Immediate Postoperative Aspirin Improves Vein Graft Patency Early and Late After Coronary Artery Bypass Graft Surgery
A Placebo-Controlled, Randomized Study

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Background. The efficacy of aspirin for prevention of thrombotic graft occlusion after coronary artery bypass grafting (CABG) depends both on the dosage and time window of administration. Early and late graft patency were therefore assessed in a prospective, double-blind, randomized, placebo-controlled trial of aspirin, 324 mg daily, given within 1 hour of CABG.

Methods and Results. Angiographic graft patency was determined at 1 week (231 patients) and 1 year (219 patients) after CABG. The early vein graft occlusion rate was 1.6% on aspirin and 6.2% on placebo (p=0.004), and late graft occlusion rate was 5.8% on continued aspirin and 11.6% on placebo (p=0.01). New graft occlusion between 1 week and 1 year was less common in patients on aspirin than on placebo (4.3% versus 7.4%, p=0.013). The protective effect of aspirin against occlusion persisted in most subgroups of graft type, graft flow, diameter of recipient artery, location of grafted artery, and endarterectomy. Mean chest tube blood loss for the first 24 hours was 571 ml for the aspirin group and 563 ml for the placebo group. Red cell transfusion requirements were 902 ml in the aspirin group and 934 ml in the placebo group (p=NS). The reoperation rate was 4.8% in the aspirin group and 1% in the placebo group (p=0.1).

Conclusions. Immediate postoperative administration of aspirin (324 mg) improves early graft patency and, with continued usage, protects against further occlusion up to 1 year after CABG. Postoperative blood loss was similar in the two groups; however, aspirin was associated with a nonsignificant higher rate of reoperation. (Circulation 1991;83:1526–1533)

The patency of autologous saphenous vein grafts implanted during coronary artery bypass grafting (CABG) is improved by antiplatelet therapy initiated in the perioperative period. In recent large, randomized clinical trials, the occlusion rate of vein grafts in the placebo group was 10% within 1 month,1 15% within 2 months,2 and up to 25% within 12 months after CABG.3,4 Since these and earlier studies, there has been a resurgence of interest in the use of the internal mammary artery (IMA) as a bypass conduit. The IMA graft has had an 85–95% patency at 10 years after CABG.5,6 In most cases, however, it is still necessary to achieve complete revascularization using both saphenous vein and IMA grafts.2

In preliminary studies, we previously demonstrated a strong association between vein graft occlusion, elevated preoperative anticardiolipin antibody levels, and β-thromboglobulin levels.7,8 Biochemical data such as these have provided further evidence that excessive platelet activation and thrombosis are the predominant mechanisms of vein graft occlusion in the early postoperative period.

Although several studies of antiplatelet agents have shown conclusive benefit with aspirin therapy in preventing vein graft occlusion, the evidence of a significant benefit from dipyridamole or sulphinpyrazone therapy is less certain.9,10 The use of a preoperative aspirin regimen, which has been associated with increased blood loss and higher reoperation rate immediately after CABG,11 is currently undergoing further evaluation in clinical trials. The objective of this prospective, double-blind, randomized, placebo-controlled trial was to test the safety and efficacy of
aspirin (324 mg/day) given within 1 hour after CABG for improvement of vein graft patency both early and late after CABG.

Methods

Study Population

From August 1984 through November 1987, 237 patients satisfied entry criteria and were enrolled into a prospective, randomized, double-blind, placebo-controlled trial of aspirin therapy (324 mg/day) for the first year after CABG. The following exclusion criteria were used: age greater than 70 years, previous CABG or other cardiac surgery, need for concomitant valve surgery or aneurysm resection, use of platelet inhibitory or anti-inflammatory agents within 7 days before surgery, previous (within 5 years) history of peptic ulcer disease or gastrointestinal hemorrhage, chronic heart disease requiring aspirin or nonsteroidal anti-inflammatory drugs, cerebral ischemia requiring antiplatelet agents, thromboembolic disease requiring anticoagulant therapy, hyper-sensitivity to aspirin, history of bleeding disorder, severe chronic obstructive pulmonary disease, severe left ventricular dysfunction (ejection fraction <20%), isolated IMA grafting, diabetes mellitus (fasting plasma glucose >6.5 mmol/l), and severe peripheral vascular disease.

