Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery (Review)

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[Intervention Review]

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Editorial group: Cochrane Peripheral Vascular Diseases Group.
Publication status and date: Unchanged, published in Issue 3, 2008.
Review content assessed as up-to-date: .

Citation: Dörffler-Melly J, Büller HR, Koopman MM, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD000535. DOI: 10.1002/14651858.CD000535.

ABSTRACT

Background

Peripheral arterial disease (PAD) may cause occlusions (blockages) in the main arteries of the lower limbs. It is frequently treated by implantation of either an infrainguinal autologous (using the patient's own tissue) venous or artificial graft. A number of factors influence occlusion rates, including the material used. To prevent graft occlusion, patients are usually treated with either an antiplatelet or antithrombotic drug, or a combination of both.

Objectives

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

Search strategy

The reviewers searched the Cochrane Peripheral Vascular Diseases Group Specialised Register, (last searched April 2003), and the Cochrane Central Register of Controlled Trials (CENTRAL) (last searched Issue 1, 2003). Additional trials were sought through reference lists of papers and by reviewing proceedings from the vascular surgical society meetings.

Selection criteria

The methodological quality of each trial was assessed independently by two reviewers (JD, MMK), with emphasis on concealment of randomisation.

Data collection and analysis

Details of the studies selected were extracted independently by two reviewers (JD, MMK), and an 'intention-to-treat' analysis performed. The treatment and control groups were compared for important prognostic factors and differences described. If any data were not available, further information was sought from the author. Data were synthesized by comparing group results.

Main results

The administration of a variety of platelet-inhibitors resulted in improved venous and artificial graft patency compared to no treatment. However, analysing patients for graft-type indicated that patients receiving a prosthetic graft were more likely to profit from administration of platelet-inhibitors than those treated with a venous graft.

Authors' conclusions

Antiplatelet therapy with aspirin had a slight beneficial effect on the patency of peripheral bypasses, but seemed to have an inferior effect on venous graft patency compared with artificial grafts. The effect of aspirin on cardiovascular outcomes and survival was mild and not statistically significant; this might be due to the fact that the majority of patients receiving a peripheral graft have an advanced stage of PAD with critical ischaemia. These patients are usually seriously ill with respect to cardiovascular diseases with high mortality rates of 20% per year. Additionally, the number of patients included in this analysis might still be too small to reach a statistically significant effect for mortality and cardiovascular morbidity.

PLAIN LANGUAGE SUMMARY

Aspirin might help prevent blood clots blocking arteries after bypass graft surgery in the legs, but more research is needed

Peripheral arterial disease is narrowing or blockage of the arteries (major blood vessels) in the legs. This can cause intermittent claudication (pain on walking). It can worsen and lead to ischaemia, with poor circulation causing ongoing pain, ulcers (sores) and/or gangrene. Bypass graft surgery may be an option, where a graft keeps the artery open by bypassing the blockage. A possible complication is thrombosis (the formation of blood clots which might block the artery). The review of trials found some evidence that aspirin can sometimes prevent thrombosis after artery bypass graft surgery in the legs, but more research is needed.

BACKGROUND

Symptomatic peripheral arterial disease (PAD) of the lower extremities may present itself as either intermittent claudication (IC), i.e. as pain on walking, or at a more progressive stage, as critical limb ischaemia (CLI), i.e. as pain at rest, ulceration and gangrene. The implantation of a femoropopliteal or femorodistal bypass graft (a makeshift blood vessel used to bypass a blockage in the main artery of the thigh) is one treatment option for patients who are at risk of losing a limb, or whose walking ability is greatly impaired because of the disease. By placing a graft in the groin area (infrainguinal graft), the blocked arterial segment is bypassed, thereby improving blood flow through the limb. This then relieves the symptoms of claudication or rest pain, and avoids the need for amputation due to ulceration and gangrene (limb salvage).

