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Antiplatelet Therapy and Other Interventions after Revascularisation Procedures in Patients with Peripheral Arterial Disease: a Meta-analysis

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Objectives: *to evaluate the efficacy of conservative adjuvant therapy after revascularisation procedures in patients with peripheral arterial disease.*
Design: *meta-analysis.*
Materials: *English-language studies published from 1976 to 1997.*
Methods: *reports on conservative therapies in patients with peripheral arterial disease after percutaneous transluminal angioplasty, endarterectomy, thromboendarterectomy or bypass grafting were eligible. Uncontrolled or retrospective studies, double reports or trials without clinical outcomes were excluded. Included studies were graded as level 1 (randomised and double- or assessor-blind), level 2 (open randomised), or level 3 (non-randomised comparative). (Loss of) patency, amputation, vascular events and mortality were the outcomes considered. When feasible, end-of-treatment results, either continuous or binary, were combined with appropriate statistical methods.*
Results: *thirty-two studies were included. Compared to non-active control, aspirin with dipyridamole improved (loss of) patency (odds ratio (OR) 0.69, 95% confidence interval (CI), 0.53 to 0.90) and mortality (OR 0.80, 95% CI, 0.57 to 1.14); ticlopidine improved (loss of) patency (OR 0.53, 95% CI, 0.33 to 0.85) and amputation (OR 0.29, 95% CI, 0.08 to 1.01). Data on the effectiveness of vitamin-K inhibitors were not conclusive.*
Conclusions: *patients with peripheral arterial disease improve their outcome by receiving aspirin with dipyridamole or ticlopidine after a revascularisation procedure.*

Key Words: Peripheral arterial disease; Adjunct treatment; Revascularisation procedure; Meta-analysis.

Introduction

In Europe, the incidence of newly detected peripheral arterial disease reaches 1% per year after the age of 65. Within 10 years, up to 25% of the affected patients will need revascularisation procedures.[1–4] Without additional treatment, reocclusion will occur in 20–60% of cases within 5 years of intervention.[5–9]

Rethrombosis and neointimal fibrous hyperplasia are considered the main pathogenic steps involved in reocclusion.[7] The use of anticoagulant or antiplatelets agents represents a rational prophylactic approach in order to improve the long-term patency of the reopened vessel.[10] Moreover, since mortality in these patients is increased, as compared to the general population,[11] antithrombotic agents have the potential of improving survival since they reduce the incidence of myocardial infarction and stroke,[12] which are the main causes of death in these patients. However, their effectiveness, both for maintaining patency and preventing death in this group of patients, is debated.[13–17]

Therefore, we sought to evaluate the evidence coming from published clinical trials on the efficacy of any prophylaxis in maintaining long-term arterial patency after revascularisation procedures (bypass-grafting, percutaneous transluminal angioplasty, endarterectomy), as well as to assess the effect on survival.

Materials and Methods

We performed a Medline search on the English-language medical literature, published from 1976 to 1997, with the keywords "atherosclerosis, arteriosclerosis obliterans, peripheral vascular disease". In

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addition, references of articles and pertinent reviews were evaluated to identify additional trials. Studies were eligible for inclusion if they evaluated the efficacy of any prophylaxis after revascularisation procedures in patients with peripheral arterial disease, regardless of Fontaine stage of disease[18] and study design. Studies on selected populations (diabetics, hypertensive, dyslipidaemic patients), concerning analgesic treatment, case reports, reviews and meta-analysis, were not eligible. The quality of this selection process was evaluated using a random sample of one hundred articles analysed by three independent operators (BG, EB, MHP) with a Kappa statistic ranging from 0.90 to 0.95.

Eligible studies were excluded if they were uncontrolled, duplicated other published material, were retrospective, or did not adequately assess at least one of the following outcomes: mortality, cardio- or cerebrovascular events, amputation, (loss of) patency, reocclusion, ankle–brachial index, walking distance, side-effects. When feasible, reocclusions were converted to (loss of) patency rates.

The included studies were graded by two independent observers (BG, EB) for the quality of their design in the following categories: level 1 (randomised, double- or single-blind or with blind assessment of the outcome), level 2 (open randomised) and level 3 (non-randomised comparative) studies. Level 3 studies were considered for analysis only if level 1 studies were not available. Since our purpose was to give a quantitative summary estimate of treatment effect, the criterion used for inclusion in the final summary measure of efficacy was that the report enabled direct extraction or derivation of the exact proportion of the outcome events in each group (in case of binary outcome measures), or of a difference in effect between the treatment groups and the common standard deviation (in case of continuous outcome measures). Extracted outcome data were then summarised in tabular format, expressed as proportions or as means and standard deviations, and, whenever possible and justifiable, combined with appropriate statistical methods.[19,20] The statistical advisability of combining the results of different trials was addressed with a statistical test of heterogeneity, which considers whether differences in treatment effect over individual trials are consistent with natural variation around a constant effect. Results were expressed as (common) differences of the means or as (common) odds ratios, with 95% confidence interval (CI). In case of disagreement at any step of the entire meta-analytical process, consensus was reached with the help of a third observer (MHP).

