Prevention of Early Aortocoronary Bypass Occlusion by Low-Dose Aspirin and Dipyridamole

Ginés Sanz, MD, Antonio Pajarón, MD, Eduardo Alegria, MD, Ignacio Coello, MD, Mariona Cardona, MD, Juan Antonio Fournier, MD, Manuel Gómez-Recio, MD, Javier Ruano, MD, Ricardo Hidalgo, MD, Alfonso Medina, MD, Gloria Oller, MD, Thierry Colman, MD, Felix Malpartida, MD, Xavier Bosch, MD, and the Grupo Español para el Seguimiento del Injerto Coronario (GESIC)*

To analyze the efficacy of low-dose aspirin in preventing early aortocoronary vein graft occlusion, 1,112 consecutive patients were enrolled in a multicenter, randomized, double-blind, placebo-controlled trial comparing 50 mg t.i.d. aspirin, 50 mg aspirin plus 75 mg t.i.d. dipyridamole, and placebo. All patients received 100 mg q.i.d. dipyridamole for 48 hours before surgery, and assigned treatment was started 7 hours after surgery. Vein graft angiography was performed in 927 patients (83%) within 28 days of surgery (mean, 10 days). Aspirin plus dipyridamole significantly (p=0.017) reduced the occlusion rate of distal anastomoses from 18% (placebo) to 12.9%. Occlusion rate in the aspirin group was 14%, which approached statistical significance (p=0.058). Furthermore, only aspirin plus dipyridamole reduced (p=0.01) the number of patients with occluded grafts (placebo, 33%; aspirin, 27.1%; aspirin plus dipyridamole, 24.3%). Mediastinal drainage was slightly higher (p=0.04) in the aspirin plus dipyridamole group (713±456 ml) than in the other two groups (placebo, 670±437 ml; aspirin, 629±337 ml), but hospital mortality (average, 4.6%) and early reoperation (average, 3.9%) rates were similar among the three groups. Thus, low-dose aspirin plus dipyridamole safely improves early saphenous vein aortocoronary graft patency; this effect is an added benefit to a preoperative regimen of dipyridamole. (Circulation 1990;82:765–773)

The results of several controlled trials have demonstrated that platelet-inhibiting drugs may prevent early aortocoronary vein graft occlusion1–2; however, some questions such as the optimal combination and doses of antiaggregant agents remain undetermined.3 Because large doses of aspirin prevent the production of thromboxane A2 but also inhibit the formation of the wall vessel antiaggregant prostacyclin, it has been suggested that a lower dose of aspirin may improve both clinical efficacy and tolerance.4,5 However, the clinical benefit of such low doses on graft patency has not yet been proved in a large-scale clinical trial.

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Address for correspondence: G. Sanz, MD, Unidad Coronaria, Hospital Clinic, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain.
Participating hospitals and investigators are listed in the “Appendix.”
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The timing of antiplatelet treatment has also been a matter of controversy. Previous experimental and clinical studies suggest that because endothelial graft damage begins during vein extraction and manipulation, the best therapeutic regimen to prevent graft occlusion is the preoperative administration of dipyridamole followed soon after surgery by antiplatelet drug therapy.6–8 However, there is no evidence that postoperative treatment adds further benefit when the patient has received antiplatelet drugs before surgery.

The goals of this multicenter, double-blind, placebo-controlled trial were to compare the efficacy of early saphenous vein graft patency of two different postoperative treatments (low-dose aspirin or low-dose aspirin plus dipyridamole) and to analyze whether postoperative antiaggregant treatment adds any clinical benefit to preoperative dipyridamole.
Methods

Study Population

The study was conducted by the Grupo Español para el Seguimiento del Injerto Aortocoronario (Spanish Group for Aortocoronary Bypass Follow-up [GESIC]), a working group of the Spanish Society of Cardiology.

All patients less than 71 years old who were undergoing elective aortocoronary bypass surgery with saphenous vein grafts at the six participating institutions were considered eligible for the study. Exclusion criteria included previous cardiac surgery, heart valve disease requiring surgical repair, documented peptic ulcer disease with previous bleeding or a recent (within 3 months) history of ulcer symptoms, thromboembolic episodes requiring either anti-coagulant or antiplatelet treatment, allergy or intolerance to contrast material or drugs used in the trial, history of cerebrovascular accident, renal failure during chronic dialysis, type I diabetes mellitus, severe chronic obstructive pulmonary disease, any condition that would increase the risk of aortocoronary vein graft angiography, and lack of informed consent.

