CLINICAL STUDIES

CORONARY ARTERY BYPASS GRAFTING

Effects of Low Dose Aspirin (50 mg/day), Low Dose Aspirin Plus Dipyridamole, and Oral Anticoagulant Agents After Internal Mammary Artery Bypass Grafting: Patency and Clinical Outcome at 1 Year

JAN van der MEER, MD, AART BRUTEL de la RIVIÈRE, MD,* WIEK H. van GILST, PhD, HANS L. HILLEGE, MD, MATTHIAS PFISTERER, MD, FACC,† GERRIT J. KOOTSTRA, MD,‡ PETER H. J. M. DUNSELMAN, MD,§ BARBARA J. M. MULDER, MD,|| KONG I. LIE, MD, FOR THE CABADAS RESEARCH GROUP OF THE INTERUNIVERSITY CARDIOLOGY INSTITUTE OF THE NETHERLANDS#

Groningen, Nieuwegein, Breda and Amsterdam, The Netherlands and Basel, Switzerland

Objectives. This study was performed to compare the efficacy and safety of aspirin, aspirin plus dipyridamole, and oral anticoagulant agents in the prevention of internal mammary artery graft occlusion.

Background. Antithrombotic drugs increase vein graft patency after coronary artery bypass surgery. Their benefit after internal mammary artery grafting has not been established.

Methods. Angiographic internal mammary artery graft patency at 1 year was assessed in 494 patients who received both internal mammary artery and vein grafts. These patients were a subgroup of a prospective, randomized vein graft patency study in 948 patients assigned to treatment with aspirin, aspirin plus dipyridamole, or oral anticoagulant agents. The design was double-blind for both aspirin groups and open for oral anticoagulant treatment. Dipyridamole (5 mg/kg body weight per 24 h intravenously, followed by 200 mg twice daily) and oral anticoagulant agents (prothrombin time target range 2.8 to 4.8 international normal-

ized ratio) were started before operation, and low dose aspirin (50 mg/day) after operation. Clinical outcome was assessed by the incidence of myocardial infarction, thrombosis, major bleeding or death.

Results. Occlusion rates of distal anastomoses were 4.6% in the aspirin plus dipyridamole group and 6.8% in the oral anticoagulant group versus 5.3% in the aspirin group (p = NS). Overall clinical event rates were 23.3% and 13.3% in the aspirin plus dipyridamole group and the aspirin group, respectively (relative risk 1.75, 95% confidence interval 1.09 to 2.81, p = 0.025), and 17.1% in the oral anticoagulant group.

Conclusions. Internal mammary artery graft patency at 1 year is not improved by aspirin plus dipyridamole or oral anticoagulant agents over that obtained with low dose aspirin alone. However, there is evidence that the overall clinical event rate increases if dipyridamole is added to aspirin.

(J Am Coll Cardiol 1994;24:1181–8)

In patients who undergo coronary artery bypass surgery, the internal mammary artery is considered to be the bypass conduit of choice. There is evidence (1–4) that, compared with saphenous vein grafts, internal mammary artery grafts improve long-term survival and decrease the incidence of recurrent angina and cardiac events. This beneficial clinical outcome has

been associated with superior early and late patency rates of internal mammary artery grafts. One year after operation, 76% to 93% of vein grafts are open and at the end of 10 years only 41% to 63% remain patent (1, 5–7). The yearly attrition rate increases from 2% for the 2nd to 7th postoperative year to 5% over the next 5 years (5). In contrast, 1-year and 10-year patency rates of internal mammary artery grafts are 88% to 96% and 69% to 83%, respectively (1,6,7). Early vein graft occlusion is frequently due to thrombosis and probably intimal hyperplasia, whereas progressive atherosclerosis of the graft is the main determinant of late occlusion (5,6,8). Atherosclerosis has rarely been observed in internal mammary artery grafts (5,6).

