood replacement therapy or intensive care).

*Search strategy for identification of studies*

Data was collected by seeking reports of all randomized clinical trials that compare anticoagulant therapy, antiplatelet therapy, or other pharmacological measures after angioplasty with no treatment, placebo, or any other vasoactive drug using the search strategy adopted by the Cochrane Review Group on Peripheral Vascular Diseases. This strategy includes handsearching of relevant medical journals and extensive MEDLINE and EMBASE searches. In order to be as comprehensive as possible, the following search strategies and sources were also employed:

- The Cochrane Controlled Trials Register
- Handsearching of relevant journals
- Additional MEDLINE and EMBASE searches (using OVID and PubMed) using the key words: 'Arteriosclerosis' or 'peripheral arterial disease' or 'PAOD' and - arterial occlusion/reocclusion- percutaneous transluminal angioplasty OR PTA, OR angioplasty- stent-implantation OR stent- laser-assisted angioplasty- subintimal angioplasty- thrombolysis-streptokinase, urokinase, rtPA- pharmacological treatment- aspirin, ticlopidin, antiplatelets, vasoactive drugs, analogues and derivatives- anticoagulants, coumarins, warfarin, analogues and derivatives- heparins, analogies and derivatives- prostaglandins- ticlopidine- buflomedil-clopidogrel- NSAID- Pentoxifylline- RGD-peptides- GPIIb/IIIa inhibitors- Thrombin-inhibitors- Hirudin- TFPI- Pentasaccharides.

All languages were included. Pharmaceutical companies and investigators were contacted if necessary and sources of information are listed in the full review.
Data Extraction

The included literature was assigned to summary score A or B, and allocation score A or B. Excluded trials were listed separately. This was done by two independent observers. The same reviewers assessed the methods of the trials by extracting details of randomization, blinding, determination of disease stage of included patients, presence or absence of occlusion, length of occlusion treated if available, quality of in- and out-flow if available, angiography or duplex sonography for patency evaluation, time-points of patency controls, patency rates, recording of drug administration, dosage, duration, adverse effects, risk factor profiles, possibility of intention-to-treat analysis. The data were double-checked and disagreements discussed.

The number of patients allocated to different treatment groups in each trial was extracted in order to allow an intention-to-treat analysis. Data collected from each trial was inserted onto a computerized form, including columns for: reference; study design (clinical trial, journal article, multicenter study); summary score (A, B); allocation concealment (score A or B); indication (PAOD stage, segment obstructed); technique used (PTA, subintimal PTA, laser-assisted PTA, stent implantation, I.I., PTEE); type of: anticoagulant, heparin, antiplatelet drug, vasoactive drug; time schedule: start and stop of drug therapy; dose; number of patients (age, sex, risk factors); previous interventional or surgical treatment; episodes of cardiovascular disease before intervention; number and time-point of reocclusion; number of patencies; number controlled by angiography or duplexsonography; number of deaths, stroke, myocardial infarction, amputation, major bleedings; special remarks (out-flow, in-flow, technical difficulties).

Statistical analysis

Analysis was based on intention-to-treat data from the individual clinical trials. To examine the effects of binary outcomes, such as reocclusion, amputation and major bleeding, odds ratios were computed using a random effects model if data were available.

The following comparisons were performed:
- Aspirin versus placebo
- Aspirin high dose versus aspirin low dose
- Aspirin/dipyridamole versus phenprocoumon
- Suloeptidil versus phenprocoumon
- Aspirin versus ticlopidine
Results

Retrieved Studies

Of fifteen potentially eligible clinical trials, 9 could be included for a formal analysis (Heiss, Swedish, Minar, Weichert, Dai-Do, Schneider, Mahler, Heinz) while six had to be excluded because of lack of a control group, double report on the same patient cohort, lack of randomization, and selection or performance bias. (Bulvas, Horrocks, Ranke, Tetteroo, Zeitler). The study of Heiss et al\textsuperscript{24} appears in two comparison categories, i.e. in ASA versus placebo and in ASA high dose versus ASA low dose, because the study compares high dose ASA/DIP versus low dose ASA/DIP versus placebo. None of the identified trials was performed after percutaneous thrombectomy of local or systemic lysis, nor after stent implantation. All comparisons were performed after conventional angioplasty. Secondary endpoints such as myocardial infarction, stroke, death, and bleeding complications could not be evaluated due to limited data.