From June 1984 through August 1988, 1,647 patients were considered eligible; 1,149 of these patients (69.8%) entered the study. The remaining 498 patients (30.2%) met at least one exclusion criterion: patient refusal (82), emergency surgery (207), antiplatelet treatment (119), other diseases (57), and technical reasons (33).

Of the 1,149 patients who entered the study, 1,112 were randomized to receive aspirin, aspirin plus dipyridamole, or placebo according to a randomization code determined at the coordinating center. To ensure the comparability of the treatment groups, the randomization was performed separately for each institution with the block method. Thus, at the end of each block of 60 patients under treatment, an equal number of patients (20) had been assigned to each treatment in that particular institution. The criteria for not randomizing the remaining patients were intraoperative death (26), angina attributed to preoperative dipyridamole (seven), and early bleeding (four).

Protocol

All patients received 100 mg q.i.d. dipyridamole orally beginning 48 hours before surgery, the last dose administered at 6:00 AM on the day of surgery. One hour after surgery, 100 mg dipyridamole was given via a nasogastric tube that was clamped for 90 minutes. Patients were then randomized into three groups, and the treatment began, via the nasogastric tube, 7 hours after surgery.

Beginning on the day after surgery, patients received three times a day in a double-blind fashion a capsule containing either 50 mg aspirin, 50 mg aspirin plus 75 mg dipyridamole, or placebo. Aspirin was administered in a three-time-a-day dosing schedule to effect convenient administration together with dipyridamole three times a day. Previous research has shown that at this particular dose and schedule, aspirin inhibits both in vitro platelet aggregation and thromboxane release.\(^9\) Drugs and placebo were provided by Boehringer Ingelheim SA, Barcelona, Spain, in individual kits containing 28-day supplies (preestablished maximal length of follow-up). At each hospital, drug compliance was checked daily by one of the investigators through patient interview and review of the charted medications.

The study protocol was approved by the ethics committee of each institution and by the National Committee for Clinical Trials. When the protocol was designed, the inclusion of a placebo group was considered to be ethical because no definitive data were available in the literature concerning benefits of postoperative antiaggregant treatment after patients receive preoperative antiplatelet drugs.

Surgical Procedure

No attempt was made to establish a uniform surgical protocol; saphenous vein grafts were implanted according to institution’s usual technique. Although internal mammary artery grafts were implanted in some patients, only saphenous vein grafts are considered for this study. Calibrated probes were used to assess the diameter of the grafted artery. Among hospitals, the number of distal anastomoses per patient averaged 2.4 and ranged from 1.9 to 3.2 and the number of vein grafts per patient averaged 2.03 and ranged from 1.8 to 2.4. Anticoagulants were not used. Both total blood loss through chest tubes and transfusion requirements were recorded for each patient.

Coronary Angiography

Preoperative angiograms were analyzed at each institution by the principal investigators to determine percent stenosis and quality of distal vessels. Ejection fraction was computed from 30° right anterior oblique angiograms.

A graft was considered occluded when the occluded origin was selectively visualized or when the origin could not be visualized and the contrast material failed to flow through the graft into the grafted artery on the aortic root injection. A distal anastomosis was considered occluded if the entire vein graft was occluded at the origin or the contrast agent failed to flow from the vein graft into the grafted artery. For the purpose of this study, graft patency and occlusion refer to patency and occlusion of distal anastomoses.

A randomly selected sample constituting 10% of all preoperative and postoperative angiograms was examined independently by two qualified cardiovascular angiographers at the coordinating center. There was complete agreement among the independent reviewers and the participating institutions regarding the classification of occluded and patent grafts.
Data Management and Statistical Analysis

All data were recorded on specially designed, computerized forms and sent to the coordinating center for review, storage, and analysis. Definitions were established in advance for each variable. The study protocol has been reported in the Registry of Prospective Trials of the International Committee on Haemostasis and Thrombosis; the patient forms and the protocol are available on request. The coordinating center regularly reviewed the otherwise confidential interim results.

