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Randomised placebo controlled trial of aspirin and dipyridamole in the prevention of coronary vein graft occlusion

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SUMMARY Treatment with the combination of aspirin and dipyridamole is believed to reduce the incidence of coronary vein graft occlusion. A double blind randomised controlled trial was carried out in which aspirin 990 mg and dipyridamole 225 mg daily or placebo were added to the routine postoperative managment (warfarin for three months) of 320 patients undergoing coronary bypass grafting. The trial treatment was given for 12 months, after which the results were assessed by coronary and graft angiography. The two randomised groups, each of 160 patients, were comparable in age, sex, symptomatic state, angiographic findings, and operative procedure. Repeat coronary arteriography was carried out on 266 patients, 133 in each group. All grafts and distal anastomoses were patent in 68% (91/133) of the placebo patients and in 75% (100/133) of those receiving active treatment. Overall graft patency was 87% (306/352) and 89% (342/385) respectively. Retrospective subgroup analysis showed patency rates of 72% (26/36) and 78% (39/50) of grafts to vessels requiring preliminary endarterectomy, and 80% (36/45) and 91% (40/44) of distal anastomoses to vessels measured at operation to have a diameter of ≤ 1 mm. None of these differences was significant at the 5% level.

Thus in this group of patients with high graft patency rates, treatment with aspirin and dipyridamole conferred no appreciable advantage.

One of the main causes of recurrent or persistent angina after an aortocoronary bypass operation is graft occlusion.[1-3] This complication, whether it occurs early from thrombosis or later from progressive subintimal proliferation,[4,5] is believed to result from perioperative endothelial damage followed by deposition of platelets on to the subendothelial tissues,[6] and, in the experimental animal, its occurrence can be limited by treatment with the combination of aspirin and dipyridamole.[7,8] Moreover, this combination has been shown to decrease lipid accumulation in the intima of vein grafts implanted into the arterial circulation of both normolipaemic and hyperlipaemic monkeys.[9] Several clinical trials of platelet inhibitor and anticoagulant treatment have been reported,[10-19] but the findings have been conflicting and in many instances do not withstand critical scrutiny.[20] We report a randomised placebo controlled trial in which we assessed the effect of the combination of aspirin and dipyridamole on coronary vein graft patency one year after operation. The treatment was added to our routine management with conventional anticoagulation for the first three months and was started in the early postoperative period.

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Patients and methods

SELECTION OF PATIENTS

Consecutive patients of either sex up to the age of 70 years, who had undergone coronary arteriography and had been referred for aortocoronary bypass grafting, were considered for entry into the trial. Patients were excluded for the following reasons: (*a*) previous coronary bypass operation; (*b*) coexistent valvar heart

disease; (*c*) history of peptic ulceration, hiatus hernia, or indigestion; (*d*) known intolerance to aspirin or dipyridamole; (*e*) habitual use of aspirin or other anti-inflammatory drugs; (*f*) recognised indication for antiplatelet treatment (for example, transient cerebral ischaemic attacks) or the need for anticoagulant treatment which was likely to extend beyond three months after operation; (*g*) significant bleeding disorder or reduced platelet count; (*h*) any condition which might increase the risk of elective coronary and graft angiography (for example, cerebrovascular disease); (*i*) more than four months between coronary arteriography and surgery; and (*j*) refusal to take part.

The purpose and potential risks of the trial were explained to each patient, and signed consent was obtained. The protocol was approved by the ethics committee of the National Heart and Chest Hospitals.

RANDOMISATION

Patients were randomised in equal numbers to the placebo or active treatment groups. Whenever possible the long saphenous vein was used for the bypass grafts, but when this was unsuitable another vein from the leg or arm vein was used. After its removal, and before implantation, the vein was kept in heparinised blood. The internal mammary artery was not used routinely for bypass grafting but when, in occasional patients, this technique seemed most appropriate such grafts were excluded from the analysis. The size of the grafted arteries was measured with a probe; vessels of ≤ 1 mm diameter were considered to be small. The presence of disease at the site of the distal anastomosis and the performance of endarterectomy were also recorded. The distal anastomoses were constructed with continuous 6/0 or 7/0 prolene and were carried out according to the preference of the individual surgeon, either with the heart fibrillating and the temperature allowed to drift to 28°C or with the heart arrested by cold cardioplegia.