It has been demonstrated persuasively (9,10) that patency of vein grafts at 1 year is improved by antiplatelet drugs. Whether these or other antithrombotic drugs have a similar favorable effect on internal mammary artery grafts is not known. To compare the effects of various antithrombotic drug regimens in patients who had received internal mammary

artery grafts, we analyzed the data derived from CABADAS (Prevention of Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamole and Acenocoumarol/Phenprocoumon Study) (11). The primary objective of this prospective, randomized clinical trial was a comparison of the efficacy and safety of 1) a low dose of aspirin, 2) a low dose of aspirin plus dipyridamole, and 3) oral anticoagulant agents in the prevention of vein graft occlusion during the 1st year after coronary bypass surgery. Aspirin and aspirin plus dipyridamole were compared in a placebo-controlled, double-blind design. Oral anticoagulant agents were evaluated in a third open treatment arm because of logistic reasons associated with the necessary laboratory control for dose adjustments in patients receiving these drugs. More than half of the patients received internal mammary artery grafts in addition to vein grafts. This subgroup was the subject of the present study.

Methods

Study patients. From July 1987 through August 1990, 948 patients who underwent elective aortocoronary bypass surgery with saphenous vein grafts for treatment of disabling angina were entered into the trial by 10 participating hospitals. The present study group contained 494 of these patients who received internal mammary artery grafts in addition to vein grafts. Exclusion criteria have been described in detail previously (11) and included age >70 years; unstable angina or myocardial infarction <2 and <7 days before operation, respectively; previous or concurrent cardiac operation; need for continued antithrombotic drug therapy; increased risk of bleeding; known allergy or intolerance to the trial medication; impaired renal or hepatic function; concomitant severe disease, and allergy to contrast agent impeding ability to repeat coronary angiography. The use of previously prescribed antiplatelet drugs or oral anticoagulant agents had to be discontinued ≥14 and ≥5 days, respectively, before operation. All patients gave informed written consent. The protocol was approved by the ethics committee of each participating hospital.

Study medication. Patients were randomly allocated to receive either aspirin plus dipyridamole placebo, aspirin plus dipyridamole, or oral anticoagulant agents. They were assigned to one of these drug regimens on the day before operation by the pharmacist of the participating hospital, according to a randomization list provided by the study coordinating center. Patients were stratified by center. Treatment was started either before (dipyridamole, oral anticoagulant agents) or after (aspirin) operation. Dipyridamole was administered by intravenous infusion (5 mg/kg body weight per 24 h) from 8 PM on the day before operation until midnight after operation and was continued orally in a slow release form (200 mg twice daily). Treatment with aspirin (50 mg once daily) was started at midnight after operation; the first dose was administered through a nasogastric tube. Oral anticoagulant treatment was started on the day before operation and continued on the 1st postoperative day. The dose of oral anticoagulant agents, either acenocoumarol or phenprocoumon, was adjusted to

prothrombin times at a target range of international normalized ratio (INR) between 2.8 and 4.8. Antiplatelet drugs, unless assigned, were not allowed. Acetaminophen was provided as a substitute for aspirin as analgesic.

Surgery. Internal mammary artery grafts were implanted according to the routine techniques of each participating hospital. The decision to use these grafts was made by the surgeon before randomization. Internal mammary artery grafts were single (one distal anastomosis) or sequential (more than one distal anastomosis), and free grafts were used occasionally. The lumen of the grafted coronary artery was measured by calibrated probes at the arteriotomy site and as distally as possible. Endarterectomy was performed at the discretion of the surgeon if coronary arteries were narrowed diffusely. Heparin, administered during operation, was antagonized by protamine sulfate at the end of the procedure unless the introduction of an intraaortic balloon pump required prolonged heparinization. Total postoperative blood loss through chest tubes and any required blood transfusions were recorded.

Follow-up. After discharge from the hospital, follow-up visits were scheduled at 3-month intervals and coronary angiography at 1 year after operation. A questionnaire was addressed to the cardiologist 1 year after operation if a patient had been withdrawn from the trial. At follow-up visits, clinical and laboratory data were collected and an electrocardiogram (ECG) was recorded. Compliance was assessed by pill count in both aspirin groups. Prothrombin time was measured regularly in patients who received oral anticoagulant agents. Coronary angiography was not performed 1 year after operation if it had been done for medical reasons <3 months previously or if previous angiography already showed vein graft occlusion, a primary end point of the vein graft patency study.

Angiographic end points. Internal mammary artery grafts were visualized by selective injection. A graft was classified as undefined if selective injection failed for technical reasons and no retrograde filling of the graft with contrast agent at coronary angiography was demonstrated. A graft was defined as occluded if occlusion was visualized at selective injection. A distal anastomosis was defined as occluded if contrast agent failed to flow from the graft into the grafted artery. If a sequential graft was occluded at its origin, all associated distal anastomoses were considered occluded unless a retrograde flow of contrast agent from the grafted artery into the graft was demonstrated.