The number of patients required for the trial (290 per group) was calculated in advance to detect a 50% reduction in the risk of occlusions, assuming that 25% of the patients in the control group would have one or more occluded grafts and specifying an α error of 5% (two-sided) and a β error of 10%.

The statistical analysis was performed with the BMDP package from the University of Barcelona. Baseline characteristics of treatment groups were compared by χ² test for qualitative variables and a one-way analysis of variance corrected by the Bonferroni test for quantitative variables. The variables that did not show a normal distribution were analyzed by the Kruskal-Wallis test.

Because there is no agreement in previous studies concerning whether patency and occlusion of distal anastomoses within the same patient are dependent events, a test of independence was performed by χ² analysis in which patency and occlusion of distal anastomoses within patients were compared. The results showed that these are dependent events (χ², 1,152; p<0.0001), and therefore the cluster form of analysis is considered the most appropriate. Thus, graft patency data were analyzed by the cluster sampling approach, which assumes that occlusion or patency of distal anastomoses within the same patient are dependent events so patients can be considered to represent clusters of distal anastomoses (see “Appendix”), and by comparison of the proportion of patients with at least one occluded graft.

In addition, a stepwise logistic regression analysis was also applied to patency data; the occlusion or patency of distal anastomoses was considered the dependent variable. Independent variables included both graft- and patient-specific characteristics as well as a dichotomous variable that indicated whether the administered therapy was aspirin, aspirin plus dipyridamole, or placebo. Although this technique assumes that patency or occlusion of grafts in a patient are independent events, it allows for adjustment of possible imbalances of the treatment groups and testing of whether a particular variable contributes with a significant amount of information toward predicting graft occlusion, while also adjusting for the effect of other variables in the model. This type of analysis allows calculation of the odds ratio, an estimate of the risk of occlusion of grafts in each treatment group relative to that in the placebo group while all other covariates remain constant.

Results

Patient Data

Of the 1,647 eligible patients, 1,112 were randomized. Patients included in the study were comparable to those excluded with regard to most of the recorded variables; however, excluded patients had a significantly higher prevalence of peripheral vascular disease (17.6% versus 12.6%, p<0.005), rest angina (31.1% versus 21.7%, p<0.0001), angina during the 48 hours before surgery (29.9% versus 23.6%, p<0.005), and history of congestive heart failure (7.7% versus 3.2%, p<0.001).

Of the 1,112 patients, 927 underwent postoperative vein graft angiography; 185 patients were excluded because of death (27), patient refusal (50), drug intolerance (26), complications (69), and protocol deviation (13). Table 1 summarizes the baseline characteristics of the study population. There were no statistically significant differences with respect to any of the studied variables (including clinical, angiographic, and surgical characteristics) among the treatment groups. There also were no differences in the timing of postoperative angiography relative to surgery.

Occlusion rate per graft. The vein graft occlusion rate (distal anastomoses) was 18% for the placebo group compared with 14.2% and 12.9% for the aspirin and aspirin plus dipyridamole groups, respectively. Differences between aspirin plus dipyridamole and placebo groups achieved statistical significance (p=0.017). The comparison between aspirin and placebo groups showed a trend toward significance with a p value of 0.058 (Figure 1 and Table 2). Table 2 also displays the results of subgroup analysis. There were no statistically significant differences between the active treatment groups regarding graft patency.

Univariate analysis showed that occluded grafts were more frequent when they had been implanted in arteries with smaller diameters (p<0.0001), with poorer distal beds (p<0.0001), or in the left circumflex artery (p<0.0001) compared with open grafts. Sequential grafts were also less frequently occluded than simple grafts.

Multivariate analysis selected these four variables as well as antiplatelet treatment as independent predictors of early patency (Table 3). In comparison with placebo, the odds ratio for the aspirin group was 0.73 (95% confidence limit [CL] range, 0.54–0.99) and for the aspirin plus dipyridamole group was 0.59 (95% CL range, 0.43–0.82). Considering that distal anastomoses within the same patient do not act independently, the CLs of the odds ratios of both groups might be slightly larger.