Of 712 patients screened for entry, 237 (33%) were enrolled in the trial, five refused to participate, and 470 (66%) patients were excluded by the above criteria. The prevailing reasons for exclusion were age greater than 70 years (14%), use of aspirin or other antiplatelet agents within 7 days of surgery (33%), peptic ulcer disease (14%), previous CABG surgery (6%), and diabetes mellitus (5%).

Study Protocol

After informed consent was obtained before surgery, patients were randomized to therapy in a double-blind fashion by the dispensing pharmacist. Patients were stratified by each of the five participating surgeons at St. Vincent's Hospital. Of the 237 patients entered into the study, 127 were assigned to aspirin and 110 to placebo. Most patients (84%) underwent CABG with three of the five participating surgeons, and a minority underwent CABG with the two remaining surgeons. Of this larger group, 102 patients were assigned to aspirin and 98 to placebo, whereas of the minority (16%), 25 were assigned to aspirin and 12 to placebo. The original randomization schedule allowing for 100 patients under each surgeon was incompletely drawn for the two less-busy surgeons and resulted in a chance imbalance of aspirin and placebo for this smaller group of patients.

The protocol conformed to the National Health and Medical Research Council guidelines for human experimentation and was approved by the Ethics and Research Committee of the host institution.

Study Medication and Compliance

The study medication consisted of aspirin (324 mg) or a matching placebo and was given within 1 hour of leaving the operating theater and given daily thereafter. The tablet was dissolved in 30 ml water and was given by way of a nasogastric tube (90-minute clamp time) and repeated daily until the patient had satisfactory oral intake. The medications were kindly provided by Bayer Australia Ltd. Paracetamol was provided for analgesia to discourage inadvertent casual use of aspirin-containing compounds, and a list of “prohibited” medications were supplied to each patient and the local medical officer at the time of discharge. Patients were given four monthly supplies of the study medication with tablet record diaries to encourage compliance.

At the first of three follow-up visits, pill counts were performed, and a midmorning urine sample was collected. This was stored at -20°C for a qualitative test for salicylic acid, performed at the end of the study with a 5% ferric chloride solution to detect aspirin ingested within the previous 12 hours.

Surgery

Cardiopulmonary bypass surgery was initiated according to the standard protocol for this institution, with myocardial preservation by means of multiple dose cold blood cardioplegia (5-7°C) and systemic cooling to 24-27°C. The saphenous vein was carefully harvested, gently distended with heparinized whole blood, and stored in blood until implantation. From February 1986, the IMA was used as a conduit in selected cases. Distal anastomoses were performed with 7/0 Prolene sutures, and proximal anastomoses were performed with 5/0 Prolene sutures while rewarming was in progress. Grafts were constructed as single, sequential, or occasionally branched Y grafts. Coronary endarterectomy was performed in diffusely diseased native arteries at the discretion of the surgeon. Coronary artery diameter at the point of anastomosis was measured with calibrated probes, and vein graft blood flow was measured with precalibrated electromagnetic flow probes (Cliniflow II, Carolina Medical Products, King, N.C.) immediately before chest closure.

Patients were given heparin according to body weight at the commencement of CABG, and this was reversed with protamine sulphate before removal of the aortic cannula. Transfusion requirements during and after CABG were tabulated for each patient, and chest tube blood loss was measured and recorded hourly until removal of drains. Technical aspects of the perfusion, bypass and cross-clamp times, postoperative support, and complications were recorded.