Patency rates for femoropopliteal and femorocrural grafts (the number of bypasses remaining patent after a certain period of time) depend on several risk factors, such as graft material, length of the bypass, site of the distal anastomosis (surgical connection of the graft to the existing artery), outflow conditions in the calf (flow of blood out of the graft), and female gender (Cooper 1990; Tangelder 2000). Thus, autologous saphenous vein (i.e. vein from the patient's calf) is superior to artificial materials such as Dacron or polytetrafluoroethylene (PTFE) (Rutherford 1988). Where the distal anastomosis is above the knee there is a lower risk of graft failure, and patients with two or three patent calf arteries have a better outcome than those with only one patent artery. Graft failure occurs for two reasons: most frequently, at the site of the distal or proximal anastomosis (surgical connection at the far or near ends), smooth muscle cells of the medial (middle) layer of the vessel wall grow into the intimal (inner) layer, known as intimal hyperplasia. This in turn causes the diameter of the perfused graft to become smaller, known as stenosis. When more than 70% of the perfused diameter is reduced, blood flow through the vessel is significantly reduced, causing intermittent claudication. Graft occlusion (closure) is often followed by the formation of a thrombosis (clot) at the stenotic site. If blood flow in the failed graft cannot be restored and further bypass surgery is not possible, then blood flow may 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 at one year after the operation vary between 15 and 75 %, depending on the various risk factors described above (Abbott 1997; Consensus 1991). In addition, in patients with lower limb atherosclerosis (progressive hardening of the arteries), platelet aggregation (leading to clot formation) is frequently increased. Moreover, the body's physiological stress response to surgery is to cause a prothrombotic state (where the body is preparing to form a clot). 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 (Fujitani 1988).

To prevent graft occlusion, patients are usually treated with either an antiplatelet or antithrombotic drug, or a combination of both. It is not known which regimen is best to prevent infrainguinal graft occlusion. The aim of this analysis was to evaluate whether antiplatelet treatment improves graft patency, limb salvage and survival in patients with chronic PAD undergoing infrainguinal bypass surgery.

OBJECTIVES

To determine the efficacy of antiplatelet drugs in patients with lower limb atherosclerosis undergoing femoropopliteal and femorodistal bypass grafting. Outcomes include the overall success of therapy (graft patency and limb salvage rates) and complications of treatment. The null hypothesis is that antiplatelet therapy does not improve graft patency and limb salvage rates after femoropopliteal and femorodistal bypass surgery for lower limb atherosclerosis.

RESULTS

Analysis for amputation, side-effects, bleeding complications, cardiovascular events or death are only described where sufficient data were available. Otherwise, these outcomes are not mentioned. Quality of life was not measured in any of the trials included in this review.

Aspirin (ASA) or aspirin/dipyridamol (ASA/DIP) versus no aspirin

Primary graft patency

The effect of ASA or ASA/DIP on infrainguinal bypass patency was studied in six trials (Clyne 1987; Donaldson 1985; Goldman 1984; Green 1982; Kohler 1984; McCollum 1991), with a total of 966 patients randomised, 501 in the treatment group and 465 in the control group. Peto odds ratio (Peto OR) and 95% confidence interval for primary occlusion at 12 months for all grafts was 0.59 (95% CI fixed 0.45 to 0.79), showing a positive, statistically significant effect of ASA on infrainguinal grafts within one year.

When analysis was performed for venous grafts alone (two trials - Clyne 1987; McCollum 1991), this effect was attenuated to OR 0.69 (95% CI 0.48 to 0.99). This attenuated effect of ASA became even more evident when Peto OR was calculated for time points one, three, six, and 24 months postoperatively, with values of 0.76 (95% CI fixed 0.26 to 2.24) at one month, 0.85 (95% CI fixed 0.54 to 1.35) at three months, 0.88 (95% CI fixed 0.59 to 1.31) at six months, and 0.72 (95% CI fixed 0.51 to 1.00) at 24 months. Analysis for prosthetic grafts, however, showed a much stronger positive and statistically significant effect of ASA on primary patency, as calculated from four RCTs (Clyne 1987; Donaldson 1985; Goldman 1984; Green 1982), (Peto OR 0.22; 95% CI fixed 0.10 to 0.50 at one month, 0.33; 95% CI fixed 0.17 to 0.68 at three months, 0.23; 95% CI fixed 0.13 to 0.42 at six months, and 0.22; 95% CI fixed 0.12 to 0.38 at 12 months).

Amputation

Amputation could not be evaluated as a second endpoint, due to missing data. Only Clyne 1987 reported a positive, statistically non-significant effect for ASA in a total number of 148 patients (78 in the ASA group and 70 in the control group).

Cardiovascular events

Analysis of cardiovascular events was performed in four trials (Clyne 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 0.71; 95% CI fixed 0.47 to 1.08). OR for postoperative death in general was 0.82 (95% CI fixed 0.54 to 1.23), showing a slight tendency in favour of ASA or ASA/DIP.