Results

Out of 51 potentially eligible studies, three were uncontrolled,[21–23] eight were double reports,[24–31] and eight were retrospective;[32–39] thus, 32 trials were left for inclusion. Twenty-two studies compared an active treatment with a non-active control[2,17,40–59] (Table 1); one of these[47] as well as 10 other studies[13–16,60–65] evaluated two or more active drugs (Table 2).

Active treatment versus non-active control

Aspirin and dipyridamole

Eleven studies evaluated the efficacy of aspirin versus control; seven were level 1,[2,17,40–43,47] three were level 2[44,45,48] and one was a level 3 study,[46] not further considered (Table 1). In nine studies,[2,17,40–45,47] aspirin was administered in conjunction with dipyridamole, while in two studies it was administered alone.[46,48]

Eight studies evaluated the efficacy of aspirin (with dipyridamole) after infrainguinal bypass graft, two after percutaneous transluminal angioplasty and one after endarterectomy. In one study[44] a bypass reconstruction was performed in 60% of the enrolled patients while the remaining 40% underwent endarterectomy. Another study[17] enrolled patients after percutaneous transluminal angioplasty of the common iliac, femoral and popliteal arteries.

Sample sizes ranged from 49 to 549. Fontaine stage of disease[18] ranged from I to IV, but in three studies the exact stage was not reported.[40,41,44] The daily dose of aspirin varied from 50 to 990 mg, while the daily dosage of dipyridamole ranged from 225 to 450 mg. Control patients received placebo tablets in level 1 studies, and no treatment at all in level 2 studies. Treatment duration ranged from the in-hospital period up to 51 months. The main outcomes evaluated in the included trials were (loss of) patency, reocclusion, amputation, cardiovascular events and mortality (Fig. 1).

The end-of-treatment pooled results of level 1 studies, with regard to (loss of) patency after bypass graft, percutaneous transluminal angioplasty or endarterectomy together, show an advantage for aspirin-with-dipyridamole-treated patients compared to control (common OR 0.76, 95% CI, 0.58 to 0.99, $p=0.04$). Although the test for heterogeneity was marginally positive ($p=0.034$), all individual results of level 1 studies are compatible with the estimate of the overall treatment effect. When including the single level 2 study the treatment effect increased (common OR 0.69, 95% CI, 0.53 to 0.90, $p=0.005$) (Fig. 1).

Table 1. Clinical trials evaluating the efficacy of antiplatelets, anticoagulants, physical training and smoking cessation compared to non-active control in patients with peripheral arterial disease after revascularisation procedure.

	Level*	Sample†	Stage‡	Procedure§	Site‖	Regimen¶	Duration
Aspirin and dipyridamole							
After bypass graft							
Green, 1982[40]	1	32/17††	ns	ptfe bg	infra in	975 ± Dipyridamole 225	12 months
Kohler, 1984[41]	1	44/44‡‡	ns	asv/ptfe bg	infra in	975 + Dipyridamole 225	24 months
Goldman, 1984[2]	1	22/31	II–IV	d/ptfe bg	fp	900 + Dipyridamole 225	12 months
Donaldson, 1985[42]	1	33/32	II	d bg	fp	990 + Dipyridamole 225	12 months
McCollum, 1991[43]	1	286/263	III–IV	asv bg	fp	600 + Dipyridamole 300	36 months
Harjola, 1981[44]	2	144/67§§	ns	60% bg, 40% ea	supra a, ll‖‖	500 ± Dipyridamole 450	Hospital period
Clyne, 1987[45]	2	70/70	II–III	asv/ptfe bg	fd	300 + Dipyridamole 400	6 weeks
Satiani, 1985[46]	3	93 (?/?)	ns	av, ptfe bg	fp, d	650	1–51 months
After pta or ea							
Heiss, 1990[47]	1	122/67¶¶	I–III	pta	Mainly fp	(300 or 990) + Dipyridamole 225	6 months
Bergqvist, 1994[17]	1	108/115	II–IV	pta	ci, f, p	50 + 400 Dipyridamole	3 months (12 follow-up)
Lassilla, 1991[48]	2	72/72	II–IV	90% ea, bg	ns	250	3 months
Ticlopidine							
Castelli, 1986[49]	1	23/23	II–IV	tea	fp	500	6 months
Becquemin, 1997[50]	1	122/121	IIb–IV	asv bg	fp, fd	500	24 months
Vitamin-K inhibitors							
Arfvidsson, 1990[51]	2	61/55	II–IV	v/ptfe bg, tea	fp, fd	coumarin***	long term (6 years)
Kretschmer, 1992[52]	2	66/64	II–IV	rsv bg	fp	phenprocoumon†††	long term (10 years)
Suloctidil							
Mahler, 1987[53]	1	48/51‡‡‡	II	pta	fp	600	12 months
Dextran 40							
Rutherford, 1984[54]	2	73/83	ns	bg, te, tea, ea	fp, infra p	75–100 ml/h iv§§§§	3 days (1 week follow-up)
PGE_1							
Gruß, 1997[55]	2	42/41‖‖‖‖	III–IV	pp, pta, ptfe/d bg	deep f, af	60 µg/2 h iv bid	3 weeks (5 year follow-up)
Physical training							
Lundgren, 1988[56]	2	25/25	II	asv/ptfe bg, tea	above knee	exercise programme	6 months (12 follow-up)
Smoking cessation							
Provan, 1987[57]	3	107/187	II–IV	asv/p bg	abf, fp	Quit smoke advice, assessed with interview	60 months
Lassilla, 1988[58]	3	53/125	II–IV	bg, tea, pp	ai, acf, fp	Quit smoke advice, assessed with interview	36 months
Powell, 1992[59]	3	120/130	II–IV	asv/p bg	fp	Quit smoke advice, assessed with blood test check	12 months