Our original intention had been to start the trial treatment as soon as the patient had given his consent and to continue it up to the night before operation. The fourth patient, however, died during his operation mainly as a result of severe bleeding. The operation had been technically difficult and prolonged, but he had been taking the active treatment; thereafter the capsules were started on the second or third postoperative day as soon as the chest drains had been removed and the patient was able to take tablets by mouth. The medication was packaged and labelled for double blind administration and each capsule contained either placebo or aspirin 330 mg plus dipyridamole 75 mg and was given three times daily. At the same time treatment was started with warfarin and this was continued, maintaining the prothrombin time between two and three times control (British Comparative Thromboplastin), for the first three months. Administration of the trial capsules was continued until the patient's readmission for assessment by graft and coronary angiography after one year. Patients were asked not to take additional aspirin, dipyridamole, sulphinpyrazone, or other anti-inflammatory drugs during this period, and paracetamol was recommended for mild pain.

COMPLIANCE

Compliance with the prescribed treatment was assessed by questioning the patient and by a urine test for aspirin at the first postoperative outpatient visit (usually eight weeks after operation).

DATA ANALYSIS AND STATISTICS

The grafts were characterised as patent or occluded. Grafts with multiple distal anastomoses (sequential grafts) were considered both in terms of the patency of each anastomosis and of the graft itself. The data were analysed on the "intention to treat" principle, and the two groups were compared by their overall graft patency rate and by the proportion of patients with all grafts patent. Based on a consecutive series of patients who were reinvestigated during 1975–76 after aortocoronary bypass grafting at the London Chest Hospital, in which the graft patency after one year of treatment with warfarin for the first three months was 83% and the mean number of grafts was 2·5 per patient, we estimated that the inclusion of 150 patients would give a 90% probability of detecting a 50% reduction in graft occlusion rate. To allow for withdrawals from the trial and to increase its power while limiting the recruitment period we decided to enroll 300 patients, and this figure was subsequently increased to 320 with the realisation that the placebo patency rate was likely to be higher than had been expected.

In addition, the influence of treatment on the disease in segments of bypassed arteries which were proximal to the distal vein graft anastomosis was assessed by comparing the preoperative and postoperative angiographic appearances of bypassed vessels which, on the first angiogram, were patent between their origin from the aorta and the site of the subsequent anastomosis. The disease was defined as having progressed if the artery was occluded on the second angiogram; no attempt was made to assess lesser degrees of progression.

Angiography was carried out and analysed without knowledge of the patient's randomisation. The code was broken for an individual patient only when there was a medical requirement to know whether he had been receiving active treatment; any decision to withdraw the trial capsules was made on the assumption that active treatment was being given. A preliminary

analysis was made after the entry of 200 patients, and it was at this stage that the high placebo group vein graft patency was discovered and the decision to increase the recruitment to 320 patients was taken.

Results

During the recruitment period from 11 October 1978 to 3 October 1982 a total of 1054 patients had a primary isolated coronary artery bypass operation carried out at the London Chest Hospital. Seven hundred and thirty four patients were excluded from the trial, 400 (54%) because their angiogram was more than four months old, 23% because of known intolerance to aspirin, a previous history of peptic ulceration, hiatus hernia, or indigestion, and 10% because they refused to take part. The remaining 17% were too old, lived abroad, required regular anti-inflammatory drugs, were considered unsuitable for elective reinvestigation, or were omitted for administrative reasons.

Three hundred and twenty patients agreed to take part and were randomised, 160 to receive placebo and 160 to receive active treatment. There were no significant differences between the two groups in age, sex, the severity of their symptoms, coronary disease and left ventricular function, or in the number of grafts subsequently implanted. There were similar numbers of cigarette smokers and patients with hypertension and hyperlipidaemia but over twice as many diabetic patients ($p<0.05$, χ^2 test) in the active than in the placebo group (Table). Three patients died preoperatively, and two refused operation after randomisation, so that 315 (156 in the placebo group and 159 in the active group) actually underwent aortocoronary bypass grafting. Seven patients (six in the active group, one in the placebo group) died in the perioperative period before starting the trial medication. One patient in the active group, as mentioned previously, who was pretreated, also died perioperatively. There were five late deaths, two in the active and three in the placebo group.