Side effects

Gastrointestinal side effects as evaluated in 966 patients from six studies (Clyne 1987; Donaldson 1985; Goldman 1984; Green 1982; Kohler 1984; McCollum 1991), were more frequent in patients receiving aspirin, although this was not significant (OR 1.44; 95% CI fixed 0.92 to 2.24). Major bleeding was also more frequent in the ASA group when evaluated in two trials (Green 1982; McCollum 1991) without reaching statistical significance (OR 1.88; 95% CI fixed 0.85 to 4.16).

Aspirin (ASA) or aspirin/dipyridamol (ASA/DIP) versus pentoxifylline (PTX)

Primary patency

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 time point six months postoperatively. Thereby, 78 patients were assigned to ASA or ASA/DIP treatment and 73 to PTX with a Peto OR of 1.40 (95% CI fixed 0.63 to 3.11), showing an equal or slightly favouring, statistically non-significant effect of PTX on primary graft patency. At other time points, only the study of Raithel (Raithel 1987), provided raw data, showing a similar effect on graft patency of both drugs (Peto OR 1.00; 95% CI fixed 0.28 to 3.63 at 3 months and 0.92; 95% CI fixed 0.41 to 2.07 at 12 months).

Aspirin/dipyridamol (ASA/DIP) versus indobufen (IND)

Primary patency

The one 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 three months postoperatively on graft patency, but this was not

statistically significant (Peto OR 1.64; 95% CI fixed 0.52 to 5.20). This effect was attenuated within one year postoperatively (Peto OR 1.33; 95% CI fixed 0.62 to 2.90).

Aspirin/dipyridamol (ASA/DIP) versus vitamin K antagonists (VKA)

Primary graft patency

Primary graft patency for all grafts, including 1356 patients in the coumarin group and 1385 in the aspirin group, showed almost no difference for coumarin versus aspirin irrespective of time point (OR 0.89; 95% CI fixed 0.69 to 1.15 at three months, 0.99; 95% CI fixed 0.81 to 1.22 at six months, 0.92; 95% CI fixed 0.77 to 1.11 at 12 months, and 0.91; 95% CI fixed 0.77 to 1.08 at 24 months postoperatively).

Intention-to-treat analysis for venous grafts included 814 patients randomised to coumarin treatment versus 823 to aspirin. Coumarins had a statistically significant favourable effect on patency rates compared to antiplatelet treatment either with aspirin alone or with a combination of aspirin and dipyridamole (OR 0.66; 95% CI fixed 0.46 to 0.93 at three months, 0.71; 95% CI fixed 0.53 to 0.95 at six months, 0.65; 95% CI fixed 0.49 to 0.85 at 12 months, and 0.59; 95% CI fixed 0.46 to 0.76 at 24 months). For patients treated with an artificial conduit, a group that had been analysed only by the BOA trialists (542 in coumarin group versus 562 in aspirin group), no statistically significant positive effect was found for coumarins (OR 1.32; 95% CI fixed 0.89 to 1.95 at three months, 1.47; 95% CI fixed 1.08 to 1.99 at six months, 1.33; 95% CI fixed 1.02 to 1.74 at 12 months, and 1.41; 95% CI fixed 1.11 to 1.80 at 24 months).

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

Limb salvage and survival

The two trials (BOA 2000; Schneider 1979), did not report data on limb salvage and survival suitable for a formal meta-analysis. However, in the BOA trial limb amputation had to be performed in 100 (7.5%) coumarin treated and 110 (8.3%) aspirin treated patients.

Side effects

In the BOA 2000 trial, haemorrhage necessitating hospital admittance was reported for 119 (9%) patients in the coumarin group and 59 (4.5%) patients in the aspirin group. Thereby, 16 (1.2%) patients died from fatal bleeding in the coumarin group and 12 (0.9%) patients in the aspirin group. In the Schneider 1979 trial adverse effects were reported for two patients (0.6%) stopping coumarin treatment for bleeding complications, and 13 patients (21%) stopping aspirin for different reasons.

Death

Three patients of each group died within two years.

Aspirin/dipyridamol (ASA/DIP) versus low molecular weight heparin (LMWH)

Primary patency

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, OR was 1.69 (95% CI fixed 0.78 to 3.65) at six months and 1.19 (95% CI fixed 0.66 to 2.15) at 12 months, showing a positive but statistically non-significant effect for LMWH.

Side effects

No major bleedings or adverse events occurred.

Death

Nine patients in the LMWH group (four with patent grafts) and two in the aspirin group died during follow-up.