* Study level (see Methods).
† Total number of patients enrolled (active/control); in level 1 studies control patients received placebo, while in level 2 or level 3 studies, they received nothing.
‡ Fontaine stage of disease; ns: not specified.
§ bg: bypass graft; pta: percutaneous transluminal angioplasty; ea: endarterectomy; te: thrombectomy; p: prosthetic; pp: profundaplasty; ptfe: polytetrafluorethylene; d: Dacron; asv: autologous saphenous vein; rsv: reversed saphenous vein.
‖ a: aorta; f: femoral; bf: bifemoral; c: common; i: iliac; p: popliteal; d: distal; in: inguinal; cr: crural; ll: lower limb.
¶ Drug dosage is expressed in oral daily mg, unless differently stated; iv: intravenous; bid: bis in die.
†† 49 patients were randomised to daily receive aspirin 975 mg (16 patients), aspirin 975 mg and dipyridamole 225 mg (16 patients), or placebo (17 patients); the first two groups were considered together in the analysis.
‡‡ Seven patients in each study group were reoperated on because of graft failure and were "randomised again"; therefore 51 grafts for each group were considered by the authors of the study for the final analysis.
§§ 283 patients were randomised into 4 groups to receive daily: aspirin 500 mg + dipyridamole 450 mg (93), aspirin 500 mg (92), dipyridamole 450 mg (93), no drug (86); the first 2 groups (144) compared with the last one (67) were considered in our analysis.
‖‖ Patients who underwent supra–aortal intervention were excluded from our analysis.
¶¶ 199 patients were randomised to receive aspirin 300 mg daily plus dipyridamole 225 mg (56), aspirin 990 mg plus dipyridamole 225 mg (66), or placebo (67); the first 2 groups are considered together versus placebo.
*** Prothrombin time 10–20%.
††† Prothrombin time 15–25%.
‡‡‡ Both groups received anticoagulant treatment.
§§§§ Subsequently all patients received antiplatelet therapy.
‖‖‖‖ All patients received oral aspirin, 500 mg daily (long-term), and subcutaneous calcium heparin 7500 IU twice daily (until discharge from the hospital).

Table 2. Clinical trials evaluating the efficacy of aspirin at different dosages or versus other active drugs in patients with peripheral arterial disease after revascularisation procedure.

Author	Level*	Sample†	Stage‡	Procedure§	Site‖	Aspirin¶	Comparison¶	Duration
Heiss, 1990[47]	1	66/56††	I–III	pta	fp	990 + Dipyridamole 225	Aspirin 300 + Dipyridamole 225	6 months
Weichert, 1994[13]	1	111/112	II–IV	pta	ll	1000‡‡	Aspirin 300‡‡	6 months
Ranke, 1994[14]	1	175/184	II–IV	pta	ai, fp	900	Aspirin 50	12 months
Minar, 1995[16]	1	107/109	II–IV	pta	fp	1000	Aspirin 100	24 months
D'Addato, 1992[60]‖‖	1	57/56	III–IV	ptfe bg	fp	900 + Dipyridamole 225	Indobufen 400	12 months
Fisher, 1987[61]	1	50§§/49	II–IV	asv bg	fp, cr	1500	PGE_1 iv 0.2 ng/kg/min	10 days
Lucas, 1984[62]	2	49/48	I–IV	av, d bg; tea	ai, fp	1050 + Dipyridamole 150	Pentoxiphylline 1200	6 months
Raithel, 1987[63]	2	59/59	IIb–IV	p bg	fp	1500 + Dipyridamole 225	Pentoxiphylline 1200	12 months
Bollinger, 1985[64]	2	81/39¶¶	II–IV	ea	fp	1000 ± Dipyridamole 225	Warfarin	24 months
Do, 1994[15]	2	79/81	II–IV	pta	fp	50 + Dipyridamole 400	Phenprocoumon***	12 months
Edmondson, 1994[65]	2	106/94	ns	d, ptfe, v bg	fp	900 + Dipyridamole 300	Dalteparin 2500 IU	3 months (12 follow-up)