Occlusion rate per patient. The proportion of patients with at least one occluded graft was significantly lower in the group of patients receiving aspirin
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=371)</th>
<th>Aspirin (n=373)</th>
<th>Aspirin + dipyridamole (n=368)</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>56±8.4</td>
<td>56.1±8.2</td>
<td>57.0±8.0</td>
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<td>Weight (kg)</td>
<td>73.1±10</td>
<td>73.8±9.9</td>
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<td>Height (cm)</td>
<td>166.5±8.3</td>
<td>165.8±8</td>
<td>165.5±8.1</td>
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<td>Cholesterol (mg/100 ml)</td>
<td>232.3±49.0</td>
<td>232.06±46.2</td>
<td>231.6±46.3</td>
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<tr>
<td>Length of symptoms (mo)</td>
<td>34.7±42.9</td>
<td>39.8±43.4</td>
<td>36.6±43.4</td>
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<td>LVEDP (mm Hg)</td>
<td>12.9±6</td>
<td>13.9±6.4</td>
<td>12.7±6.2</td>
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<td>Males (%)</td>
<td>90</td>
<td>89.3</td>
<td>90.1</td>
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<td>Hypertension (%)</td>
<td>38.3</td>
<td>39.8</td>
<td>39.1</td>
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<td>Diabetes (%)</td>
<td>18.1</td>
<td>18.7</td>
<td>19.8</td>
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<td>Obesity* (%)</td>
<td>30.8</td>
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<td>Vascular peripheral disease (%)</td>
<td>12.2</td>
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<td>Previous myocardial infarction (%)</td>
<td>60.5</td>
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<td>51.5</td>
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<td>Angina &lt;48 hr before surgery (%)</td>
<td>24.9</td>
<td>23.4</td>
<td>22.5</td>
</tr>
<tr>
<td>Rest angina (%)</td>
<td>20.3</td>
<td>21.5</td>
<td>23.3</td>
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<td>Congestive heart failure (%)</td>
<td>4.2</td>
<td>2.7</td>
<td>2.6</td>
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<td>Complete revascularization (%)</td>
<td>65.8</td>
<td>64.4</td>
<td>62.5</td>
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<td>Smoking (%)</td>
<td>67.7</td>
<td>65.3</td>
<td>68.6</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>56.1±12.9</td>
<td>55.5±13.3</td>
<td>57.5±12.6</td>
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<td>Three-vessel disease (%)</td>
<td>72.1</td>
<td>72.9</td>
<td>69.1</td>
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<td>Grafts to (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>280</td>
<td>294</td>
<td>269</td>
</tr>
<tr>
<td>Cx</td>
<td>266</td>
<td>252</td>
<td>268</td>
</tr>
<tr>
<td>RCA</td>
<td>204</td>
<td>199</td>
<td>205</td>
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<tr>
<td>Diameter of recipient artery (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1.0 mm</td>
<td>7.6</td>
<td>8.1</td>
<td>8.5</td>
</tr>
<tr>
<td>1.1–1.5 mm</td>
<td>52.5</td>
<td>54.3</td>
<td>50.5</td>
</tr>
<tr>
<td>&gt;1.5 mm</td>
<td>39.9</td>
<td>37.6</td>
<td>41</td>
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<tr>
<td>Good quality distal bed (%)</td>
<td>76.4</td>
<td>77.2</td>
<td>78.9</td>
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<tr>
<td>Distal anastomoses per patient (n)</td>
<td>2.4±0.09</td>
<td>2.45±1</td>
<td>2.4±1.0</td>
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<tr>
<td>Grafts per patient (n)</td>
<td>2.0±0.8</td>
<td>2.0±0.7</td>
<td>2.0±0.7</td>
</tr>
<tr>
<td>Sequential grafts per patient (n)</td>
<td>0.7±0.7</td>
<td>0.7±0.8</td>
<td>0.8±0.8</td>
</tr>
<tr>
<td>Time to graft angiography (days)</td>
<td>10.7±3.6</td>
<td>10.4±3.5</td>
<td>10.3±3.3</td>
</tr>
</tbody>
</table>

All differences are without statistical significance. *Weight 14% or more greater than that considered ideal for a given height.

LVEDP, left ventricular end-diastolic pressure; LAD, left anterior descending coronary artery; Cx, left circumflex artery; RCA, right coronary artery.

plus dipyridamole than in the placebo group (24.3% versus 33%, p<0.01). Conversely, neither differences between the aspirin and the placebo groups nor differences between both groups of active treatment achieved statistical significance (Figure 2).