Ticlopidine (TIC) versus nothing

Primary patency

Intention-to-treat analysis of one trial (Becquemin 1997) including 243 patients showed evidence for a strong statistically significant effect of TIC on venous bypass patency at six, 12, and 24 months postoperatively (OR 0.26; 95% CI fixed 0.11 to 0.63 at six months, 0.38; 95% CI fixed 0.19 to 0.75 at 12 months, and 0.37; 95% CI fixed 0.21 to 0.64 at 24 months). Additionally, the results show that for early occlusion rates, i.e. within one month, TIC does not seem to have any advantage in contrast to the medium-term patency rates (OR 3.00; 95% CI fixed 0.12 to 74.37).

Aspirin versus prostaglandin E1 (PGE1)

In the PGE1 group there were only two of 50 patients observed with early occlusion within the first three postoperative days, while there were seven of 50 patients in the ASA group. Between day four and dismissal, there were three more occlusions found in both groups.

DISCUSSION

Antiplatelet effect on bypass patency

In the present meta-analysis the effect of postoperatively administered antiplatelet treatment was evaluated in PAD 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 0.59; 95% CI fixed 0.45 to 0.79). 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 time points one,

three, six, and 12 months postoperatively (OR 0.22; 95% CI fixed 0.10 to 0.50, 0.33; 95% CI fixed 0.17 to 0.68, 0.23; 95% Ci fixed 0.13 to 0.42, and 0.22; 95% Ci fixed 0.12 to 0.38 respectively). In contrast, the effect of ASA/DIP in patients receiving venous bypasses was clearly less (OR 0.76; 95% CI fixed 0.26 to 2.24, 0.85; 95% CI fixed 0.54 to 1.35, 0.88; 95% CI fixed 0.59 to 1.31, and 0.72; 95% CI fixed 0.51 to 1.00 respectively). It should be noted that a formal test for interaction to statistically demonstrate a differential effect of antiplatelet agents by graft-type was not performed.

A comparison of ASA or ASA/DIP with VKA was possible in a large group of patients. Results indicated that overall there was no difference between the drugs. However, in accordance with the effect 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 in venous bypasses (OR 0.66; 95% CI fixed 0.46 to 0.93 at 3 months and OR 0.59; 95% CI fixed 0.46 to 0.76 at 24 months). The effect on patients treated with an artificial conduit showed a statistically significantly stronger effect of ASA in comparison to VKA (OR 1.32; 95% CI fixed 0.89 to 1.95 at three months, 1.47; 95% CI fixed 1.08 to 1.99 at six months, 1.33; 95% CI fixed 1.02 to 1.74 at 12 months and 1.41; 95% CI fixed 1.11 to 1.80 at 24 months). It should be noted that in this group of patients treated by ASA, the dose was only 80 mg daily, while patients in other trials using ASA doses ranged from 600 to 1500 mg daily. This might influence the effect of ASA on patency rates in venous bypasses of the BOA trial.

Cardiovascular events and side effects

The effect on cardiovascular events including myocardial infarction and stroke as performed in four 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

Ticlopidine (TIC), another agent preventing platelet aggregation, was evaluated in one trial including 243 patients undergoing venous bypass surgery (Becquemin 1997). Primary patency was significantly improved at six, 12, and 24 months postoperatively (OR 0.26; 95% CI fixed 0.11 to 0.63, 0.38; 95% CI fixed 0.19 to 0.75 and 0.37; 95% CI fixed 0.21 to 0.64 respectively]. Thus, TIC seems to be the only antiplatelet agent achieving as favourable an effect on venous graft patency as that of treatment with vitamin K antagonists (VKA) (BOA 2000; Schneider 1979). Unfortunately, the trial did not include a subgroup for artificial grafts.

Non-antiplatelet drugs with an antiplatelet effect

For pentoxifylline (PTX) the data are inconclusive. ASA/DIP was compared with 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.

Prostaglandin E1 seems to have a favourable effect on early graft occlusion, but was only evaluated in comparison to ASA in a single small study.

Heterogeneity of included studies

It is striking that the test for heterogeneity was significant in the analysis on patency, amputation, death, side-effects, and gastrointestinal side-effects of ASA or ASA/DIP versus nothing, when all studies were included, whereas in the separate analysis for venous or artificial grafts, the test for heterogeneity was not significant. This implies that studies including different graft types are not suitable for combining to obtain overall results. However, heterogeneity of the included studies might also be due to the fact that administration of ASA was started at different time points; thus, most of the trialists started one to two days prior to surgery, while Kohler 1984 started on the first postoperative day. Other differences between trials, such as percentage of included claudicants and patients with critical limb ischaemia, or percentage of infragenicular anastomosis, or veins more than 4 mm in diameter used as bypass, might also affect the statistical results (see Patient characteristics, Table 02).