* Study level (see Methods).
† Total number of patients enrolled (active/control).
‡ Fontaine stage of disease; ns: not specified.
§ bg: bypass graft; pta: percutaneous transluminal angioplasty; ea: endarterectomy; p: prosthetic; ptfe: polytetrafluoroethylene; d: Dacron; v: vein.
‖ f: femoral; a: aorta; i: iliac; p: popliteal; cr: crural; ll: lower limb.
¶ Expressed in oral daily mg, unless differently stated.
†† 199 patients were randomised to receive daily aspirin 990 mg plus dipyridamole 225 mg (66 patients), aspirin 300 mg plus dipyridamole 225 mg (56) or placebo (67); the former two groups are considered for the comparative analysis.
‡‡ Both groups received heparin up to 5 days after the intervention.
§§ Two patients had thromboangiitis obliterans; both groups also received subcutaneous or intravenous 15 000 IU heparin for 10 days.
‖‖ A seven days' wash-out period preceded the active drug administration.
¶¶ Patients were randomised to receive daily aspirin 1000 mg alone (40 patients), aspirin 1000 mg plus dipyridamole 225 mg (41), warfarin (39); the first two groups are considered together for the analysis; warfarin was monitored by patient's physicians; mean prothrombin time 34%.
*** Prothrombin time (INR) 2.3 ± 0.8.

With regard to the effects of aspirin with dipyridamole after bypass graft only, six studies[2,40–44] reported (loss of) patency results at the end of treatment, while five studies[2,40–43] reported these results at 12 months (raw data not shown). Both analyses showed an advantage for actively treated patients (common OR 0.72, 95% CI, 0.53 to 0.99, $p = 0.05$, and common OR 0.76, 95% CI, 0.50 to 0.85, $p = 0.002$, respectively).

The efficacy of aspirin with dipyridamole on (loss of) patency after percutaneous transluminal angioplasty or endarterectomy was evaluated in two level 1 studies.[17,47] After 6 months of treatment a trend in favour of aspirin-plus-dipyridamole-treated patients was observed (OR 0.66, 95% CI, 0.42 to 1.04; $p = 0.075$) (raw data not shown). Pooled end-of-treatment obervations show an advantage for aspirin-plus-dipyridamole-treated patients (common OR, 0.63, 95% CI, 0.40 to 0.98, $p = 0.04$).

Three studies provided data on amputation rates at the end of follow-up after a graft procedure[43,45] or after percutaneous transluminal angioplasty.[17] The difference observed between the groups was not statistically significant (Fig. 1). Data on mortality were available from five level 1[2,17,40,41,43] and two level 2 studies.[45,48] Pooling data, a reduction in mortality was observed in actively treated patients, although the difference did not reach statistical significance (common OR 0.80, 95% CI, 0.57 to 1.14, $p = 0.2$) (Fig. 1).

Ticlopidine

Two level 1 studies were included[49,50] (Table 1). Sample size ranged from 46 to 243 patients, belonging to Fontaine II to IV stage of disease and treated with thromboendarterectomy[49] or autologous saphenous bypass graft.[50] With regard to (loss of) patency, pooled end-of-treatment results[49,50] show a statistically significant advantage in favour of actively treated patients (common OR 0.53, 95% CI, 0.33 to 0.85, $p = 0.009$) (Fig. 1).

According to one study,[50] ipsilateral amputation was reduced in the ticlopidine-treated patients (OR 0.29, 95% CI, 0.08 to 1.01, $p = 0.052$) (Fig. 1). End-of-treatment pooled results do not show differences in terms of death between ticlopidine- and placebo-treated patients[49,50] (Fig. 1).

Vitamin K inhibitors

Two level 2 studies were included[51,52] (Tale 1). Sample sizes ranged from 116 to 130; enrolled patients belonged to Fontaine II to IV stage of disease, and