Details of the 9 studies are described in the appendix. In 5 of the 9 trials criteria for category 1 studies were fulfilled, while 4 of the 9 trials reported an adequately concealed randomization procedure.

1. ASPIRIN/DIPYRIDAMOLE VERSUS PLACEBO

Heiss 1990, Study group 1994

A formal meta-analysis could be performed for reocclusion 6 months after PTA, while at 1, 3, and 12 months only data from the Swedish Study were available. Results for the incidence of reocclusion at 6 months show a statistically non-significant overall effect favouring the administration of ASA given at low doses with an odds ratio (OR) and 95% confidence interval of 0.69 [0.44, 1.10] (Fig 1). OR for the Heiss 1990 trial was better (0.51) than for the Swedish trial. Heiss et al used 100 mg of ASA, while the Swedish Trial Group administered only 50 mg ASA daily. In the Swedish Study death within 30 days after PTA occurred in 2 patients in each group (1.7% placebo, 2.2% ASA/DIP), amputation in 5 of the placebo group (5.8%) and 1 in the ASA group (1%), bleeding at the puncture site in 5 of the placebo (6%) and 7 (8%) of the ASA group; these data do not reveal any significant differences between treatment groups. Gastrointestinal side effects were not mentioned. The data on amputation and death incidence could not be pooled, as Heiss et al did not report on these outcomes. In the Swedish Study group 60% of all patients were claudicants and 40% suffered from critical limb ischemia, while the great majority of the patients in the Heiss 1990 trial 96% had claudication.
Figure 1. Comparison: ASA (50 and 100 mg) versus placebo for patency rates at 6 months follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>ASA/DIP n/N</th>
<th>Placebo n/N</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiss 1990</td>
<td>41/66</td>
<td>51/67</td>
<td>0.51 [0.24, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Study Gr 1994</td>
<td>28/108</td>
<td>34/115</td>
<td>0.83 [0.46, 1.50]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>69/174</td>
<td>85/182</td>
<td>0.69 [0.44, 1.10]</td>
<td></td>
</tr>
</tbody>
</table>

2. ASPIRIN HIGH DOSE VERSUS ASPIRIN LOW DOSE IN CONVENTIONAL PTA

Four trials were truly randomised, published between 1990 and 1995 including 930 patients at timepoint 6 months after PTA and 798 patients at 1 and 3 months (Heiss 1990, Minar 1995, Ranke 1994, Weichert 1994). High dose ASA included 900 or 1000 mg with the exception of 330 mg in the Heiss 1990 trial, which combined ASA with DIP, whereas low doses ranged from 50 to 300 mg. Only the Heiss 1990 used a combination of ASA/DIP (Asasantin), while the other trials compared ASA purely. Early occlusion, i.e. within one month after intervention, could be assessed in three trials (Minar, Ranke, Weichert), showing no advantage for the administration of high doses of ASA (OR 1.45 [0.63, 3.36]). At six months after PTA the results were not much different, again showing no positive effect for high dose ASA (OR 0.99 [0.63, 3.36]). Among the four trials there were two showing a slight advantage for higher doses (Heiss, OR 0.78) and Minar (0.90). It is striking that the trial with the lowest high dose (300 mg, Heiss et al) showed the most positive effect.