Complications and drug intolerance. Blood loss through the chest tube was slightly but significantly (p=0.04) higher in the aspirin plus dipyridamole group (713±456 ml) than in the other two groups (placebo, 670±437 ml; aspirin, 629±337 ml). There were no differences among the three groups in total blood transfused (1,247±801, 1,174±681, and 1,265±798 ml, respectively) or reoperation rate (4.5%, 3.3%, and 4%, respectively).

The intraoperative mortality rate was 2.3%. Postoperative hospital mortality (randomization to 28

![Figure 1. Bar graph of percent of occluded grafts (distal anastomoses) in each treatment group. By cluster analysis, p value for the comparisons between aspirin and placebo was 0.058 and between aspirin plus dipyridamole and placebo groups was 0.017.](http://circ.ahajournals.org/)}
days) rates were similar among the three groups: 1.3% for placebo, 3.4% for aspirin, and 2.4% for aspirin plus dipyridamole. Drug intolerance occurred in 48 patients and was severe enough to discontinue treatment in 26; benign gastrointestinal side effects were slightly more frequent among patients receiving active treatment than among those receiving placebo. Complications occurred in 82 patients and were the cause of dropout for 69 patients (Table 4).

**Discussion**

The results of this investigation demonstrate that a therapeutic regimen consisting of dipyridamole beginning 2 days before surgery and followed 6 hours after surgery by low-dose aspirin plus dipyridamole improves early aortocoronary vein graft patency compared with preoperative antiplatelet treatment alone. It has been shown that endothelial loss or damage is a characteristic finding in the saphenous vein surgically prepared for coronary artery bypass grafting; as a consequence, platelet deposition begins as soon as the flow through the graft is restored. Clinical experience confirms this experimental data; it has also demonstrated that an antiplatelet treatment should be initiated soon after surgery to improve the graft patency. It has been suggested that a preoperative treatment with dipyridamole in patients undergoing elective coronary bypass surgery contributes to the reduction of early graft occlusion. Furthermore, preoperative dipyridamole reduces myocardial platelet deposition and cardiac thromboxane release during reperfusion and is thought to reduce ischemic injury. The present investigation demonstrates that antiplatelet treatment should be maintained after surgery to prevent early bypass occlusion because the thrombotic process continues for several weeks after surgery.

The rationale for the use of low-dose aspirin relies on previous experimental work showing that aspirin effects on platelets and vascular endothelium are dose dependent; thus, while aspirin inhibits both the formation of thromboxane A2 in platelets and the synthesis of prostacyclin in endothelial cells, the former effect is achieved at lower drug concentra-

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**Table 2. Frequency of Vein Graft Occlusion**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Aspirin</th>
<th>Aspirin + dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grafts (n)</td>
<td>750</td>
<td>745</td>
<td>742</td>
</tr>
<tr>
<td>Occluded grafts (distal anastomoses) (n) (%)</td>
<td>135 (18)</td>
<td>106 (14)*</td>
<td>96 (12.9)†</td>
</tr>
<tr>
<td>Sequential grafts (n) (%)</td>
<td>28/203 (13.8)</td>
<td>24/215 (11.2)</td>
<td>15/217 (6.9)</td>
</tr>
<tr>
<td>Grafted artery (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>40/280 (14.3)</td>
<td>31/294 (10.5)</td>
<td>17/269 (6.3)</td>
</tr>
<tr>
<td>Cx</td>
<td>57/266 (21.4)</td>
<td>44/252 (17.4)</td>
<td>50/268 (18.6)</td>
</tr>
<tr>
<td>RCA</td>
<td>38/204 (18.6)</td>
<td>31/199 (15.6)</td>
<td>29/205 (14.1)</td>
</tr>
<tr>
<td>Lumen diameter (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1.0 mm</td>
<td>25/51 (49)</td>
<td>20/55 (36.3)</td>
<td>18/55 (32.7)</td>
</tr>
<tr>
<td>1.1–1.5 mm</td>
<td>59/352 (15.1)</td>
<td>50/369 (13.1)</td>
<td>41/325 (12.6)</td>
</tr>
<tr>
<td>&gt;1.5 mm</td>
<td>35/268 (13.1)</td>
<td>26/256 (10.2)</td>
<td>19/264 (7.2)</td>
</tr>
<tr>
<td>Distal bed (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>85/550 (15.4)</td>
<td>72/546 (13.2)</td>
<td>57/563 (11.2)</td>
</tr>
<tr>
<td>Poor</td>
<td>43/170 (25.3)</td>
<td>33/161 (20.5)</td>
<td>37/151 (24.5)</td>
</tr>
</tbody>
</table>