Angiograms were reviewed by independent experienced cardiologists, members of the angiography classification committee who had no knowledge of the patient's group assignment, and a consensus was reached.

Clinical end points. Myocardial infarction, thromboembolism, major bleeding and death were primary clinical end points. Myocardial infarction was diagnosed according to ECG criteria. Thromboembolism was established by appropriate techniques. Bleeding was defined as major if life-threatening or fatal and if blood transfusion or a repeat operation was necessary. Death was classified as cardiac, due to thrombosis, due to bleeding or due to other causes, according to

clinical evidence or autopsy findings. Secondary clinical end points were residual or recurrent angina, heart failure and symptomatic arrhythmias. Criteria for the clinical end points and the review procedure have been described more extensively elsewhere (11).

Statistical analysis. The aim of the statistical analysis was to compare the incidence of graft occlusion (primary end point) and the incidence of clinical events (secondary end points). The occurrence of graft occlusion was analyzed by comparison of distal anastomoses and grafts that were occluded and by comparison of the proportion of patients with one or more occluded grafts. Because grafts within the same patient act in a dependent way with respect to the occurrence of occlusion, the ratio estimate as applied to a cluster sampling approach was used (12). To exclude bias due to an unequal distribution of patients who could not be evaluated by angiography, such patients were substituted arbitrarily as follows in an additional analysis. Grafts were classified as occluded in patients who were withdrawn from the trial or died, unless autopsy showed patent grafts. Patients who completed follow-up but refused angiography and those in whom angiography failed were substituted in the same way if myocardial infarction had been demonstrated during the study period. Clinical outcome was analyzed by comparison of 1) the incidence of separate clinical end points, 2) the proportion of patients with at least one primary clinical end point, and 3) the proportion of patients with any primary or secondary clinical end point. The study comprised two evaluations as reflected by its design, which was double-blind and placebo-controlled for both aspirin regimens and open for oral anticoagulant therapy. Therefore, aspirin plus dipyridamole versus aspirin and oral anticoagulant agents versus aspirin were compared separately. A difference was quantified by the relative risk and the calculated 95% confidence interval (CI). If the 95% CI did not encompass 1, the difference was statistically significant at a 5% level ($p < 0.05$).

The treatment groups were compared with respect to baseline and surgical characteristics by the chi-square test or the Fisher exact test for qualitative variables. The Student t test or the Mann-Whitney U test was used for quantitative variables. Continuous variables, unless indicated, are expressed as mean value ± SD. A two-tailed p value < 0.05 is considered to indicate statistical significance.

Data analysis was performed according to the intention to treat. Patients were excluded from analysis if they withdrew consent before the start of the trial medication or if they received only arterial grafts and thus did not meet the inclusion criterion of the vein graft patency study.

Results

Patients. Of 948 patients entered into the vein graft patency trial, 7 withdrew their consent before assigned treatment was started and 29 did not receive vein grafts. The internal mammary artery was used as an additional bypass conduit in 494 of the remaining 912 patients. Their clinical and internal

mammary artery graft baseline characteristics (Table 1) did not differ significantly among treatment groups, except for a lower total cholesterol serum level in the aspirin plus dipyridamole group than in the aspirin group. Grafts were single in 71%, sequential in 26% and both in 3% of patients. Most single grafts (87%) were placed to the left anterior descending coronary artery; 86% of sequential grafts were placed to a diagonal branch and then to the left anterior descending coronary artery.

Repeat angiography was performed in 429 patients (87%), equally distributed among the groups. The median time from operation to angiography was 372 days for each group. Angiograms were not available in 65 patients because of death (n = 6), withdrawal from the trial (n = 33), refusal of repeat angiography at completed follow-up (n = 23) or complications of the angiographic procedure (n = 3). Patients were classified as having withdrawn if randomly assigned drug therapy was discontinued prematurely and angiography was not repeated. Reasons for withdrawal were the occurrence of a primary clinical end point (n = 5) or drug intolerance (n = 2); medical reasons (n = 3); logistic problems (n = 3); and the patient's request (n = 20). Angiography was complicated by dissection of the iliac artery in two patients and transient neurologic signs after lidocaine in one patient. At angiographic assessment 8.9% of arterial grafts were classified as undefined.