At timepoints 3 and 12 months there were 798, respectively 575 patients included (Minar, Ranke, Weichert), (Minar, Ranke), with OR 1.38 [0.85, 2.23] and 0.98 [0.64, 1.48]. Follow-up until two years after PTA was only performed in the trial of Minar et al, including 85 patients with similar results as described for the earlier timepoints (OR 1.07 [0.62, 1.85]). It should be noted that Ranke et al had strikingly low reocclusion rates in both groups.

Gastrointestinal side effects were reported by Ranke et al to be 35/175 (20 %) in the high dose group and 32/184 (17 %) in the low dose group; with 8/175 peptic ulcers and 2/184, respectively. Minar et al described discontinuation of drug therapy due to mainly gastrointestinal side effects in 30 patients (32%) of the high dose and 11 (12%) of the low dose group.
3. ASPIRIN/DIP VERSUS VKA

Dai-Do 1994: Comparison of the incidence of reocclusion between 79 patients assigned to ASA/DIP and 81 to phenprocoumon resulted in a strong, statistically significant effect favouring ASA/DIP with OR 0.49 [0.26, 0.94] (Figure 2)

**Figure 2.** Comparison Aspirin/DIP versus Phenprocoumon for reocclusion at 12 months follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>ASA/DIP</th>
<th>Phen</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai-Do 1994</td>
<td>24/79</td>
<td>38/81</td>
<td>0.49 [0.26, 0.94]</td>
</tr>
<tr>
<td>Total</td>
<td>24/79</td>
<td>38/81</td>
<td>0.49 [0.26, 0.94]</td>
</tr>
</tbody>
</table>

4. SULOCTIDIL VERSUS VKA

Mahler 1987: 12 Months after PTA suloctidil had no positive effect on patency, when added to phenprocoumon (OR 1.87 [0.66, 5.31]) Gastro-intestinal side-effects occured in two patients of each group. There were no bleeding complications reported. The trialists had excluded the dropouts from the final analysis, that we reincluded for the calculation of the odds ratio.

5. VKA VERSUS TICLOPIDINE

Schneider 1987: Treatment with VKA had to be stopped in 11% of the patients, only 4 due to side effects, the others for unknown reasons, while 34% of the patients in the ticlopidine group stopped drug intake within one year for mainly gastrointestinal side effects.

6. ASPIRIN/DIPYRIDAMOLE VERSUS TAPROSTEN

Heinz 1996: Early occlusion, i.e. within 72 hours occurred in 2 patients treated with Taprosten low dose, 1 in the Taprosten high dose group, and 1 reocclusion was found within 3 months in the Taprosten low dose group.
Discussion

In this systematic review, data from included trials were analysed to evaluate the efficacy of antiplatelet or antithrombotic agents administered in patients suffering from symptomatic PAOD with an occlusion or a stenosis in the femoropopliteal arteries, who were treated with balloon angioplasty. We found an approximately 30% reduction of reocclusion with the administration of aspirin at doses 50 to 100 mg combined with dipyridamole as compared to placebo at 6 months of follow-up. This effect was not statistically significant and evaluated in only a small group of 356 patients. When looking at OR of the single trials, it was striking that Heiss et al reported a considerably stronger effect than the Swedish group (odds ratios 0.51 vs 0.83, respectively). This difference might be due to the fact, that in Heiss et al's study 96% of the patients presented with claudication, with only 4% of participants suffering from critical limb ischemia, while in the Swedish trial there were only 59% patients with claudication included and 41% with critical limb ischemia, the latter being a risk factor for a poor outcome. The incidence of death, amputation, and bleeding at the puncture site, as recorded in the Swedish group, were not different for patients receiving aspirin. This is a surprising result, when other data are considered showing clearly the benefit of ASA on secondary prevention of myocardial infarction and stroke. Possible reasons for this lack of effect might be the small number of patients (only one trial including 223 patients), short follow-up, and endpoint not being evaluated systematically in all patients.