*p=0.058, †p=0.017 compared with placebo.

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**Table 3. Logistic Regression Analysis of Data for All Grafts Comparing Groups Receiving Placebo, Aspirin, and Aspirin Plus Dipyridamole, Adjusting for Other Four Significant Covariates and Assuming the Independence of Anastomosis Response Within Each Patient**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>p</th>
<th>Odds ratio* (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiaggregant treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>-0.31148</td>
<td>&lt;0.005</td>
<td>0.73 (0.54–0.99)</td>
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<tr>
<td>Aspirin + dipyridamole</td>
<td>-0.51993</td>
<td></td>
<td>0.59 (0.43–0.82)</td>
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<tr>
<td>Diameter of distal vessel</td>
<td>0.79428</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>Angiographic quality of distal vessel</td>
<td>0.41409</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>Sequential graft</td>
<td>-0.61479</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Grafted artery</td>
<td>-0.70015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CL, confidence limits.

*Ratio of odds of occlusion (for treatment) compared with placebo group.
Inhibition of platelet aggregation and prolongation of bleeding time at doses as low as 20–40 mg/day have been reported in healthy subjects as well as in patients who survived an acute myocardial infarction. In both studies, altered platelet function occurred without concomitant changes in urinary 6-keto-prostaglandin and prostaglandin F₁α excretion. Hence, with the use of low-dose aspirin, it appears to be possible to inhibit the production of thromboxane A₂, a potent aggregant factor, without affecting the beneficial actions of endothelium prostacyclin. Furthermore, with the use of lower doses of aspirin, a reduction in the rate of undesirable effects, particularly gastrointestinal complications, can be expected because the production of these side effects has been associated with the aspirin reduction of prostaglandin I₁ in the gastric mucosa.

The efficacy of the aspirin plus dipyridamole treatment used in the present study was evident, regardless of the type of statistical analysis performed (i.e., cluster analysis or considering the number of patients with occluded grafts). Furthermore, the logistic regression analysis selected the antiaggregant treatment as an independent predictor of early graft patency. These results are comparable to those previously observed in several trials using larger doses of aspirin in combination with dipyridamole. In 1982, Chesebro et al reported the first large trial in which antiplatelet treatment was started before surgery. These authors demonstrate that compared with placebo, an antiaggregant treatment combining 325 mg aspirin plus 75 mg dipyridamole three times a day reduced the incidence of early graft occlusion from 13% to 3%. More recently, the Veterans Administration Cooperative Study has demonstrated that a regimen containing 325 mg aspirin plus 75 mg t.i.d. dipyridamole improves short-term aortocoronary bypass patency, reducing graft occlusion from 14.8% to 8.1%. Similar results have been obtained using other antiplatelet drugs, such as sulfinpyrazone and trifusul.

Conversely, the administration of aspirin alone at a dose of 50 mg t.i.d. had a less pronounced effect on graft patency. The patency rate of distal anastomoses showed a trend toward significance among patients receiving aspirin compared with those receiving placebo (p=0.058). When comparing the proportion of patients with occluded grafts in each group, the differences did not achieve statistical significance. For any type of analysis and for any subgroup of patients, the effect of aspirin administered alone was intermediate between that of placebo and that of aspirin plus dipyridamole (Table 2). However, the differences between both groups receiving active treatment were small and did not achieve statistical significance. These data, along with the results of multivariate analysis (Table 3), suggest that at the doses used in the present investigation, aspirin has some effect on early graft patency; this effect is modest and can be potentiated by the addition of dipyridamole. These results differ from those obtained by Lorenz et al, who found that 100 mg aspirin was effective in preventing graft occlusion 4 months after aortocoronary bypass surgery. However,
in this series, only 46 patients of the 60 initially randomized had angiography 4 months after surgery, and the proportion of patients with occluded grafts in the placebo group (62%) was unusually high. On the contrary, larger doses of aspirin, such as those used in the Veterans Administration Cooperative Study, cause a significant reduction in graft occlusion, from 14.8% to 6.5%.2

