Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study*

STEVEN GOLDMAN, M.D., JACK COPELAND, M.D., THOMAS MORITZ, M.S., WILLIAM HENDERSON, PH.D., KAREN ZADINA, R.N., M.A., THERON OVITT, M.D., JAMES DOHERTY, M.D., RAYMOND READ, M.D., ELLIOT CHESLER, M.D., Y. SAKO, M.D., PH.D., LARYENTH LANCASTER, M.D., ROBERT EMERY, M.D., G. V. R. K. SHARMA, M.D., MIGUEL JOSA, M.D., IVAN PACOLD, M.D., ALVARO MONToya, M.D., DINESHKANT PARikh, M.D., GULSHAN SETHI, M.D., JOHN HOLT, M.D., JAMES KIRKlin, M.D., RALPH SHABETAI, M.D., WILLIAM MOORES, M.D., JANERIO ARLDRIDGE, M.D., ZAKI MASUD, M.D., HENRY DEMOTS, M.D., STORM FLOten, M.D., CLAIR HAAKENSON, R.PH., M.S., and LAURENCE A. HARKER, M.D.

ABSTRACT To determine whether specific antiplatelet therapies improved vein graft patency after coronary artery bypass grafting (CABG) we compared (1) aspirin, 325 mg daily, (2) aspirin, 325 mg three times daily, (3) aspirin plus dipyridamole (325 mg and 75 mg, respectively, three times daily), (4) sulfinpyrazone (267 mg three times daily), and (5) placebo (three times daily). Therapy, except aspirin, was started 48 hr before CABG. When aspirin was a treatment, one 325 mg dose was given 12 hr before surgery and therapy was maintained thereafter according to the assigned regimen. Angiographic graft patency data were obtained within 60 days of surgery. Analysis of early graft patency in 555 patients (1781 grafts), revealed the following graft patency rates: aspirin daily, 93.5%; aspirin three times daily, 92.3%; aspirin and dipyridamole, 91.9%; and sulfinpyrazone, 90.2%. All aspirin-containing therapeutic regimens improved (p<.05) graft patency compared with placebo (85.2%). Chest tube drainage measured within the first 35 hr after CABG revealed that the median loss with aspirin daily (965 ml), aspirin three times daily (1175 ml), and aspirin plus dipyridamole (1000 ml) exceeded (p<.02) that with placebo (805 ml), while median loss with sulfinpyrazone (775 ml) did not. The reoperation rate was greater (p<.01) in all the treatment groups that received aspirin (6.5%) compared with the two nonaspirin groups (1.7%). Overall operative mortality was 2.3%, without significant differences among treatment groups. Transient renal insufficiency occurred in 5.3% of patients taking sulfinpyrazone. Thus, early vein graft patency was improved after CABG with all aspirin-containing drug regimens. However, aspirin also increased blood loss and the rate of reoperation after CABG.

times daily, and (5) placebo. The study was designed to compare therapies in men both early (7 to 10 days) and late (1 year) after operation. The results, based on data from early postoperative angiograms obtained within 60 days of surgery, are presented in this report.

Methods

Study population. This study, organized by the Cooperative Studies Program of the Veterans Administration Medical Research Service, consisted of data from 772 male patients entered into the study at 12 participating hospitals from June 1983 to July 1986. The following exclusion criteria were used: preoperative decision to perform only internal mammary grafting, previous coronary artery bypass or other cardiac surgery, recent history (1 year) of documented gastrointestinal ulcer disease, history of bleeding disorder, thromboembolic disease that required treatment with anticoagulant therapy, presence of functionally significant valvular heart disease requiring surgery, allergy to any of the potentially prescribed medications, female sex, allergy to contrast material, chronic disease requiring study drugs or prostaglandin inhibitor drugs, and evidence of hepatic dysfunction defined by an elevated prothrombin time. In addition to these exclusion criteria, all antiplatelet and nonsteroidal antiinflammatory agents were discontinued 7 days before entry into the study.

These 772 patients represented 20.9% of all the patients undergoing elective coronary artery surgery at these institutions during the study period. Of the 1464 patients eligible according to the protocol, 772 (52.7%) patients consented and were enrolled during this period. Of the 3688 patients undergoing CABG at the 12 institutions, the predominant reason for eliminating 2224 patients were emergency operations and scheduling problems that precluded the administration of study medications for 48 hr preoperatively, other diseases requiring the long-term use of aspirin or other prostaglandin inhibitors, previous CABG, and need for concomitant valve replacement.