Graft patency. Graft occlusion rates are shown in Table 2. These data represent the results obtained from 302 single and 120 sequential internal mammary artery grafts (in total 551 distal anastomoses). Occlusion rates by distal anastomosis were 4.6% in the aspirin plus dipyridamole group and 6.8% in the oral anticoagulant group versus 5.3% in the aspirin group. At least one internal mammary artery graft was occluded in 5.6% of patients who received aspirin plus dipyridamole and 8.4% of patients who received oral anticoagulant agents compared with 6.7% of patients who received aspirin (p = NS). Analysis of graft patency including patients who were not evaluable by angiography also showed no significant differences. Occlusion rates by distal anastomosis were 14.4% (aspirin plus dipyridamole) and 13.2% (oral anticoagulant agents) versus 13.6% (aspirin). Graft occlusion was demonstrated in 14.1%, 13.9% and 14.5% of patients, respectively.

Analysis of subgroups defined by type of graft, type of distal anastomosis, location of distal anastomosis and lumen diameter of the recipient coronary artery revealed no significant differences in occlusion rates between the two aspirin groups (Table 3). A risk-unadjusted comparison of oral anticoagulant agents with aspirin suggested improved patency of single grafts by aspirin and an opposite effect for sequential grafts. Endarterectomy was performed in eight vessels, representing 1.2% of all distal sites. None of the grafts to these arteries was occluded.

Blood loss, transfusion requirement and reoperation. Chest tube drainage was 1,111 ± 633 ml in the aspirin group, compared with 1,301 ± 732 ml in the aspirin plus dipyridamole group (p = 0.011) and 1,143 ± 699 ml in the oral anticoagulant group (p = 0.948). The median transfusion requirement for red blood cells was 1.0 (donor) U (range 0 to 20) in the aspirin

Table 1. Baseline Characteristics of 494 Patients

	Aspirin + Placebo	Aspirin + Dipyridamole	Oral Anticoagulant Agents
Patients (no.)	173	163	158
Age (yr)	58 ± 9	58 ± 8	58 ± 7
Weight (kg)	79 ± 10	78 ± 10	79 ± 10
Height (cm)	174 ± 7	173 ± 8	174 ± 8
Men (%)	89	86	91
Angina (NYHA class)			
II (%)	33	26	27
III (%)	55	58	54
IV (%)	12	16	19
Previous myocardial infarction (%)	54	49	45
Hypertension (%)	32	34	41
Diabetes mellitus (%)	10	9	10
Hyperlipidemia (%)	41	35	43
Smoking (%)	79	78	84
Medication before operation (%)			
Nitrates	78	77	77
Beta-blocking agents	82	72	78
Calcium channel antagonists	62	59	63
Lipid-lowering drugs	12	12	10
Oral anticoagulant agents*	16	17	21
Platelet inhibitors*	14	15	16
Total cholesterol (mmol/liter)	7.1 ± 1.4†	6.8 ± 1.3†	7.0 ± 1.3
HDL cholesterol (mmol/liter)	1.0 ± 0.3	1.0 ± 0.3	1.1 ± 0.8
Triglycerides (mmol/liter)	3.0 ± 1.8	2.7 ± 1.6	2.8 ± 1.8
Internal mammary artery grafts			
Single grafts/patient	0.7	0.8	0.8
Sequential grafts/patient	0.3	0.3	0.3
Distal anastomoses/patient	1.4	1.4	1.4
Location of distal anastomosis (%)			
LAD	69	69	68
Diagonal branch	25	21	24
LCx	6	10	7
RCA	0	0	1
Diameter of recipient artery (%)			
≤1.0 mm	5	6	3
1.1-1.5 mm	42	36	39
1.6-2.0 mm	39	44	43
>2.0 mm	14	14	15

*Oral anticoagulant agents and platelet inhibitors were discontinued at least 5 and 14 days before operation, respectively. †p = 0.035, comparing aspirin + dipyridamole and aspirin + placebo. Values are mean value ± SD unless otherwise indicated. HDL = high-density lipoprotein; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NYHA class = New York Heart Association classification; RCA = right coronary artery.

group versus 2.0 U (range 0 to 10) in the aspirin plus dipyridamole group (p = 0.118) and 1.0 U (range 0 to 13) in the oral anticoagulant group (p = 0.743).