Graft Angiography

Vein graft angiography was performed by the same investigator (T.P.G.) in 231 of 237 patients (97%), a median of 7 days after CABG (range, 6–60 days). Late vein graft angiography was then performed in
219 of 237 patients (92%), a median of 363 days after 
CABG (range, 222–430 days). The early postoperative 
angiogram was not obtained in six patients 
because of patient refusal in two (one given placebo 
and one given aspirin), death within 6 days of CABG 
in three (one given placebo and two aspirin), and 
tolerance of study medication in one (given place-
bo). The early angiogram was delayed beyond 8 days 
in 11 patients because of sternal infection in three, 
postoperative cerebrovascular accident in two, prac-
tical constraints in four, and respiratory complica-
tions in another two patients.

Two patients (one given placebo and one given 
aspirin) refused to undergo early angiography but 
derwent the late study.

The late postoperative angiogram was not ob-
tained in an additional 12 patients because of refusal in 
four (one given placebo and three given aspirin), 
death since early angiogram in three (one given placebo 
and two given aspirin), gastrointestinal bleeding in one (given aspirin), pulmonary embolus in one (given aspirin), cerebrovascular accident in one (given placebo), and loss to follow-up in two patients (one given placebo and one given aspirin).

Early and late graft angiography were performed 
by the transfemoral Judkins’ technique. Selective 
injections of vein grafts and IMA grafts were made in 
orthogonal views on cineangiographic films. If the 
origin of the graft was unable to be selectively 
engaged and visualized, then biplane aortic root 
angiography was performed. Each angiogram was 
reviewed by two independent, experienced angiogra-
phers who had no knowledge of the patient’s as-
signed medication. A vein graft was classified as 
patent if contrast was seen to flow through the graft 
into the distal native coronary artery. A distal 
anastomosis was defined as patent (in single, sequential, 
or Y grafts) if contrast was seen to flow into the 
graffted artery. If the graft was occluded at its origin, 
then all downstream distal anastomoses were consid-
ered occluded. In this study, graft patency is used to 
refer to patency of distal anastomoses. In the event of 
disagreement regarding graft patency, a third ob-
server reviewed the angiogram, and a consensus 
opinion was reported.

Statistical Analysis

Data were collated by use of the computer data 
entry program Datatar (marketed by Miconpro, Inter-
national Corporation, San Rafael, Calif.). Unless 
stated otherwise, values are expressed as mean±SD.

For the analysis of patient clinical and surgical data, 
the standard χ2 test on the statistical package SP-
IDA12,13 was used. Vein graft occlusion (or patency) 
rates were expressed per patient (with one or more 
distal anastomoses occluded) and per distal anastomo-
sis. The proportion of patients on aspirin and placebo 
with one or more graft occlusions was compared by 
use of the conditional binomial exact test.14 The 
comparison of proportions of occluded distal anasto-
moses (assuming grafts within each patient were not

### Table 1. Preoperative Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Aspirin</th>
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<tbody>
<tr>
<td>n</td>
<td>110</td>
<td>127</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56±7</td>
<td>56±8</td>
</tr>
<tr>
<td>M:F sex ratio</td>
<td>92:18</td>
<td>110:17</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>39</td>
<td>45</td>
</tr>
<tr>
<td>FH angina/MI (%)</td>
<td>54</td>
<td>62</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>7.0±1.3</td>
<td>7.1±1.4</td>
</tr>
<tr>
<td>Angina class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II (%)</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>III and IV (%)</td>
<td>33</td>
<td>27</td>
</tr>
</tbody>
</table>

FH, family history; MI, myocardial infarction.

independent) involved the use of the ratio estimate as 
applied to cluster sampling, a statistical technique 
ewly applied in this clinical context.15

### Results

**Patients**

The clinical parameters of the study population are 
shown in Table 1. There were no differences with 
respect to clinical characteristics and risk factors for 
coronary artery disease between the two treatment 
groups. Of the 237 patients entered into the study, 127 
were randomized to aspirin and 110 to placebo. Graft 
patency data pertain to 231 patients (97%) who un-
derwent early postoperative angiography (105 given 
placebo and 126 given aspirin) and to 219 patients 
(92%) who underwent late angiography (100 given 
placebo and 119 given aspirin). Both early and late 
angiography were performed in 217 patients (91%). 
There was no difference in the timing of angiography 
in relation to CABG between the treatment groups. 
The number of distal anastomoses and endarterecto-
 mies did not differ between the treatment groups. 
There were 810 distal anastomoses performed in the 
237 enrolled patients giving an average of 3.5 distal 
anastomoses per patient (Table 2).