After the patients had signed the consent form to participate, randomization took place at each institution. Patients were stratified at each hospital to ensure that comparable numbers of patients with single-, double-, and triple-vessel disease were included in each treatment group at individual institutions. This stratification was based on the interpretation of the preoperative angiograms. Stratification was not performed for individual surgeons at each institution.

Treatment regimens. Therapy, except that with aspirin, was started 48 hr before surgery. When aspirin was one of the active treatment regimens, 325 mg was received as a single dose 12 hr preoperatively. Thereafter, aspirin dosing was carried out according to the assigned regimen. The patients were given their first dose of postoperative medication 6 hr after surgery by a nasogastric tube, which was then clamped for 1 1/2 hr. Therapy was continued by nasogastric tube every 8 hr until regular oral dosing could be substituted. The dipyridamole and matching placebo were provided by Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, the sulfinpyrazone and matching placebo were supplied by Ciba Pharmaceutical Co., Summit, NJ, and the aspirin and matching placebo were provided by Glenbrook Laboratories, New York. Disalcid (salsalate) was supplied by Riker Laboratories, St. Paul, MN.

All medication was provided in individualized patient kits, each containing a 12-month supply of blister cards. The initial card was designed to accommodate the perioperative dosing schedule and all cards were identical with this exception.

Compliance was assessed by pill counts at 2 and 6 weeks postoperatively and then at 3 month intervals. Additional compliance testing for aspirin involved measurements of urine salicylates by a qualitative colorimetric method. The presence of salicylates in the urine indicated that the patient had taken aspirin within the last 12 hr. Compliance testing for sulfinpyrazone was carried out by measuring serum uric acid levels periodically at a central laboratory. Because of the uricosuric effect of sulfinpyrazone, a reduction in serum uric acid compared with the baseline value was interpreted as evidence of compliance. To discourage patients from taking medications that might modify platelet activity, a "patient drug checklist" was given to each patient. Each patient was instructed to refer to this list before taking any over-the-counter preparations. Acetaminophen or salsalate were provided for use as analgesics when needed. All patients were seen at 3 month intervals by both their physicians and data coordinators.

Surgery. Saphenous vein CABG was carried out by the usual protocol for each of the study institutions. At the beginning of the study, the surgeons were encouraged to use single-vein grafts with one distal anastomotic site whenever possible. When sequential grafts were used, the average number of anastomotic sites per graft was 2.2 in all but the aspirin treatment group, in which it was 2.3. No circular sequential grafts were used. While no attempt was made to establish a uniform technique for performing coronary artery bypass surgery, those institutions chosen to participate in the study were selected on the basis of experience and expertise as documented by yearly statistics compiled by the Veterans Administration Central Office. Detailed data forms covering technical aspects of the perfusion, cardiopлегic solutions, time of operation, arrest period, technical considerations regarding vessel and graft size, cardiac function, postoperative support, and bleeding were maintained for each patient.

Angiographic analysis. For the early postoperative angiogram, each aortic anastomosis was selectively engaged and injected. When the origin of a graft was not visualized, an aortic root angiogram was obtained. All angiograms were read at both the participating institution and the central angiographic laboratory. In the central angiographic laboratory, each angiogram was read independently by two cardiovascular radiologists using a cineanalysis system that was developed for this study and included a Vanguard projector and a high-resolution camera to record the images. The images were digitized and the information was entered into an integrated image processor–computer system. Images were then displayed on the integrated memory plane and computer printouts were obtained of vessel margins, stenoses, and calculated percent stenoses. The cine-frames for analysis were selected by the radiologist. By an interactive computer program, images were displayed, processed, and then refilmed for storage in hard copy format. The preoperative angiogram was analyzed with respect to absolute measurement of coronary vessel size, percent stenosis, and size of the distal vessel. All vessels greater than 1 mm in diameter were analyzed and recorded. On the early postoperative angiogram, only the grafts were analyzed. For this analysis, absolute diameters were calculated and stenoses in the graft or at the anastomotic site were recorded. A single-vein graft was defined as patent if the origin was visualized and contrast material was seen to flow through the graft into the distal vessel, either by selective injection or by aortic root angiography. When analyzing sequential or Y grafts, a distal anastomosis (either side-to-side or end-to-end) was defined as patent if the contrast material was seen to flow from the vein graft into the grafted artery. If the graft was occluded at its origin, all associated distal anastomoses were considered occluded. The definition of graft patency was used to refer to the patency of distal anastomoses to avoid confusion when discussing sequential and Y grafts. If there was a difference of opinion regarding patency, the films...
were reviewed and a consensus opinion was reported. The results presented in this report are the early vein graft patency data from the central laboratory.