Cardiopulmonary bypass time was 95 ± 28 min in the aspirin group versus 105 ± 38 min in the aspirin plus dipyridamole group (p = 0.005) and 97 ± 30 min in the oral anticoagulant group (p = 0.501). Reoperation rates (within 24 h) were 2.3% (aspirin), 6.1% (aspirin plus dipyridamole) and 4.4% (oral anticoagulant agents). Operative mortality (within 30 days) was 0.6%, 0.6% and 0.0%, respectively (p = NS).

Clinical end points. Of 95 primary clinical end points, a majority (72%) occurred in the perioperative period (within 30

days after operation). Myocardial infarction, thrombosis and major bleeding were observed somewhat more frequently in the aspirin plus dipyridamole group, as was major bleeding in the oral anticoagulant group, as compared with findings in patients who were treated with aspirin (Table 4). Only the difference between the two aspirin groups with respect to thrombosis reached statistical significance. Of six patients who died, three in each aspirin group, a cardiac cause was found in four patients (two in each aspirin group), bleeding in one patient (aspirin only group) and thrombosis in one patient (aspirin plus dipyridamole group). Any primary clinical end point occurred in 13.3% (aspirin only), 23.3% (aspirin plus dipyridamole) and 17.1% (oral anticoagulant agents) of pa-

Table 2. Frequency of Internal Mammary Artery Graft Occlusion

Unit of Analysis	Aspirin + Placebo	Aspirin + Dipyridamole	Oral Anticoagulant Agents	Relative Risk; 95% Confidence Interval		p Value	
				*	†	*	†
Distal anastomoses‡	5.3% (11/209)	4.6% (8/174)	6.8% (11/161)	0.87; 0.33–2.31	1.30; 0.52–3.25	0.786	0.578
Grafts	6.4% (10/157)	5.0% (7/139)	8.7% (11/126)	0.79; 0.31–2.02	1.37; 0.60–3.12	0.809	0.600
Patients	6.7% (10/150)	5.6% (7/124)	8.4% (10/119)	0.85; 0.33–2.16	1.26; 0.54–2.93	0.922	0.760

*Aspirin + dipyridamole versus aspirin + placebo. †Oral anticoagulant agents versus aspirin + placebo. ‡Comparison by ratio estimate analysis. Values for the three treatment groups represent percent of grafts occluded and (in parentheses) number of occluded grafts/total number of grafts.

tients. The relative risk for aspirin plus dipyridamole versus aspirin was 1.75, 95% CI 1.09 to 2.81 (p = 0.025).

Angina at any time during the follow-up period was reported in 14.5% (aspirin only), 14.1% (aspirin plus dipyridamole) and 16.5% (oral anticoagulant agents) of patients. At the end of the 1st year 90.4%, 93.0% and 90.4% of the treatment groups, respectively, were free from angina. Heart failure and symptomatic arrhythmias were observed less frequently in patients who received aspirin. The overall event rate, including primary and secondary clinical end points, remained higher in the aspirin plus dipyridamole group. This difference was borderline significant for both aspirin groups (relative risk 1.34, 95% CI 0.99 to 1.81, p = 0.058).

Compliance and level of oral anticoagulation. Pill counts showed that 85% of the trial medication had been taken by patients in each aspirin group. In patients who received oral anticoagulant agents a mean of 17 prothrombin time measurements/patient were performed over the follow-up period. The number of days spent within the target range of adequate anticoagulation (2.8 to 4.8 INR), expressed as percent of the

total treatment time, averaged 54% of the follow-up period/patient. Underanticoagulation (<2.8 INR) was found for 41% and overanticoagulation (>4.8 INR) for 5% of the follow-up period/patient.

In 76 patients, of whom 33 were withdrawn from the trial, assigned treatment was discontinued because of a primary clinical end point (n = 19), drug intolerance (n = 22), medical reasons (n = 9), logistic reasons (n = 4) or the patient's request (n = 22). Aspirin was discontinued in 26 patients (15.0%), aspirin plus dipyridamole in 34 (20.9%) and oral anticoagulant agents in 16 (10.1%). In 67 (88%) of the 76 patients, the trial medication was replaced by another antithrombotic drug regimen that contained aspirin, dipyridamole or oral anticoagulant agents in various doses and combinations. Drug intolerance was characterized by either headache or nausea with vomiting, or both, in 18 patients (6, aspirin plus placebo; 12, aspirin plus dipyridamole), and allergy in 4 patients (3, aspirin plus placebo; 1, aspirin plus dipyridamole). Complaints disappeared in 19 patients whose treatment was continued with aspirin alone.