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

No other pooled data could be extracted for other comparison groups due to the small number of trials. However, one study comparing ASA/DIP with vitamin K antagonists (VKA) (Do-Dai et al) interestingly found that antiplatelet therapy improved patency after femoropopliteal angioplasty in contrast to VKA (OR 0.71, Fig.4). Unfortunately, this is the only trial, which has compared the two treatment strategies in a relatively small number of 160 patients. However, these results are suggestive for platelet activation playing a more important role in the pathomechanism of arterial reocclusion in dilated artery segments than the local coagulation system does, which is in contrast to the results reported in our met-analysis on patency of infrainguinal venous bypasses.

Ticlopidine, a thienopyridine derivative, which was combined with a VKA was more effective than VKA alone in one trial including 197 patients.
In conclusion, the presented data are highly suggestive for antiplatelet agents to be the optimal therapy compared with no therapy or with VKA. Apparently, a dose between 50 and 300 mg reaches maximum efficacy, whereas higher doses will not provide further improvement, but more frequent adverse effects. Pathophysiologically, these results are consistent with the fact, that platelet activation and aggregation in atheromatous arteries treated by a balloon-catheter represent a high risk factor for reocclusion, necessitating some potent antiplatelet treatment. Further trials investigating new antiplatelet agents, e.g. clopidogrel, interfering with the ADP pathway, might be promising, especially if combined with ASA, thus providing a more potent inhibition of platelet aggregation, as was recently revealed in the CURE trial in patients with acute coronary syndromes.

Finally, it should be noted that only a small number of RCT have been performed to evaluate optimal secondary prevention strategies, although angioplasty is a frequently applied intervention in a wide-spread disease, and that larger numbers of patients should included for more valid evidence.
References


Heiss HW, Just H, Middleton D, Deichsel G. Reocclusion prophylaxis with dipyridamole combined with acetylsalicylic acid following PTA. Angiology 1990; 41(4):263-9

Swedish Study Group


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Appendix

1. ASPIRIN (ASA) VERSUS PLACEBO
Heiss 1990
A randomized, double-blind, single center clinical trial of 199 patients assigned to either placebo (67), high dose aspirin with ASA 330 mg and dipyridamole (DIP) 75 mg daily, or low dose ASA (100 mg) combined with DIP (75 mg) per day. It was not specified, whether patients were all initially heparinised. All patients suffered from PAOD stage I, II, or III of the Fontaine’s classification. Randomisation was performed one to two hours following successful angioplasty of a femoral or popliteal segment without specification of the randomization procedure. Duration of treatment and follow-up was six months. Side effects were not assessed. Concurrent events were not defined. The primary outcome studied was reocclusion. Other outcomes such as myocardial infarction, stroke, and death were not evaluated. 156 patients completed the study, 43 withdrew for the following reasons: Placebo: 7 lack of effect, 7 concurrent events, 2 other; ASA/DIP low dose: 9 concurrent events, 3 other; ASA/DIP high dose: 4 lack of effect, 9 concurrent events, 2 other. These patients were reincluded for the intention to treat analysis. Summary score: A (double-blinded study); allocation score: B.

Swedish study Group 1994
A randomized multicenter (12 hospitals in Sweden) double-blind clinical trial. Randomization to treatment or control groups was performed in blocks of 10 by a sealed envelope system. 223 Patients suffering from PAOD were allocated to either ASA 25 mg and Dipyridamole 200 mg given twice daily as a combination tablet (Asasantin) or to identical placebo tablets. Treatment was started 1 day before PTA and continued for 3 months. Usually 5000 IU of heparin were administered during PTA. Patients with angiographically documented stenoses or occlusions of up to 6 cm in length in either the common iliac, external iliac, superficial femoral, or popliteal arteries were included. Patient characteristics did not differ between groups regarding age, gender, smoking habits, diabetes mellitus, coronary heart disease, hypertension, previous PTA at another site, previous vascular surgery. However, there were more patients with cerebrovascular disease in the placebo group (4 versus 11%). 59% of the patients in both groups had intermittent claudication and were mostly treated in the above groin segments (54 in ASA/DIP, 71 in placebo). These patients were included in our analysis. Approximately 20% of all patients had occlusions and 80% had stenoses in both groups. Recurrence of stenosis or reocclusion were the outcomes evaluated at discharge and 1, 3, 6, and 12 months after PTA. Some patients were dilated in more than one segment, 6 in the ASA/DIP group and 4 in the placebo group. This small proportion was not taken into account in the analysis. The 5 patients of the placebo group and 3 of the treatment group, who had been excluded by the trialists for different reasons (unsuccessful or partially successful PTA, early occlusion) were reincluded in our analysis, because randomization was performed and treatment was started before PTA. Summary score: A (double-blinded study); allocation score: A
2. ASPIRIN HIGH DOSE VERSUS ASPIRIN LOW DOSE