COMPLICATIONS

The trial capsules were withdrawn from 35 patients after the development of complications or symptoms which were suspected of having been caused by aspirin. Minor gastrointestinal disturbances, such as abdominal discomfort, heartburn, nausea, or vomiting, occurred in 18 patients receiving active treatment and in 10 of those receiving placebo. Two patients, one from each group, developed uncomplicated duodenal ulcers. Life threatening complications occurred in five patients: three receiving active treatment had severe gastrointestinal haemorrhages within the first two weeks, while one placebo group patient had a perforated duodenal ulcer one week postoperatively and another a severe gastrointestinal haemorrhage after two months. Eight additonal active group patients reported minor side effects but continued to take the trial treatment. The difference in frequency of side effects between the two groups is statistically significant ($p<0.01$, χ^2 test).

In the active group there was a marginally significant decline in haemoglobin concentration between the initial and final assessments ($p<0.05$, paired t test; measured decrease 0·39 g/dl), and haemoglobin concentrations were higher in the placebo group than in the active group at the final evaluation ($p<0.01$, t test).

COMPLIANCE

In the placebo group 123 (77%) patients took the trial capsules substantially as instructed, whereas in the active group 116 (73%) complied with the treatment. Of the patients who underwent coronary and graft angiography after one year, the compliance rates were 87% and 83% respectively.

Thirty six patients (19 in the placebo and 17 in the active group) who were alive one year after their operations either withdrew from the trial or were not recatheterised because of medical reasons which might have increased the risk of complications from the procedure.

CORONARY AND GRAFT ANGIOGRAPHY

Repeat coronary arteriography was carried out on 266 patients, 133 in each group. The mean time to reinvestigation after surgery was 12·4 (SD 1·7) months in the active group, and 12·2 (SD 2·1) months in the placebo group. In all but six cases the graft or a distinct stump were selectively catheterised. One graft which was not entered was seen to be patent on an aortogram; the others (two in the placebo and three in the active group) were assumed to be occluded. In two placebo group patients there was uncertainty about the patency of one anastomosis of a sequential graft; both were designated as occluded.

In the placebo group there was a total of 352 vein grafts (including 16 sequential grafts) with 369 distal anastomoses (mean 2·8/patient). There were three internal mammary grafts. Vein graft patency was 87% (306/352) and distal anastomosis patency 86% (318/369). Endarterectomy was carried out on 36 arteries, and the grafts to 26 (72%) of these vessels were patent. All the grafts were patent in 72% (96/133) of the patients and all the distal anastomoses in 68% (91/133).

In the active group 360 vein grafts (including 24 sequential grafts) were implanted with 385 distal anastomoses (mean 2·9/patient) and two internal mammary grafts. Vein graft (321/360) and distal anas-

Table *Characteristics of patients receiving either placebo or active treatment. Figures are numbers (%) of patients unless stated otherwise*

	Placebo	*Active*
No of patients randomised	160	160
Men/women	143/17	139/21
Age (range) (yr)	54·5 (26–70)	54·2 (33–69)
Hypertension (>160/90 mm Hg)	35 (22)	32 (20)
Diabetes	6 (4)	15 (9)
Serum cholesterol concentration (mmol/l)	7·13 (SD 1·35)	7·16 (SD 1·4)
Serum triglyceride concentration (mmol/l)	2·30 (SD 1·82)	2·30 (SD 1·67)
Smoking (>10 cigarettes/day):		
Preoperatively	71 (44)	81 (51)
Postoperatively	22 (14)	26 (17)
Peripheral vascular disease	12 (7)	9 (6)
Angina grade*:		
0	6 (4)	4 (3)
1	6 (4)	1 (0)
2	46 (29)	57 (36)
3	43 (27)	33 (21)
4	59 (37)	65 (41)
Previous myocardial infarctions:		
0	73 (46)	73 (46)
1	64 (40)	71 (44)
2	17 (11)	14 (9)
>2	6 (4)	2 (1)
Electrocardiogram:		
Normal	47 (29)	50 (31)
Abnormal	113 (71)	110 (69)
No of coronary arteries with >75% stenosis (LMS)†:		
1	42	31
2	58 (2)	54 (6)
3	60 (7)	75 (7)
Left ventricle—No of abnormal segments ‡:		
0	48 (30)	50 (31)
1	74 (46)	67 (42)
2	30 (19)	35 (22)
3	8 (5)	8 (5)
Operation—No of distal vein graft anastomoses:		
1	10 (6)	7 (4)
2	43 (28)	36 (23)
3	81 (52)	79 (50)
>3	22 (14)	36 (23)
No of arteries endarterectomised	36 (10)	50 (13)
No of arteries of <1 mm diameter (% of distal anastomoses)	45 (12)	44 (11)