Table 3. Frequency of Internal Mammary Artery Graft Occlusion According to Type of Graft and Distal Anastomosis, Location of Distal Anastomosis and Coronary Artery Lumen Diameter

	Aspirin + Placebo	Aspirin + Dipyridamole	Oral Anticoagulant Agents	Relative Risk; 95% Confidence Interval		p Value	
				*	†	*	†
Single grafts	2.9% (3/105)	1.9% (2/105)	12.0% (11/92)	0.67; 0.11–3.91	4.18; 1.20–14.54	1.000	0.028
Sequential grafts							
Grafts	13.5% (7/52)	14.7% (5/34)	0% (0/34)	1.09; 0.38–3.16	—	1.000	0.039
Distal anastomoses	8.4% (9/107)	8.6% (6/70)	0% (0/71)	1.02; 0.38–2.74	—	1.000	0.012
Distal anastomoses							
End to side	4.5% (7/156)	3.5% (5/142)	8.7% (11/127)	0.78; 0.25–2.42	1.93; 0.77–4.83	0.898	0.235
Side to side	7.3% (4/55)	8.6% (3/35)	0% (0/36)	1.18; 0.28–4.95	—	1.000	0.150
Location of distal anastomosis							
LAD	4.2% (6/144)	4.8% (6/126)	7.1% (8/112)	1.14; 0.38–3.45	1.71; 0.61 4.80	1.000	0.446
Diagonal branch	7.0% (4/57)	6.1% (2/33)	2.6% (1/38)	0.86; 0.17–4.46	0.38; 0.04–3.23	1.000	0.645
LCx	10.0% (1/10)	0.0% (0/18)	16.7% (2/12)	—	1.67; 0.18–15.80	0.357	1.000
RCA	0% (0/0)	0% (0/0)	0% (0/1)	—	—	—	—
Lumen diameter (mm)							
≤1.0	9.1% (1/11)	0.0% (0/10)	50.0% (2/4)	—	5.50; 0.67–45.37	1.000	0.154
1.1–1.5	4.4% (4/90)	1.8% (1/57)	1.9% (1/54)	0.39; 0.05–3.44	0.42; 0.05–3.63	0.649	0.650
1.6–2.0	6.4% (5/78)	8.0% (6/75)	9.9% (7/71)	1.25; 0.40–3.92	1.54; 0.51–4.63	0.946	0.637
>2.0	0% (0/24)	3.6% (1/28)	4.2% (1/24)	—	—	1.000	1.000

*Aspirin + dipyridamole versus aspirin + placebo. †Oral anticoagulant agents versus aspirin + placebo. Values for the three treatment groups represent percent of grafts occluded and (in parentheses) number of occluded grafts/total number of grafts.

Table 4. Occurrence of Primary and Secondary Clinical End Points

	Aspirin + Placebo (n = 173)	Aspirin + Dipyridamole (n = 163)	Oral Anticoagulant Agents (n = 158)	Relative Risk; 95% confidence interval *	†	p Value *	†
Primary clinical end point							
Myocardial infarction	8.7% (15)	9.2% (15)	7.6% (12)	1.06; 0.54–2.10	0.88; 0.42–1.81	1.000	0.876
Perioperative	7.5% (13)	6.7% (11)	5.7% (9)	0.90; 0.41–1.95	0.76; 0.33–1.72	0.952	0.658
Thrombosis	0.6% (1)	4.9% (8)	1.3% (2)	8.49; 1.07–67.14	2.19; 0.20–23.92	0.017	0.607
Perioperative	0.6% (1)	1.2% (2)	0.6% (1)	2.12; 0.19–23.19	1.09; 0.07–17.36	0.613	1.000
Major bleeding	5.8% (10)	8.0% (13)	8.2% (13)	1.38; 0.62–3.06	1.42; 0.64–3.15	0.562	0.510
Perioperative	4.0% (7)	7.4% (12)	6.3% (10)	1.82; 0.73–4.51	1.56; 0.61–4.01	0.281	0.490
Death	1.7% (3)	1.8% (3)	0% (0)	1.06; 0.22–5.18	—	1.000	0.249
Perioperative	0.6% (1)	0.6% (1)	0% (0)	1.06; 0.07–16.83	—	1.000	1.000
Secondary clinical end point							
Angina	14.5% (25)	14.1% (23)	16.5% (26)	0.98; 0.58–1.65	1.14; 0.69–1.89	1.000	0.725
Heart failure	1.2% (2)	3.1% (5)	2.5% (4)	2.65; 0.52–13.49	2.19; 0.41–11.79	0.271	0.430
Arrhythmias	2.3% (4)	3.7% (6)	3.8% (6)	1.59; 0.46–5.54	1.64; 0.47–5.71	0.532	0.528
Any clinical end point							
Primary	13.3% (23)	23.3% (38)	17.1% (27)	1.75; 1.09–2.81	1.29; 0.77–2.15	0.025	0.418
Primary or secondary	28.9% (50)	38.7% (63)	31.6% (50)	1.34; 0.99–1.81	1.09; 0.79–1.52	0.058	0.672