**Early Graft Patency**

Data on IMA graft patency are not included in the 
analysis of vein graft patency. The vein graft patency 
rate (by distal anastomosis) was 98.4% in the aspirin

### Table 2. Perioperative Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early angiography (n)</td>
<td>105</td>
<td>126</td>
</tr>
<tr>
<td>Late angiography (n)</td>
<td>100</td>
<td>119</td>
</tr>
<tr>
<td>Distal anastomoses/patient (n)</td>
<td>3.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Endarterectomy (%)*</td>
<td>5.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Early angiogram (day)</td>
<td>7 (6–60)</td>
<td>7 (6–44)</td>
</tr>
<tr>
<td>Late angiogram (day)</td>
<td>363 (222–430)</td>
<td>363 (277–426)</td>
</tr>
<tr>
<td>Aortic cross-clamp (min)</td>
<td>47.9</td>
<td>46.9</td>
</tr>
</tbody>
</table>

n, number of patients. Range in parentheses.

*Percentage of distal anastomoses with endarterectomy.
group and 93.8% in the placebo group ($p=0.004$ using the ratio estimate technique$^{15}$). The proportion of patients with one or more occluded distal anastomoses was significantly lower in the aspirin than in the placebo group (4% versus 14.3%, $p=0.003$) (Figure 1).

**Late Graft Patency**

At 1 year after CABG, the vein graft patency rate was 94.2% in the aspirin group and 88.4% in the placebo group ($p=0.01$) (Figure 2). The proportion of patients with one or more occluded distal anastomoses was again significantly lower in the aspirin than in the placebo group (11.9% versus 29.5%, $p<0.001$).

**Late Graft Occlusion**

In 217 patients who had undergone early and late angiography, the incidence of further vein graft occlusion between 1 week and 1 year was 15 of 352 (4.3%) in the aspirin group and 23 of 310 (7.4%) in the placebo group ($p=0.013$). Thus, new graft occlusion after early angiography occurred in 9.2% of patients on aspirin and 18.4% on placebo ($p=0.032$).

The occlusion rate was consistently lower in the aspirin group (with the exception of the small number of branched Y grafts) at the time of early and late angiography when grafts were subgrouped by diameter of the distal vessel, the type of graft, and the type of recipient artery (Table 3). Grafted arteries of a luminal diameter of 1.5 mm or less were evenly distributed among the aspirin and placebo groups (71% and 65%, respectively) in this study ($p=0.14$). There was significant benefit of aspirin at early angiography in single vein grafts with flow less than 20 ml/min and with diameter of recipient vessel of 1.5 mm or less. Single grafts to the left anterior descending and circumflex coronary arteries had improved patency with aspirin at both early and late angiography (Table 4).

![Figure 1. Bar graph showing percentage of patients with graft occlusion in placebo-treated and aspirin-treated groups. Angiographic results at 1 week and 1 year are presented. Late, patient group with both angiograms and new occlusion evident only after early angiography.](image1.png)

![Figure 2. Bar graph showing percentage of occluded distal anastomoses in placebo-treated and aspirin-treated groups. Angiographic results at 1 week and 1 year are presented. Late, patient group with both angiograms and new graft occlusion evident only after early angiography.](image2.png)