Weichert 1994

A randomized clinical trial of 223 patients assigned to receive either 300 mg ASA (112 patients), or 1000 mg ASA (111 patients) daily, during a period of 6 months. Patients were included 2-5 days after PTA, if the latter was successful. PTA was performed either in the pelvic arteries or in the leg arteries. Patients who stopped drug intake for side effects, were considered as having reocclusion. The trialists excluded patients with early occlusions, occurring i.e. within 24 h, because they were considered to have technical failure. We did not reinclude these patients, because randomisation and therapy start was only 2 to 5 days after PTA. Contraindication for ASA or need for treatment with anticoagulants were exclusion criteria. Follow-up visits were at 3 and 6 months, or when a restenosis or reocclusion was suspected by the patient. Reocclusion in the treated leg, occlusion on the contralateral leg, myocardial infarction (MI), stroke, death due to MI or stroke were primary outcomes. Discontinuation of drug therapy due to side effects was considered as a secondary outcome. Outcome evaluation included ABPI (diminution of at least 0.2 was considered as an indicative of reocclusion and was followed by an angiography. Summary score: B; allocation score B.

Ranke 1994

A randomized double-blind two-center trial comparing 175 patients assigned to 900 mg ASA with 184 patients receiving 50 mg ASA. Patient characteristics did not differ significantly between treatment groups. 89% of all patients suffered from claudication. Patients were randomised after successful PTA and were stratified into three groups; 40% with iliac artery stenosis (A), 40% with femoral artery stenosis < 3 cm (B) and 20% with femoral artery stenosis 3 - 10 cm (C). Before PTA all patients received a loading dose of 1000 mg ASA. Follow-up was at 1 day, 1, 3, 6, 9, and 12 months. Angiographically confirmed occurrence of restenosis with > 50% diameter reduction, as well as intolerable adverse effects, death, stroke, MI, were the primary outcomes. Summary score A; allocation score: A.

Minar 1995

A randomized, open single center clinical trial including 216 patients suffering from PAOD and treated by PTA in the femoropopliteal segment. 107 patients were assigned to receive 1000 mg ASA and 109 to a dose of 100 mg. Patient characteristics including the usual risk factors in the two treatment groups were well matched. Impaired inflow was regarded as an exclusion criteria. 87% of the patients suffered from claudication. Before PTA and on the 2 following days, all patients were administered 500 mg ASA iv. In addition, 5000 IU heparin was administered during PTA, followed by iv heparin 1000 IU/hr until aPTT reached 3 times of its normal value for the 3 days after PTA. Randomisation was started thereafter. Thus, patients in whom early reocclusion occurred (i.e. within 3 days after PTA), were excluded from the study and not reincluded in our analysis. The follow-up duration was 24 months. Reocclusion or restenosis
(angiographically confirmed stenosis > 50% narrowing lumen) were the primary endpoints. Summary score: A; allocation score:A.