*Aspirin + dipyridamole versus aspirin + placebo. †Oral anticoagulant agents versus aspirin + placebo. Values for the three treatment groups represent percent of events and (in parentheses) number of events.

Discussion

The present study shows similar 1-year patency rates of internal mammary artery grafts among patients who were treated with a low dose of aspirin (50 mg/day) plus dipyridamole, oral anticoagulant agents or aspirin alone. However, the addition of dipyridamole to aspirin was associated with an increased risk of clinical events.

Antithrombotic drugs. Aspirin was given in a lower dose (50 mg/day) than is commonly used. This dose was based on experimental evidence that 40 to 80 mg of aspirin is sufficient to inhibit platelets through a decrease in the production of the proaggregatory platelet constituent thromboxane A_2 and a less pronounced inhibition of the endothelial production of its counterpart, prostacyclin (13). In the meantime, a low dose of aspirin has been demonstrated to be effective (14,15) in patients with unstable angina (75 mg/day) and in patients with cerebral transient ischemic attacks (30 mg/day). A benefit has also been suggested (16) after vein coronary bypass graft surgery (100 mg/day).

Dipyridamole was administered perioperatively by intravenous infusion and after operation by a slow release form in a dose of 200 mg twice daily. Both regimens differed from those used in previous trials and were designed to provide an appropriate assessment of the effects of this drug in combination with aspirin. Dipyridamole is believed to potentiate the platelet-inhibiting effect of aspirin, but the clinical relevance of this property remains controversial (17). We assumed that its vasodilating effect might be as or even more important, particularly in maintaining graft patency during and soon after coronary bypass surgery (18). Therefore, we preferred continuous intravenous infusion of dipyridamole to other modes of administration for the perioperative period.

Oral anticoagulant agents, although potent antithrombotic drugs, are not used widely after coronary bypass surgery. Surgeons are reluctant to start oral anticoagulant therapy before operation. The required laboratory control has also limited the use of these drugs. Moreover, a beneficial effect on vein graft patency was not demonstrated when oral anticoagulant agents and aspirin plus dipyridamole were compared (11,19).

Graft patency. The presented 1-year occlusion rates are in the range of previously reported rates of 4% to 12% (1,6,7). It remains questionable whether the patency of internal mammary artery grafts is improved at all by antithrombotic drug therapy. Only Goldman et al. (20,21) have reported on this subject, and they found no differences in early and 1-year patency rates of internal mammary artery grafts in patients receiving aspirin versus placebo. Because we had no placebo control group for ethical reasons, we were not able to assess the possible absolute benefit of the respective drug regimens. Nevertheless, oral anticoagulant agents showed a beneficial effect for sequential grafts in contrast to single grafts. This observation suggests a difference in the mechanism of thrombotic occlusion apparently related to the hemodynamic characteristics of these grafts, as most occlusions were found at similar distal sites on the left anterior descending coronary artery with a lumen diameter >1.5 mm. Because of high shear rates at distal sites, single grafts might be more prone to thrombosis that is mediated by deposition of platelets. By contrast, a fibrin clot might be propagated by lower shear rates at the distal sites of sequential grafts.