**Table 3. Frequency of Vein Graft Occlusion According to Type and Location of Graft and Diameter of Recipient Vessel**

<table>
<thead>
<tr>
<th>Location</th>
<th>Early</th>
<th>1 yr</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Aspirin</td>
<td>Placebo</td>
</tr>
<tr>
<td>LAD</td>
<td>8 (132)</td>
<td>0 (147)*</td>
<td>12 (127)</td>
</tr>
<tr>
<td>RCA</td>
<td>5 (85)</td>
<td>3 (90)</td>
<td>16 (83)</td>
</tr>
<tr>
<td>Cx</td>
<td>6 (120)</td>
<td>2 (145)</td>
<td>8 (118)</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>8 (185)</td>
<td>1 (214)‡</td>
<td>15 (174)</td>
</tr>
<tr>
<td>Sequential</td>
<td>4 (151)</td>
<td>1 (159)</td>
<td>7 (154)</td>
</tr>
<tr>
<td>Branched Y</td>
<td>0 (2)</td>
<td>13 (9)</td>
<td>100 (1)</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.25</td>
<td>33 (24)</td>
<td>8 (24)‡</td>
<td>38 (21)</td>
</tr>
<tr>
<td>1.25–1.5</td>
<td>4 (197)</td>
<td>1 (249)†</td>
<td>9 (193)</td>
</tr>
<tr>
<td>1.6–2.0</td>
<td>5 (105)</td>
<td>2 (105)</td>
<td>12 (105)</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>0 (12)</td>
<td>0 (4)</td>
<td>0 (10)</td>
</tr>
</tbody>
</table>

Values represent percentage of grafts occluded, and number of distal anastomoses is in parentheses. Late, denotes patient group with both angiograms and late occlusion after early angiogram.

LAD, left anterior descending and diagonal arteries; RCA, right coronary artery; Cx, circumflex coronary artery.

*p<0.001, †p<0.02, ‡p<0.01, §p<0.05 compared with placebo.
TABLE 4. Frequency of Occlusion of Single Vein Grafts According to Location, Graft Flow, and Diameter of Recipient Vessel

<table>
<thead>
<tr>
<th>Location</th>
<th>Early</th>
<th>1 yr</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Aspirin</td>
<td>Placebo</td>
</tr>
<tr>
<td>LAD</td>
<td>11 (61)</td>
<td>0 (64)*</td>
<td>14 (59)</td>
</tr>
<tr>
<td>RCA</td>
<td>5 (64)</td>
<td>3 (71)</td>
<td>18 (61)</td>
</tr>
<tr>
<td>Cx</td>
<td>8 (60)</td>
<td>1 (79)†</td>
<td>13 (54)</td>
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Graft flow (ml/min)

<table>
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<th>Aspirin</th>
<th>Placebo</th>
<th>Aspirin</th>
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<tbody>
<tr>
<td>&lt;20</td>
<td>41 (17)</td>
<td>0 (15)*</td>
<td>33 (15)</td>
<td>7 (15)</td>
<td>0 (10)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>20–60</td>
<td>6 (100)</td>
<td>2 (107)</td>
<td>16 (93)</td>
<td>9 (59)</td>
<td>13 (88)</td>
<td>7 (97)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>4 (57)</td>
<td>1 (80)</td>
<td>6 (54)</td>
<td>1 (72)</td>
<td>4 (53)</td>
<td>0 (69)</td>
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Diameter (mm)

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<th></th>
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<th>Aspirin</th>
<th>Placebo</th>
<th>Aspirin</th>
<th>Placebo</th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.25</td>
<td>33 (13)</td>
<td>9 (11)‡</td>
<td>36 (11)</td>
<td>9 (11)†</td>
<td>22 (9)</td>
<td>0 (10)†</td>
</tr>
<tr>
<td>1.25–1.5</td>
<td>6 (99)</td>
<td>0 (132)*</td>
<td>14 (91)</td>
<td>6 (120)‡</td>
<td>11 (84)</td>
<td>6 (113)</td>
</tr>
<tr>
<td>1.6–2.0</td>
<td>6 (70)</td>
<td>3 (80)</td>
<td>13 (70)</td>
<td>4 (76)‡</td>
<td>8 (63)</td>
<td>2 (66)‡</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>0 (11)</td>
<td>0 (5)</td>
<td>0 (9)</td>
<td>0 (5)</td>
<td>0 (8)</td>
<td>0 (4)</td>
</tr>
</tbody>
</table>

Values represent percentage of grafts occluded, and number of distal anastomoses is in parentheses. Late, denotes patient group with both angiograms and late occlusion after early angiogram.