*0, no angina; 1–3, mild, moderate, severe, effort angina; 4, rest angina.
†No of principal arterial systems—that is, left anterior descending, right coronary artery or dominant atrioventricular circumflex, or circumflex.
‡Left ventricular free wall divided into three segments on right anterior oblique angiogram.
LMS, left main stem.

tomosis (342/385) patency were 89%. Endarterectomy was performed on 50 vessels with a subsequent graft patency of 78% (39/50). All the grafts and distal anastomoses were patent in 75% (100/133) of the patients.

To examine the possibility that active treatment might confer particular benefit to grafts implanted into small coronary arteries an analysis was made of the patency rates of grafts to vessels measured at the time of operation to have a diameter of ≤1 mm. Patency was 80% (36/45) in the placebo group and 91% (40/44) in the active group. Similarly, the two groups were compared in terms of patency of grafts to vessels in which there was disease at the site of the distal anastomosis but in which endarterectomy had not been carried out; the patency rates were 92% (68/74) for the placebo group and 93% (67/72) for the active group.

In the placebo group 28% (74/261) of bypassed arteries which were patent preoperatively had progressed to occlusion compared with 25% (68/271) in the active group.

In none of these comparisons was the difference between the two groups statistically significant at the 5% level, though in all cases there was a trend in favour of active treatment.

Discussion

Analysis of the factors which are known to influence the natural history of coronary heart disease and the results of bypass grafting indicates that the two randomised groups were well matched, though the excess of diabetes in the active group might have affected their results adversely in comparison with the placebo patients. There were, however, sources of potential bias which must be discussed.

Firstly, only 30% of the patients who underwent isolated coronary bypass grafting were entered into the trial. Those operated on more than four months after coronary angiography were excluded, and for much of the recruitment period the surgical waiting list was about six months in duration. The reason for this somewhat arbitrary time limit was our interest in the influence of treatment on progression of disease in the proximal segments of bypassed arteries; its effect was that a higher proportion of patients in the trial had been referred for early or urgent surgery compared with the overall coronary surgical practice at the London Chest Hospital. This is reflected in the high proportion with rest pain, the fact that three patients died before operation, and probably the high operative mortality of 3%. There is no obvious mechanism, however, by which this or any other of the exclusion criteria should have led to bias in favour of one group over the other or should preclude extrapolation of the results to other patients undergoing coronary vein bypass operations. A second problem arises from the patients who did not complete the trial protocol. The one year graft and coronary angiogram was not carried out on an equal number of patients in each group, though more of those in the active group had died (the majority before the trial medication was started), and of the survivors there was a higher proportion of women than among those who completed the trial protocol. Speculation on the influence of these incompletely investigated patients would be scientifically dubious, but since they comprised only 17% of the study group and, apart from the sex difference, their baseline characteristics were similar to those who completed the protocol no major bias should have been introduced.[20]

At the end of the first postoperative year the active treatment group had a higher proportion of patent grafts and a higher proportion of patients with all their grafts patent than the placebo group. Further analysis showed that almost all the difference is accounted for by grafts to small arteries and to those in which preliminary endarterectomy had been carried out: patency rates of grafts to vessels which were >1 mm in diameter and did not require endarterectomy were 89% in the placebo group and 90% in the active group. For none of these observations, however, are the observed differences statistically significant, and such subgroup analysis in a trial designed to examine overall graft patency is scientifically questionable. The results indicate, therefore, either that active treatment confers no benefit additional to that, if any, from routine anticoagulation or that a real benefit exists but is too small to have been detected by a trial of this size. In previous trials of platelet inhibitor treatment started in the postoperative period a trend in favour of active treatment has also been seen, though in only two of them was the observed advantage statistically significant: treatment with sulphinpyrazone was associated with a highly significant improvement in vein graft patency between one and two weeks postoperatively,[14] and in a trial of aspirin 1·3 g plus dipyridamole 100 mg daily graft patency was 15% higher in treated than in control patients six months after operation.[11] The second of these trials, however, was neither placebo controlled nor double blind, and only 65% of the patients were reinvestigated. Two trials of combined anticoagulant and antiplatelet treatment have been reported. Dale *et al* randomised 116 patients undergoing coronary bypass grafting to receive either aspirin 1 g plus warfarin daily or to act as an untreated control group.[18] At a mean period of 21 months after operation there was no overall statistically significant advantage from active treatment, but, of grafts which had peroperative flow rates of <50 ml/min, 76·2% in the treated group and 48·4% in the control group were patent. Harjola *et al* combined dipyridamole with warfarin and compared the results retrospectively with a group of patients managed with warfarin alone.[19] The warfarin group were restudied after about a year and the combined group after about two years. Graft patency was very much higher (95·7% *vs* 88·6%) in the combined treatment group, but a large number of internal mammary grafts was implanted and so the results do not necessarily compare with trials in which vein was used as the conduit.