In this study, patients received antithrombotic drugs for 1 year, whereas graft patency was assessed only once at the end of the 1st postoperative year. This interval was based on the results of a previous vein graft patency trial conducted by

Chesebro et al. (9), who demonstrated a significant reduction in graft occlusion rate between 1 month and 1 year in patients who received aspirin and dipyridamole for 1 year. Pfisterer et al. (19) reported a similar benefit when they compared antithrombotic drug therapy given for 3 months versus 1 year. However, Goldman et al. (10) found no reduction in new late graft occlusions after 1 year of aspirin therapy when they performed angiography within 60 days and after 1 year. Goldman et al. (22) are the only workers who have studied the effects of antithrombotic drug therapy continued for >1 year, and they found no evidence that aspirin therapy continued 1 to 3 years postoperatively improved graft patency. A minimal treatment period of 1 year seems to be justified as long as more and unambiguous data are not available.

Sequential grafts were used in 29% of all patients. These patients represented 40% to 50% of the patients randomized by three participating hospitals, but only 0% to 15% of the patients from the remaining seven hospitals. At least some of these cardiac surgeons apparently preferred sequential to single internal mammary artery grafts to obtain complete revascularization, but obviously this policy is not yet common.

Clinical outcome. Differences in clinical outcome between the three treatment groups were more pronounced. The incidence of myocardial infarction and major bleeding tended to be slightly higher and the risk of thrombosis was greater in patients who received aspirin plus dipyridamole than in the aspirin group. The patients who received dipyridamole also had greater blood loss and transfusion requirements and more major bleeding necessitating reoperation. The increased risk of surgical bleeding is probably related to the perioperative infusion of dipyridamole. It may be due to vasodilation rather than to platelet inhibition, especially as platelet preservation by dipyridamole has been demonstrated (23) in patients after coronary bypass surgery. Surgical bleeding tended also to occur more frequently in patients who received oral anticoagulant agents than in those who received aspirin alone, but this difference was not reflected by blood loss and transfusion requirement. The risk of surgical bleeding probably remained limited by the delayed anticoagulant effect of these drugs, which were started on the day before operation. Overall, any primary clinical end point occurred more frequently if dipyridamole was added to aspirin. In this respect, the aspirin and oral anticoagulant groups showed no significant difference.

Limitations and clinical implications. Our study was not adequately powered to detect small or even moderate differences in occlusion rates, given the number of patients and the low occlusion rates. This is particularly a limitation of treatment comparisons within the subgroups. However, only large differences were considered clinically important. The observed differences were too small to be relevant, even if a larger sample size would reveal statistical significance. By contrast with such a potential and probably limited benefit, there was a 75% increase in risk of major clinical events if dipyridamole was added to aspirin. Oral anticoagulant agents provided no benefit with respect to graft patency and clinical outcome. Thus, aspirin plus dipyridamole had an unfavorable

risk/benefit ratio, whereas the ratio was equal for oral anticoagulant agents and for aspirin.

In patients who receive internal mammary artery grafts exclusively in coronary bypass surgery, the need for antithrombotic drug therapy has not yet been established. These grafts have a high patency rate even after 10 to 15 years, and they are probably less prone than vein grafts to both early and late occlusion. The risk of early attrition by thrombosis may be reduced at least in part because internal mammary artery grafts are used preferentially to bypass large coronary arteries, in particular, the left anterior descending coronary artery. Long-term patency depends mainly on progressive atherosclerosis, which is uncommon in internal mammary artery grafts. However, access of the internal mammary artery is limited and revascularization procedures tend to be more extensive. Thereby, a substantial number of patients still require vein grafts in addition to internal mammary artery grafts. This group may become smaller as sequential and free internal mammary artery grafts, as well as other arterial bypass conduits like the gastroepiploic artery, are applied more widely. However, as long as vein grafts are required, patients will be treated with antithrombotic drugs that have been demonstrated to improve vein graft patency. With respect to efficacy, safety, feasibility and costs, low dose aspirin (50 mg/day) is preferable to aspirin plus dipyridamole and to oral anticoagulant agents.

Conclusions. Internal mammary artery graft patency at 1 year after coronary bypass surgery is not improved by dipyridamole if this drug is added to a low dose of aspirin (50 mg/day). Moreover, this combination of drugs is associated with an increased overall risk of major clinical events. Oral anticoagulant agents provide no benefit over that achieved with low dose aspirin.

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