LAD, left anterior descending and diagonal arteries; RCA, right coronary artery; Cx, circumflex artery.

* p<0.01; †p<0.05; ‡p<0.02; §p<0.001 compared with placebo.

When grafts were performed concomitantly with endarterectomy, the occlusion rate per distal anastomosis was one of 20 (5%) in the aspirin group and seven of 20 (35%) in the placebo group, whereas if no endarterectomy was performed, there were 17 of 366 (5%) anastomoses occluded in the aspirin group and 29 of 325 (9%) in the placebo group (p=0.025). Of 202 men studied, 11 of 110 (10%) in the aspirin group and 22 of 92 (24%) in the placebo group had one or more occlusions. Among the 35 women, four of 17 (24%) in the aspirin group and seven of 18 (39%) in the placebo group had one or more occlusions.

Left IMA grafts were performed on 47 distal anastomoses in 35 patients. These included 22 single IMA grafts and 25 sequential IMA grafts (11 double sequential and one triple sequential). A double sequential IMA graft was occluded at 7 weeks after CABG in one patient on placebo. This patient had severe sternal infection and required two additional sternotomies with debridement. There were no occlusions of IMA grafts at 1 year in the aspirin group.

Blood Loss, Transfusion Requirement, and Reoperation

The mean chest tube drainage was similar for the aspirin (571±336 ml) and placebo (563±322 ml) groups during the first 24 hours (median, 470 ml and 490 ml, respectively) and for the total drainage time (732±402 ml and 708±358 ml, respectively).

The transfusion requirements for red blood cells were 902 ml in the aspirin group and 934 ml in the placebo group (p=NS). Operative cardiopulmonary bypass and cross-clamp times were similar in both groups. The short-term reoperation rate was 4.8% (six patients) in the aspirin group and 1% (one patient) in the placebo group (p=0.1). A surgically correctable site of bleeding was found in 67% of the aspirin group who required reoperation and diffuse bleeding was observed in the remaining two patients.

Perioperative new Q wave infarction occurred in three patients (2.4%) of the aspirin group and in none of the placebo group (p=0.12). Postoperative atrial and ventricular arrhythmias were equally prevalent in both groups.

Compliance

On the basis of urine tests, quarterly pill counts, and tablet record diary entries, 92% of patients took at least 90% of their medications. Only 2% of patients took less than 80% of the tablets. Urine tests for salicylic acid were positive in 90% of the aspirin group and 3% of the placebo group. Platelet aggregation studies in the first 105 patients showed a full "aspirin defect" in all eight patients on aspirin and in one of nine patients on placebo.

Complications

Significant complications occurred in five patients during early postoperative graft angiography. A "shower" of peripheral emboli to the right foot occurred in one patient and was successfully treated with intravenous administration of heparin. Uneventful, traumatic dissection of a proximal aortic graft anastomosis occurred in one patient, and a severe allergic reaction to contrast media occurred in an additional three patients. At late angiography, two patients developed a moderate groin hematoma without significant hemodynamic compromise. No permanent sequelae resulted from these complications.

Of 127 patients receiving aspirin, 13 developed side effects. Active bleeding associated with peptic ulceration occurred in two patients (one requiring transfusion), nausea occurred in five patients (one withdrew from study), and transient minor reaction occurred in an additional six patients. Of 110 patients
on placebo treatment, five patients developed side effects that included gastrointestinal upset in three, two of whom refused to continue in the study.

Discussion

Postoperative aspirin therapy, which was begun within 1 hour after CABG in this study, was highly protective of vein graft patency during the first postoperative year. This beneficial effect of a single daily dose of soluble aspirin (324 mg) was evident at 1 week, and a further protective effect was evident 1 year after CABG. The overall benefit persisted throughout an analysis of subgroups of clinical and surgical parameters.