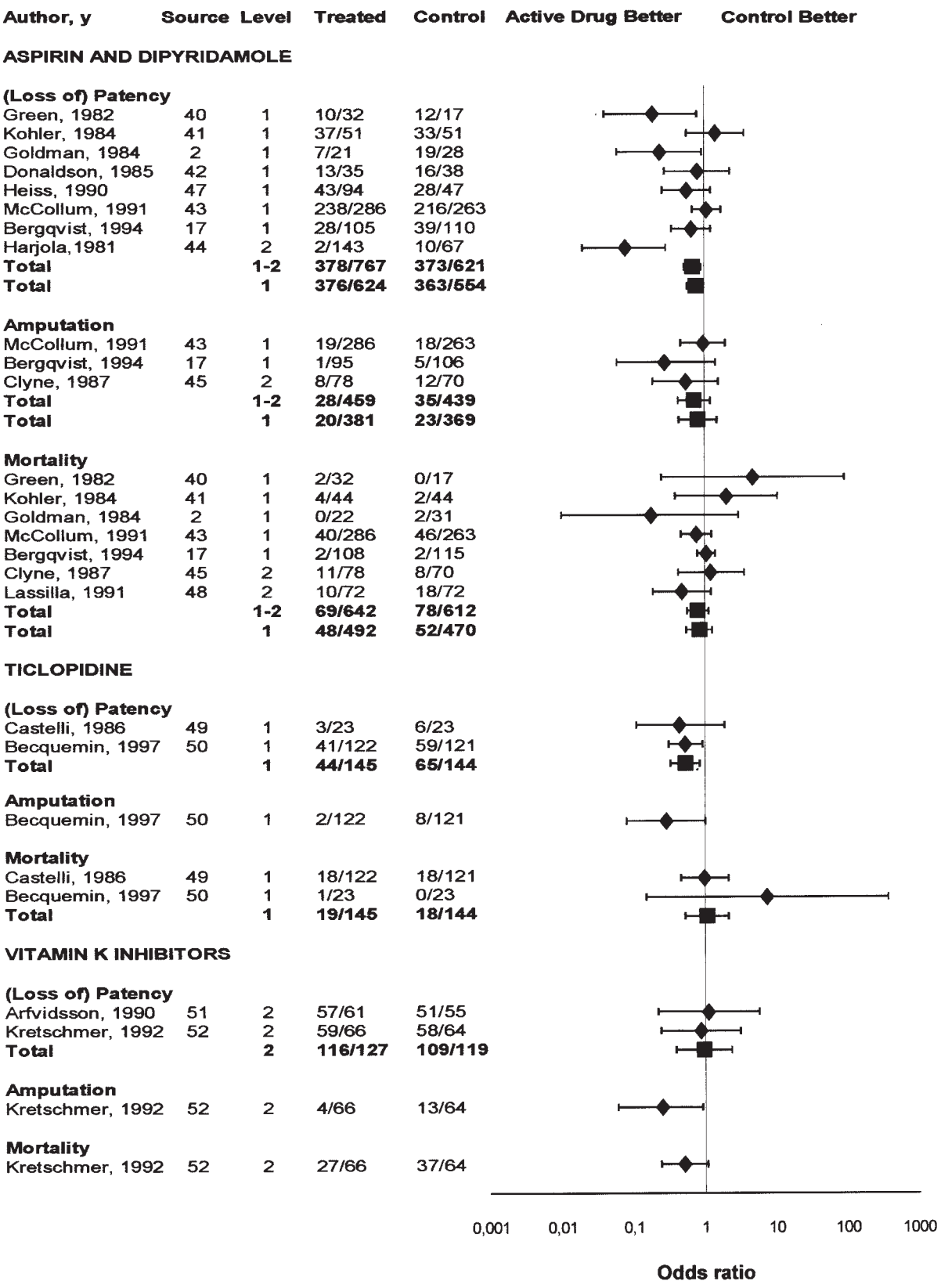

Fig. 1. Effect of aspirin with dipyridamole, ticlopidine and vitamin-K inhibitors compared to non-active control on (loss of) patency, amputation, and mortality, in patients with peripheral arterial disease and treated with revascularisation procedures; end-of-treatment results are expressed as odds ratio with 95% confidence interval, for individual and combined studies.

Table 3. Efficacy of suloctidil, dextran, PGE_1, physical training and smoking cessation, compared to non-active control, as adjunct conservative treatment in patients with peripheral arterial disease after revascularisation procedures.

Author	Level*	Results
Suloctidil		
Mahler, 1987[53]	1	Patency, stenosis and mortality were not different compared to control
Dextran 40		
Rutherford, 1984[54]	2	Occlusion, myocardial infarction and mortality were not different compared to control
PGE_1		
Gruß, 1997[55]	2	Remission to stage IIb was higher in the actively treated patients (OR 2.8, 95% CI, 1.1–7.6), as well as the reduction in major amputations (OR 0.4, 95% CI, 0.13–1.02); survival was not significantly improved in the PGE_1 group
Physical training		
Lundgren, 1988[56]	2	The supervised exercise programme significantly improved pain-free walking distance of 154 m (95% CI 74–382) compared to control; total walking distance, ankle–brachial index, calf blood flow and mortality were not different
Smoking cessation		
Provan, 1987[57]	3	Compared to control, 5 year cumulative patency resulted higher in patients who quitted smoking and with aortobifemoral graft (77% vs. 42%, $p<0.001$) or prosthetic femoropopliteal graft (43% vs. 19%, $p<0.05$), not in patients with femoropopliteal vein grafts
Lassilla, 1988[58]	3	Amputation and local "lower limbs adverse events" (†) were reduced in the quitting smoking group (OR, respectively, 0.11, 95% CI 0.02–0.85, $p=0.03$, and 0.43, 95% CI 0.2–0.93); mortality and "central adverse events" (‡) were not different compared to current smokers
Powell, 1992[59]	3	One-year patency was improved by quitting smoking both with vein (84% vs. 63%, $p<0.02$) or prosthetic grafts (87% vs. 68%, $p=0.025$)