3. ASPIRIN/DIP (ASA/DIP) VERSUS VITAMIN K ANTAGONISTS (VKA)
Dai-Do 1994
An open single center randomized clinical trial of 160 patients allocated to oral anticoagulants or ASA/DIP. Patients were treated with femoro-popliteal PTA of occlusions < 10 cm in length.
Exclusion criteria: > 80 y, pretreatment with ASA/DIP, use of other platelet inhibitors, known contraindications for ASA/DIP, other disease limiting the 12-month-follow-up. Outcome: patency of dilated segment, documented angiographically at 12 months or when endpoint reached earlier. Angiography was performed before, 1 day and 12 months after PTA. Follow-up 1 day, 3, 6, 12 months after PTA; assessment of clinical history, symptoms, ABPI, pulse-volume curves, palpable pulses. ASA 25 mg and DIP 200 mg each 2x/day for 1 year vs phenprocoumon. ASAD was started for all patients: 24-48 h before PTA until randomisation. Summary score B (open trial); allocation score B.

4. SULOCTIDIL VERSUS VITAMIN K ANTAGONISTS
Mahler 1987
A double-blind, two-center randomized clinical trial including 123 patients suffering from chronic PAOD. In all patients femoropopliteal angioplasty was performed on one leg. Allocation to either receiving oral anticoagulation combined with Sulocidil or to oral anticoagulation and placebo, was performed after successful PTA. Medication was thus started within 24-48 h following angioplasty. The study duration and follow-up was two years. Follow-up examination was 24-48 h, 3, 6, and 12 months after PTA by evaluation of clinical symptoms, palpable pulses, improvement of pulse waves distal to PTA site, reduction of ABPI-difference by at least 20 mmHg. Angiography was performed after 6 months. Remaining drug capsules were counted at each visit. No data on the distribution of diabetes, hypertension, hypercholesterinemia or on in- and outflow was reported. Allocation concealment was provided by a sealed envelope procedure. Summary score: B; allocation score A.

5. TICLOPIDINE VERSUS VITAMIN K ANTAGONISTS
Schneider 1987
A randomized multicenter (3 centers) clinical trial of 197 patients with femoropopliteal stenoses and occlusions of maximally 10 cm length due to chronic PAOD. Arterial obstructions were angiographically demonstrated. Patients were randomised to receive VKA (94 patients) or ticlopidin (103). Patients with technical failures in PTA were excluded. For randomisation sealed envelopes were used. All patients were treated double-blinded for 3 days before intervention with either 2 x 500 mg/d aspirin or 2 x 500 mg ticlopidine. After PTA, patients were decoded and those pretreated with aspirin received furtheron VKA (dicoumarole); in the other group ticlopidine administration was continued for 12 months. Clinical
evaluation including segmental pulse wave analysis, and ABPI measurement was performed directly before and after PTA, as well as 3, 6, and 12 months after PTA. A second angiography was performed one year after PTA. Endpoints were patency, restenosis or reclosure in the dilated or recanalized segment, respectively, and vascular occlusion in other segments. Secondary endpoints were drug induced side effects and patient compliance. Gender, age, risk factors, PAOD stage and concomitant diseases were matched for both groups. The number of patients with a stenosis or an occlusion in both groups was: 55 and 45, respectively, for VKA and 57 and 43, respectively, for ticlopidin. Summary score B; allocation score A.

6. ASPIRIN/DIPYRIDAMOLE VERSUS TAPROSTEN

Heinz 1996

A randomized double-blind clinical trial including 19 patients suffering from PAOD stage II to IV, who were treated with femoropopliteal angioplasty and assigned to either low dose intravenous Taprosten (12'000 ng/kg, 6 patients), high dose Tapirosten (24'000 ng/kg, 6 patients) or to 1320 mg ASA/300 mg DIP 75 mg (7 patients). Drug therapy was started two hours before angioplasty for all patients and continued for 24 hours after catheter intervention. Early occlusion was a primary endpoint as well as thrombocyte deposition as investigated by Indium-111-labeled thrombocytes and nuclear scanning. Follow-up was for 3 months. One third of the patients in each group was not only treated by PTA, but in addition by local lysis. Summary Score A; allocation score B.