Complications and Side Effects

As expected, the association of both antiaggregant drugs caused a small but significant increase in the chest tube blood loss. However, there were no differences among the three groups in either the reoperation rate or the number of bleeding complications. Although conclusions cannot be drawn by comparing different studies in which the methodologies and the surgical techniques can vary widely, it is worthwhile to point out that the mean chest tube drainage over 24 hours in patients receiving aspirin (629 ml) and aspirin plus dipyridamole (713 ml) in our series compares favorably with that observed in the Mayo Clinic study of patients receiving aspirin plus dipyridamole (613 ml in 12 hours)1 and that of patients in the Veterans Administration Cooperative Study (1,000 ml in 35 hours).2 These differences may well be explained by the use of lower doses of aspirin in the present study as well as by the fact that only dipyridamole was administered preoperatively to avoid the excessive bleeding associated with aspirin.

Study Characteristics and Limitations

The present study is the largest published trial comparing antiplatelet drug regimens for the prevention of early aortocoronary bypass occlusion. The large number of patients included in the study and the type of randomization allowed for excellent comparability of the treatment groups, not only of patient baseline variables but also of most of the graft characteristics known to be independent risk factors for occlusion. Thus, the diameter of the distal vessel, the quality of the distal arterial bed, the recipient artery, and the type of graft were evenly distributed among the three groups.

Female patients constituted 11% of the study population, a percentage similar to that of the Mayo Clinic series; some studies excluded women.2 Sixty percent of all grafted arteries in the present series had luminal diameters less than 1.5 mm, a far greater proportion than the 26–29% observed in other trials.1,2 Ethnic variations in body size may account for these differences. All of these factors may also explain the slightly lower overall graft patency compared with previous studies.1,2

There are some potential limitations of our study. Because the protocol called for a complete 48-hour period of preoperative treatment with dipyridamole, patients undergoing emergency surgery were not included. Although this obviously determined selection of patients, randomization was carried out once the surgical procedure had been accomplished and therefore could not determine imbalance among the groups. A high proportion of patients (83%) entering the study were restudied regardless of symptoms. The number as well as the causes of excluded patients were equally distributed among the three groups, making a selection bias unlikely. In any case, our final population represents 57% of the patients undergoing coronary artery bypass grafting in the six participating institutions during the time frame of the study, a figure that compares favorably with other major trials (22% and 15%).1,2

Finally, in contrast with other series, vein graft angiograms were obtained in all patients within the first month after surgery. Thus, the observed beneficial effect of antiplatelet therapy depends on the ability of these drugs to prevent both the deposition of platelets and the thrombosis that occur soon after surgery. However, recently published data from the Veterans Administration Cooperative Study21 suggest that the major benefit of antiplatelet treatment is achieved soon after surgery. In that study, the frequency of new occlusions in the patients with patent grafts at 9 days was not reduced by aspirin administration during the subsequent year.21 These results differ from those recently published by Pfisterer et al22 showing that withdrawal of active treatment after 3 months seems to lead to an increased rate of graft occlusion. Thus, long-term antiaggregant treatment after saphenous vein coronary artery bypass grafting may be justified.

Clinical Implications

Coronary artery bypass surgery is the most frequently performed cardiac surgical procedure. Internal mammary artery grafts have been considered the preferred graft because they have excellent long-term patency rates.23 However, widespread use of saphenous vein continues because of the limitations in the use of the internal mammary, such as the excessive time needed for dissection and the fact that in patients with multiple-vessel disease there is insufficient material for grafting. In this regard, a recent British survey reported by Angelini and Newby24 has shown that approximately two thirds of the grafts to the left anterior descending coronary artery were made with the internal mammary artery but only 4% of the grafts to the circumflex or right coronary arteries were so made. Therefore, improving saphenous vein graft patency rates remains a major challenge.