In accord with previous studies, we found that early aspirin therapy, compared with placebo, resulted in a marked reduction of vein graft occlusion within 1 week after CABG. Our findings strongly support the results of a Veterans Administration (VA) cooperative study, in which patients receiving a single dose of aspirin had the lowest early graft occlusion rate when compared with patients receiving aspirin or aspirin plus dipyridamole three times daily. To minimize the risks of repeated postoperative graft angiography in this study, we excluded patients with severe chronic obstructive airways disease, left ventricular ejection fraction less than 20%, and diabetes mellitus. Such patients, representing only 8% of our potential study population, were, nevertheless, eligible for enrollment in the VA cooperative study and may have a higher risk of progressive cardiac disease and graft occlusion. These exclusions in our study may have contributed to the lower 1-year graft occlusion rate in the placebo group (12%) compared with that in the VA cooperative study (22%) and the Mayo clinic trial (25%).

The present study, to our knowledge, is the first report on the use of immediate (within 1 hour) postoperative aspirin therapy. Previous investigators have given aspirin either 12 hours before surgery with additional aspirin 6 hours after surgery or commenced aspirin at 71,67 to 67 hours after surgery. In contrast to preoperative aspirin therapy, aspirin given a median of 30 minutes after leaving the operating theater was not associated with a significantly greater incidence of bleeding or transfusion requirements. The reoperation rate was not significantly higher in the aspirin group (4.8% versus 1%), and diffuse generalized bleeding was uncommon, occurring in two of the six patients receiving aspirin who required emergency reoperation. The surgical bleeding from incomplete ligation of vein graft or IMA pedicle branches generally results in immediate and progressive chest tube loss. This (bleeding) is less likely to be a direct effect of aspirin given within 1 hour after CABG with an anticipated delay of 2 additional hours before the onset of adequate systemic antiplatelet activity. After their initial report of increased chest tube blood loss and reoperation rate in patients given aspirin (325 mg) 12 hours before CABG, the VA cooperative studies group reported a second study in which early vein graft patency was similar whether aspirin was started 12 hours before or 6 hours after CABG. The complete results of that study have yet to be published, and on the basis of the favorable early and late patency rates in the present investigation, our ongoing protocol consists of soluble aspirin (324 mg) within 1 hour after CABG.

In addition to the reduction of early graft occlusion, further protection against new graft occlusion between 1 week and 1 year was observed when aspirin was continued for 1 year after CABG. These results differ from the recent VA report in which patients with patent grafts at 9 days had no further protection against new graft occlusion by aspirin given during the first 12 months. Two previous studies have also reported benefits of antithrombotic treatment continued up to 1 year in patients at risk of occlusion. In both studies, dipyridamole was combined with different dosages of aspirin, 50 mg daily in one center and 975 mg daily in the other. In the present study, we used the more conservative statistical method of cluster sampling analysis to show that aspirin alone protects against new graft occlusion without the addition of dipyridamole.

The discrepancy between the results for late graft occlusions in this study and the VA study may relate to several factors. First, in the present study, there is late angiographic follow-up in 92% of enrolled patients compared with 65% in the VA study. This is a single-center study with uniform surgical practices, and patients were further stratified by surgeon in the randomization schedule to balance for individual surgical technique between the treatment groups. This resulted in an even distribution of grafted small distal vessels (1.5 mm or less) between aspirin (71%) and placebo (65%) groups. These features with incomplete follow-up enhance the realistic assessment of longitudinal survival of vein grafts after prolonged (12 months) active or placebo therapy. Second, a larger proportion of occluded grafts may have been included in the early occlusion rate in the VA study because of the slightly later scheduling of early angiography at 9 days. The time window for development of "late" occlusion in this study is difficult to determine within the angiographic protocol, and a third postoperative angiogram at 4–6 weeks may have helped clarify this issue. Third, the earlier postoperative administration of aspirin in the present study may result in more profound suppression of early platelet deposition and mitogen release within the graft, hence inhibiting thrombotic occlusion and intimal smooth muscle proliferation at an earlier stage. These antiplatelet effects would more likely benefit high-risk grafts to narrowed, diseased coronary arteries and vessels requiring endarterectomy. Beyond the early angiogram, the new occlusion rate was significantly reduced in the aspirin subgroup of single vein grafts with lumen of the recipient vessel less than 1.25 mm. Although there is evidence of platelet dysfunction related to the use of the cardio-
pulmonary bypass pump during surgery,\textsuperscript{21} there will probably be continuing thromboxane generation by new platelets released from bone marrow stores after separation from bypass. In the VA study, aspirin (325 mg) was administered 12 hours before CABG; however, there is a paucity of data concerning immediate postoperative platelet function in patients given this dose of aspirin 15–18 hours before CABG.\textsuperscript{22}