* Study level (see Methods).
† Lower limbs adverse events: deterioration of peripheral arterial disease, ankle–brachial index decrease of 0.1 or more, Fontaine-stage worsening, major amputation, vascular reconstructive procedure.
‡ Central adverse events: angina pectoris, acute myocardial infarction, sudden heart failure, transitory ischaemic attack, stroke;
vs. versus.

underwent bypass-grafting or thrombo-endarterectomy of the femoropopliteal or femorodistal arteries. Anticoagulant treatment was administered long term in both studies (Table 1) for a mean prothrombin time ranging from 10 to 25%.

Both studies[51,52] reported results on (loss of) patency. End-of-treatment pooled results do not show any difference between treated and control patients (common OR 0.96, 95% CI 0.39–2.35) (Fig. 1). However, in these studies an advantage for the use of vitamin K inhibitors was observed after 6 months, 1 and 4 years of treatment after the vascular procedure (common OR 0.29, 95% CI 0.1–0.80, $p=0.02$; 0.58, 95% CI 0.35–0.98, $p=0.04$; and 0.46, 95% CI 0.24–0.88, $p=0.02$, respectively) (raw data not shown).

Amputation rate, according to one study,[52] was statistically significantly lowered in the treated patients after 10 years (OR 0.25; 95% CI from 0.06 to 0.91; $p=0.016$). In the other study[51] the cumulative limb salvage after 36 months was not different between the two groups (log rank $p=0.81$). Mortality was almost significantly reduced in the actively treated patients (Fig. 1) according to one study[52] (OR 0.51, 95% CI 0.24–1.08, $p=0.08$). The other study[51] showed no difference with regard to the cumulative survival rate after 48 months (50% versus 62%, log-rank test $p=0.51$).

Other interventions

Of the other interventions (suloctidil, dextran, PGE_1, physical training, smoking cessation) only a limited number of trials were available,[53–59] or the results were presented in such a way that data extraction was impossible. Main results are summarised in Table 3.

Studies comparing active drugs

Aspirin – high versus low dose

Four level 1 studies were included[13,14,16,47] (Table 2) and main results are summarised in Table 4. In general, different dosages of aspirin were equally effective with regard to (loss of) patency, reocclusion and amputation. Side-effects (mainly gastrointestinal) were significantly more frequent with higher dosages of aspirin.[14,16]

Aspirin with dipyridamole versus other active drugs

Aspirin was compared with indobufen,[60] prostaglandin E_1[61] pentoxiphylline,[62,63] vitamin-K inhibitors,[15,64] and dalteparin.[65] Dipyridamole was added to aspirin in all studies but one.[61] Study details and main results are summarised in Tables 2 and 4 and in Figure 2. In one

Table 4. Efficacy of aspirin compared with different dosages or with other active drugs in the adjunct conservative treatment of patients with peripheral arterial disease after revascularisation procedures.

Author	Level*	Results (expressed as relative effect of first versus second drug)
High vs. low aspirin dosage		
Heiss, 1990[47]	1	Patency was not different
Weichert, 1994[13]	1	Reocclusion, mortality and (mainly gastric) side-effects were not different
Ranke, 1994[14]	1	Gastroenteric side-effects were higher in the high-dose group (OR 3.9, 95% CI 1.2–13, $p=0.03$); patency and mortality were not different
Minar, 1995[16]	1	Gastroenteric side-effects were significantly higher in the high-dose aspirin group (OR 6.0, 95% CI 1.9–21.7, $p=0.001$); patency, amputation and mortality were not different
Aspirin with dipyridamole vs. indobufen		
D'Addato, 1992[60]	1	No significant differences in terms of patency (OR 0.68, 95% CI 0.33–1.42), mortality and gastrointestinal bleedings (OR 7.4, 95% CI 0.46–119.7)
Aspirin vs. PGE_1		
Fisher, 1987[61]	1	Amputation was higher in the aspirin-treated patients (OR 6.2, 95% CI from 1.2 to 31.2, $p=0.03$), while reocclusion was not different
Aspirin with dipyridamole vs. pentoxiphylline		
Lucas, 1984[62]	2	Reocclusion, amputation, mortality, PFWD, ABI and side-effects were not different
Raithel, 1987[63]	2	Patency, amputation, mortality were not different; gastrointestinal side-effects were significantly lower in the pentoxiphylline group (OR 11.2, 95% CI 5.1–25.0, $p<0.0001$)
Aspirin with dipyridamole vs. dalteparin		
Edmondson, 1994[65]	2	Patency and mortality were lower in the aspirin group compared to the dalteparin-treated patients (respectively, 64.1% vs. 79.5%, log-rank test $p=0.02$, and OR 0.2, 95% CI 0.07–0.8) (different mortality was explained by cancer imbalance between the two groups)