As a result of experimental work which showed that platelet deposition begins as soon as the vein graft is implanted, Chesebro and Fuster argued that the optimal effect from platelet inhibitor treatment could be obtained only by starting treatment before operation.[20] This belief is strongly supported by the results of their own trial carried out at the Mayo Clinic[16 17] the design of which differed from the present study in only two important respects: firstly, dipyridamole was given preoperatively with aspirin added postoperatively, and, secondly, none of the patients were treated by conventional anticoagulation. Vein graft patency was very much higher in the active treatment group than in the placebo group, both early (up to six months, median 7 days), and one year after operation; moreover, active treatment slowed the rate of graft attrition during the first year. It should be noted, however, that the one year vein graft patency in the active group was the same as that in the present trial (89%), and that the large difference between the two groups at one year in the Mayo Clinic study is, therefore, a reflection of the lower placebo graft patency rate of 75%. Similarly, 78% of patients receiving active treatment in the Mayo Clinic trial had all their grafts patent at the end of the first year compared with the 75% reported here, whereas only 53%

of the placebo treated patients had this favourable outcome compared with the 72% in the present study. In other words, the conflicting results of the two trials are associated with a striking difference in the incidence of graft occlusion in their placebo patients. While this might be caused by differences in the patients or in operative technique, a more likely explanation is that warfarin treatment for three months had a beneficial effect in our placebo group and thereby diminished a true advantage conferred by aspirin and dipyridamole to the observed non-significant level. We included warfarin treatment in both groups for its assumed prevention of peripheral venous thromboembolism; the regimen adopted was the same as that used in our unit during the previous five years and the 4% higher graft patency in the placebo group of the present study could be ascribed to a combination of chance and to the greater surgical expertise which has been acquired since our earlier experience, on which the statistical projections were based. When the present trial was designed there was no evidence to suggest that anticoagulant treatment might have a favourable influence on vein graft patency, but three investigations have since been reported: one showed clear benefit,[12] one a non-significant trend,[13] and another, though carried out on a small number of patients, no benefit.[10]

The optimal dose of aspirin for the prevention of thrombosis in patients with vascular disease is controversial, and a low dose regimen has been recommended in the belief that this will inhibit platelet throboxane production but preserve prostacyclin synthesis in the vascular endothelium. This notion had not gained widespread acceptance at the time that the present trial was planned, and our dosage schedule was based on the augmentation by high dose aspirin of the dipyridamole effect on platelet survival time which has been shown both in patients with vascular disease[21] and in those with prosthetic heart valves.[22]

Thus the place of treatment with aspirin and dipyridamole of patients who have undergone coronary bypass grafting remains uncertain, though from consideration of the results of this trial in the context of others it seems likely that such treatment does retard the process of coronary vein graft occlusion and that the effect can be optimised by starting treatment with dipyridamole before operation. The present trial suggests, however, that this regimen has little advantage over that of conventional anticoagulation for three months, particularly for patients with technically satisfactory grafts to good sized coronary arteries. In our experience the anticoagulant regimen has been generally preferable to the administration of aspirin, which was felt to be contraindicated in a large number of patients and which, despite careful exclusion of those thought to be at risk, was accompanied by a high incidence of side effects. Our results do, however, lead us to agree that the aspirin-warfarin combination exposed patients to a considerable risk from haemorrhage,[23] which was not offset by the possible small overall benefit. The main problem, however, is that of the high risk grafts to vessels requiring preliminary endarterectomy or to those of small calibre. The advantage we observed from active treatment in these circumstances would, if real, be clinically valuable; the uncertainty can be resolved, however, only by further studies.

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