The correct dose of aspirin for patients undergoing CABG has been investigated extensively in both clinical and laboratory studies. Platelet patency studies have examined the effect of aspirin alone in daily doses of 100$^{\text{23}}$, 150$^{\text{17}}$, 325$^{\text{24}}$, and 975 mg$^{\text{25,18}}$; aspirin 975 mg with dipyridamole 225 mg daily$^{2,3,18}$; aspirin 50 mg with dipyridamole 400 mg daily$^{21}$; aspirin 150 mg with dipyridamole 225 mg daily$^{17}$; and triflusal (a new antiplatelet agent) 900 mg with dipyridamole 225 mg daily.\textsuperscript{16}

Platelet patency rates have been equivalent whether aspirin 325 mg is given once or three times daily.\textsuperscript{4} The use of dipyridamole in the perioperative period provides no apparent additional benefit to aspirin alone.\textsuperscript{3,18} Although a recent study showed that the addition of dipyridamole potentiates the benefit of lower dose aspirin (150 mg) on early graft patency,\textsuperscript{17} Contrary to previous in vitro studies, newer evidence suggests that aspirin 325 mg daily is more anti-thrombolytic than is lower dose aspirin (80 mg every other day) because of greater preservation of prostacyclin production.\textsuperscript{24}

In view of the results of this study and recent larger clinical antiplatelet trials, we currently recommend aspirin 324 mg daily as standard anti-thrombolytic therapy after CABG. The compliance in this study was high with a very acceptable incidence of aspirin side effects.

The renewed interest in the IMA as a superior conduit for CABG is clearly justified by the 95\% 1-year patency rate in this study. Until February 1986, saphenous veins were routinely used and were the bypass conduit of choice in this institution. Patients continued to be enrolled in this study until November 1987, and we acknowledge that the use of this alternative bypass conduit may influence the patency of other vein grafts within a patient. When all patients having IMA grafts were excluded from the analysis, aspirin remained highly protective of vein graft patency.

We have analyzed the effects of antiplatelet therapy on the patency of distal anastomoses using the ratio estimate as applied to cluster sampling, and when comparing the proportions of patients with graft occlusion, we used the conditional binomial exact test. Such methodology was reviewed in depth recently, and the ratio estimate was deemed the most appropriate statistical method for analysis (by treatment) of patency data of distal anastomoses within the same patient.\textsuperscript{15} The ratio estimate approach in this study has yielded more conservative statistical significances than has the conditional binomial exact test.

In conclusion, this study shows that vein graft patency is significantly improved by aspirin (324 mg) given within 1 hour after CABG and continued once daily for at least 12 months. Protection against occlusion was observed at 1 week, and further significant improvement in late graft patency was observed at 1 year for grafts on smaller, diseased vessels. These benefits can be achieved without significantly greater postoperative blood loss or reoperation rate. Aspirin was highly protective against occlusion of vein grafts onto arteries requiring endarterectomy.

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24. Gavaghan et al Immediate Postoperative Aspirin

**Key Words** • antiplatelet therapy • aspirin • coronary artery bypass graft surgery • graft occlusion
Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study.

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