* Study level (see Methods);
vs. = versus.

study,[60] gastrointestinal bleedings were lower in the indobufen-treated patients compared to those treated with aspirin plus dipyridamole, while in another study,[15] severe bleedings were more frequent in the phenprocoumon-treated patients (OR 0.1, 95% CI, 0.001 to 2.2) compared to those treated with aspirin plus dipyridamole (Table 4).

Discussion

It is common clinical practice to prescribe adjuvant treatments in order to prevent reocclusion after revascularisation procedures in patients with peripheral arterial disease. Although many different strategies have long been available for this purpose, only aspirin, associated with dipyridamole, and ticlopidine have been extensively evaluated with methodologically sound studies. Oral anticoagulants were evaluated in two level 2 studies and other strategies (suloctidil, dextran, PGE_1, physical training and smoking cessation) were merely evaluated in single or level 3 studies. Patency was statistically significantly improved by aspirin with dipyridamole or by ticlopidine. Vitamin-K inhibitors improved patency at 1 and 4 years, but not at the end of follow-up. Amputation rates were reduced by ticlopidine[50] and by vitamin-K inhibitors.[52] Mortality was reduced by aspirin plus dipyridamole, although statistical significance was not reached (Fig. 1). Ticlopidine is likely to improve survival, by analogy with other studies[66] which consider patients only at stage II of disease, according to Fontaine.[18] With regard to vitamin-K inhibitors, results were not conclusive. The two level 2 studies that directly compared aspirin plus dipyridamole with vitamin-K inhibitors were small in size and produced inconsistent results.[15,64] Patency seemed improved in the aspirin plus dipyridamole compared to vitamin-K-inhibitor-treated patients (Fig. 2), while no differences were observed in terms of amputation and mortality.

Aspirin associated with dipyridamole was also compared in several small studies with other active drugs. Indobufen was as effective as aspirin in terms of patency, while mortality and gastrointestinal bleedings