Possible pathophysiological mechanisms

A possible pathophysiological mechanism explaining these results could be that tissue factor (TF) expression increased by the venous endothelium. Such a mechanism was demonstrated when saphenous vein segments were placed into a high pressure arterial system (Muluk 1998), with subsequently enhanced TF-expression. TF, as the strongest activator of the extrinsic coagulation cascade, may thus induce a prothrombotic state within the bypass, with increased local thrombin generation on the vulnerable graft endothelium. Therefore, 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 (Fujitani 1988; Nielsen 1997). However, one exception has to be noted, i.e. that TIC reached a high effect on venous graft patency, which might result in comparable strength to that achieved by VKA. One reason for this stronger effect could be that TIC, as a thienopyridine, functions differently from ASA by requiring conversion to its metabolites which are noncompetitive antagonists of the platelet adenosine diphosphate (ADP) receptor. Thus, by inhibiting the ADP induced platelet activation, TIC might not only attenuate platelet aggregation and activation, but also platelet induced coagulation (Altman 1999). Clopidogrel, another thienopyridine, might have similar effects as ticlopidine and should therefore be compared to the effect of VKA in patients receiving venous or artificial femoropopliteal infragenicular bypass surgery.

In general, data presentation was not separated for graft types regarding the site of the distal anastomosis, and the 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 were unavailable after contacting the authors.

In conclusion, according to the results of our meta-analysis, the administration of platelet-inhibitors such as ASA, ASA/DIP, TIC, 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 Dacron, shows that patients receiving a prosthetic graft are likely to profit 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 worthwhile combining aspirin and a thienopyridine, such as for example clopidogrel, that has already been shown to be effective in patients suffering from myocardial infarction (Moshfegh 2000), or being subjected to coronary stenting (Bertrand 2000; Mishkel 1999). Thus, combined antiplatelet therapy of clopidogrel and aspirin in secondary prevention of venous infrainguinal bypass surgery might be a promising strategy in the future.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, there is evidence to suggest that the administration of platelet-inhibitors such as ASA, ASA/DIP, TIC or PTX, will result in improved venous and artificial graft patency compared to no treatment. However, patients receiving a prosthetic graft may profit more from ASA or ASA/DIP administration than those treated with a venous graft. Patients receiving venous femoropopliteal, infragenicular bypasses seem to benefit more from VKA than from ASA. A combination of ASA and a thienopyridine, e.g. Clopidogrel, might be as effective for primary patency rates as VKA.

Implications for research

Randomised clinical trials with appropriate concealment of allocation are required to evaluate the efficacy of a thienopyridine such as clopidogrel, or clopidogrel in combination with aspirin, in infrainguinal venous and artificial grafts. Thereby, comparisons between clopidogrel and ASA should be made, but a comparison between clopidogrel or clopidogrel combined with ASA versus VKA would be an even more relevant clinical finding.

Presentation of data should be detailed and not only showing survival curves for overall patency. Tables showing the raw data would improve the transparency of the trial performance, allowing comparison of endpoints at consecutive time points of follow-up. Thus, the reader would be enabled to identify the number of occlusions or other endpoints at different time points in each comparison group as well as in subgroups defined by bypass material, above and below knee anastomosis, and in- and outflow conditions.

ACKNOWLEDGEMENTS

We would like to thank Dr. Elizabeth Royle for editorial assistance and Mrs Heather Maxwell for providing literature.

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* *Indicates the major publication for the study*

SOURCES OF SUPPORT

External sources of support

- Chief Scientist Office, Health Department, The Scottish Executive UK

Internal sources of support

- AMC, Dept. of Clinical Epidemiology & Biostatistics, Amsterdam NETHERLANDS
- Royal Infirmary of Edinburgh NHS Trust, Scotland UK

NOTES

Donald Adam wrote the protocol, but was not involved in the production of the full review, therefore his name does not appear in the list of authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Arteriosclerosis [*surgery]; Graft Occlusion, Vascular [*prevention & control]; Intermittent Claudication [surgery]; Peripheral Vascular Diseases [*surgery]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Thrombosis [*prevention & control]; Vascular Patency

MeSH check words

Humans