The results of multivariate analysis show that the size of the grafted artery, the quality of the distal vessel, and the type of graft are the main determinants of early patency, suggesting that the adequate selection of both patients and surgical technique are of paramount importance in determining the surgical outcome. However, this prospective randomized trial also demonstrates that an antiplatelet drug regimen consisting of the combination of low-dose aspirin plus dipyridamole started soon after surgery safely improves early saphenous vein graft patency. It also
shows that preoperative treatment with dipyridamole without postoperative antiplatelet drugs is not sufficient to avoid the early thrombotic process in the graft.

Although a direct comparison between drug treatments, including large- and low-dose aspirin, has not yet been performed, the results of the present investigation provide the rationale for such a trial and suggest the use of 100 mg q.i.d. dipyridamole for 2 days before surgery followed by 50 mg aspirin plus 75 mg t.i.d. dipyridamole 6 hours after surgery. This drug regimen provides a reasonable compromise between effectiveness and safety.

Appendix
Cluster Sampling Estimation of Percentage of Occluded Distal Anastomoses and Variance in Each Treatment Group

The ratio estimate applied to cluster sampling is a statistical analysis used to handle the lack of independence observed in the number of occluded distal anastomoses within the same patient. In this sense, patients enrolled in the study are considered to represent clusters of distal anastomoses.

With this method, the percentage of occluded distal anastomoses in each treatment group is calculated as usual, the difference being in the estimation of the variance of this proportion (ratio estimate). The latter tends to be slightly larger than the variance under the assumption that the occlusion of distal anastomoses within the same patient are independent events. This variance is estimated as:

\[
V(p) = \frac{1}{Nm^2} \times \frac{\sum_{i=1}^{n} (a_i - pm)^2}{n-1}
\]

where \(V\) is variance, \(p\) is the percentage of occluded distal anastomoses, \(N\) is the total number of distal anastomoses in the sample, \(m\) is the mean number of distal anastomoses in the patients, \(a_i\) is the number of occluded distal anastomoses in each individual patient, \(m_i\) is the total number of distal anastomoses in each individual patient, and \(n\) is the total number of patients.

Because of this larger variance, the cluster sampling method is more conservative than the standard \(\chi^2\) test used when distal anastomoses within patients are assumed to act independent of patency or occlusion. Consequently, this method tends to find fewer statistical significances when comparing between-group differences than the standard \(\chi^2\) test.

Spanish Group for Aortocoronary Bypass Follow-up Participants

Hospital Gregorio Marañón, Madrid: Principal Investigator, M. Gómez-Recio, MD; J. Duarte, MD.

Hospital Virgen del Rocio, Sevilla: Principal Investigator, J.A. Fournier, MD; J.A.P. Cortacero, MD, L. Castillón, MD.

Clínica Universitaria, Pamplona: Principal Investigator, E. Alegría, MD; R. Hidalgo, MD, F. Malpartida, MD, J. Arriola, MD, R. Llorens, MD, R. Arcas, MD, D. Martínez Caro, MD, J. Calabuig, MD.

Hospital Virgen del Pino, Las Palmas: Principal Investigator, I. Coello, MD; A. Medina, MD, E. Olaya, MD, M. Trillo, MD, A. Bethencourt, MD, E. Hernández, MD, J. Quintana, MD, E. Pardo, MD.

Hospital Clinic, Barcelona: Principal Investigator, G. Oller, MD; M. Cardona, MD, A. Betriu, MD, J.L. Pomar, MD, M. Matas, RN.

Hospital Marqués de Valdecilla, Santander: Principal Investigator, A. Pajarón, MD; J. Ruano, MD, T. Colman, MD, J.L.M. Ubago, MD, A. Figueroa, MD.

Coordinating Center
University of Barcelona School of Medicine: G. Sanz, MD.

Executive Committee
Chairman, G. Sanz, MD; A. Pajarón, MD, E. Alegría, MD, M. Cardona, MD, J.A. Fournier, MD, M. Gómez-Recio, MD, A. Medina, MD.

Angiography Review Committee
Hospital Valle de Hebrón, Barcelona, J. Angel, MD; Hospital de Bellvitge, Barcelona, E. Esplugas, MD.

Statistical Analysis
University of Barcelona School of Medicine, X. Bosch, MD.

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References


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