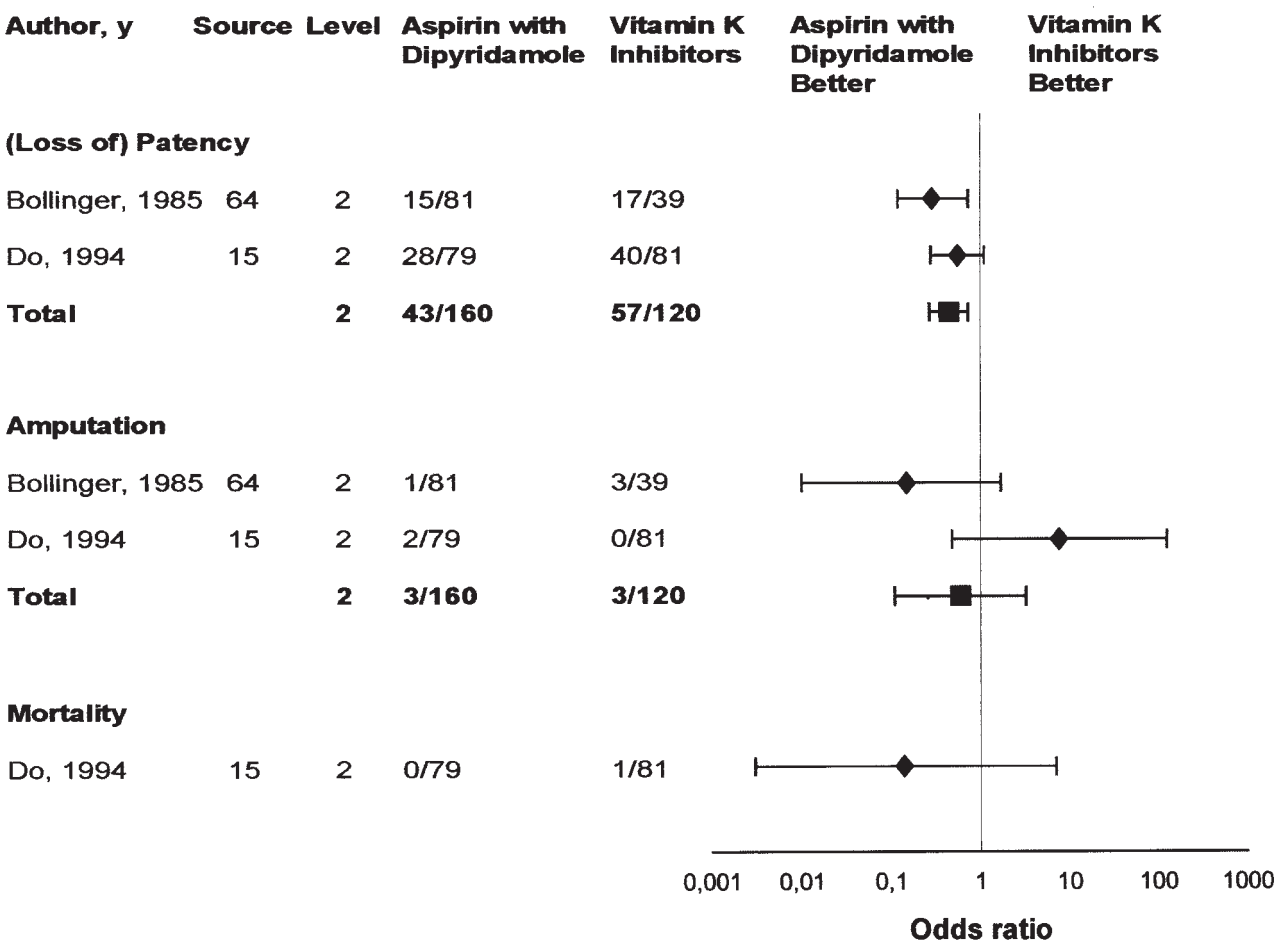

Fig. 2. Effect of aspirin with dipyridamole compared to vitamin-K inhibitors on (loss of) patency, amputation, and mortality, in patients with peripheral arterial disease and treated with revascularisation procedures; end-of-treatment results are expressed as odds ratio with 95% confidence interval, for individual and combined studies.

were not significantly different among the two groups.[60] The comparison with pentoxiphylline[62,63] was evaluated in only two level 2 studies and failed to show any difference with regard to efficacy, and was inconsistent for the occurrence of side-effects. Prostaglandin E_1 was superior to aspirin alone in preventing amputation within 10 days.[61] Three months of subcutaneous dalteparin significantly improved 1-year patency after graft surgery in comparison to aspirin.[65] Four level 1 studies showed that decreasing aspirin dosage significantly lowers side-effects without disadvantages in terms of efficacy.[13,14,16,47]

Among the other drugs that were compared with a control group, only the results of PGE_1 (limb survival and Fontaine stage improvement) and supervised physical training (improved pain-free walking distance) were promising. Quitting smoking improved patency and amputation rate in level 3 studies.

The Antiplatelet Trialists' Collaboration meta-analysis[67] demonstrated a significant 43% occlusion-rate reduction in patients treated with antiplatelets because of arterial disease, as compared to control patients. This figure is in agreement with our results restricted to patients who received revascularisation procedures because of peripheral arterial disease. However, such evidence is available only for aspirin associated with dipyridamole, and for ticlopidine; a similar positive effect can be only speculated on for other antiplatelets drugs inclusive of aspirin alone and should be evaluated in large properly designed trials. Furthermore, the Antiplatelet Trialists' Collaboration meta-analysis[12] definitely also demonstrated a statistically significant 25% reduction of vascular events (vascular death, nonfatal myocardial infarction or stroke) and a 17% reduction of total mortality in patients at high cardiovascular risk (including patients with peripheral

arterial disease) treated with antiplatelets agents. These figures are in agreement with our finding of a 20% mortality reduction in patients treated with aspirin with dipyridamole and underlines the indication to administer aspirin (with dipyridamole) to these patients because of better survival (number of patients to be treated for 1 year to save one death: 68). Although most studies used high aspirin dosages, 50–300 mg daily are as effective as higher regimens (900–1000 mg daily), according to comparative studies. Moreover, in all but two studies,[46,48] aspirin was administered in conjunction with dipyridamole. In a recent large trial, dipyridamole showed an additive positive effect on low-dose aspirin (50 mg) in preventing vascular events,[68] in patients at risk of stroke. As a consequence, our results favour the recommendation of administering aspirin with dipyridamole to these patients, since data on the use of aspirin alone are not available.

In conclusion, the available evidence suggests that 100–300 mg aspirin daily with 225–450 mg of dipyridamole should be prescribed to patients with peripheral arterial disease who undergo a revascularisation procedure, since they improve patency and (probably) prolong survival. The evidence for vitamin-K inhibitors is less convincing and a direct comparison between aspirin and these drugs in a methodologically sound, large study is warranted. Ticlopidine improves patency, amputation rates and (likely) survival, and therefore may be used when aspirin is contraindicated. Clopidogrel, a new drug derived from ticlopidine, is likely to improve the outcome of these patients compared to aspirin in terms of vascular events and survival.[69,70] However, no separate data regarding this group of patients are available.

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