Statistical analysis. Comparability of treatment groups was tested with use of the chi-square statistic on qualitative variables and the one-way analysis of variance on quantitative variables. Dunnett's statistic was used to compare active treatments with placebo. The data on chest tube drainage and blood replacement products after surgery are not normally distributed and were analyzed by use of the Kruskal-Wallis test. The patency data were analyzed three ways: (1) by comparison of grafts that were occluded, assuming grafts were not independent, (2) by comparison of grafts that were occluded, assuming each graft was independent, and (3) by comparison of the proportion of patients with one or more occluded grafts. Because independence was not assumed in the first analysis, a cluster sampling approach was used. Estimates for the mean and variance of the proportion are presented in the Appendix. The second and third analyses used the binomial formula for estimating the mean and variance of a proportion. We consider the first analysis to be the most appropriate for this type of data since grafts within the same patient do not necessarily act independently. However, the second and third analyses are also included because many of the previous publications on effect of antiplatelet therapy after CABG analyze the data in these ways.

Results

Patient data. The baseline clinical characteristics for the study population are shown in table 1. There were no differences with respect to any of the patient characteristics among the different treatment groups. There were also no differences in baseline clinical characteristics when the patients who underwent postoperative catheterization were compared with those who did not. The data on pack-years of current smokers, serum high-density lipoprotein, and serum triglycerides are presented as median values because they were not normally distributed. The elevated serum triglyceride levels may reflect sampling after an overnight fast as opposed to a 14 hr fast. The study population consisted of 772 patients who were randomized and had coronary artery surgery using vein grafts. Of these, 612 (79.2%) patients underwent catheterization. This report contains the data on the 555 of 772 (71.9%) who underwent their catheterization within 60 days of surgery and whose data were available in the central angiographic laboratory. The median time from surgery to catheterization was 9 days, with a range of 6 to 60. There were no differences in the timing of angiography in relation to surgery among the treatment groups. These patients had 1781 grafts, for an average of 3.2 grafts/patient (table 2). Because of the long-term design of this study, the 57 angiograms that were obtained later than 60 days after surgery will not be ignored but will be included in future analyses.

The postoperative catheterization was not performed in 160 patients because of patient refusal in 111, death during hospitalization in 20, scheduling problems in 11, and postoperative complications in 18. The specific complications were perioperative myocardial infarction in two, cerebral vascular accident in three, deep vein thrombosis in two, pulmonary embolus in one, mediastinitis in one, wound infections in four, renal insufficiency in one, new diagnosis of leukemia in one, mental confusion in two, and urinary tract complications in one.

Graft patency data. The vein graft patency data include the results obtained from 1056 single, 685 sequential, and 40 Y grafts (tables 2 and 3). Data on 149

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline patient characteristics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Aspirin daily</th>
<th>Aspirin tid</th>
<th>Aspirin/dipyridamole</th>
<th>Sulfinpyrazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>153</td>
<td>154</td>
<td>155</td>
<td>162</td>
<td>148</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 7</td>
<td>58 ± 8</td>
<td>59 ± 7</td>
<td>58 ± 8</td>
<td>59 ± 7</td>
</tr>
<tr>
<td>Angina</td>
<td>147</td>
<td>145</td>
<td>138</td>
<td>153</td>
<td>138</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75</td>
<td>73</td>
<td>65</td>
<td>77</td>
<td>68</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>87</td>
<td>86</td>
<td>97</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Past smokers</td>
<td>45</td>
<td>49</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Current smokers (pack-years)</td>
<td>38</td>
<td>40</td>
<td>39</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>223 ± 45</td>
<td>229 ± 50</td>
<td>225 ± 45</td>
<td>226 ± 47</td>
<td>225 ± 45</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>186</td>
<td>192</td>
<td>180</td>
<td>203</td>
<td>183</td>
</tr>
<tr>
<td>Serum HDL (mg/dl)</td>
<td>32</td>
<td>35</td>
<td>33</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Canadian functional class (I–IV)</td>
<td>3.2 ± 0.8</td>
<td>3.2 ± 0.8</td>
<td>3.1 ± 0.9</td>
<td>3.2 ± 0.8</td>
<td>3.2 ± 0.9</td>
</tr>
</tbody>
</table>

Values are absolute numbers for the clinical characteristics and mean ± SD for other variables except pack-years of current smokers, serum triglycerides, and serum HDLS, which are median values. There were no differences with respect to any of these variables among treatment groups.

HDL = high-density lipoprotein.
internal mammary grafts were collected to obtain estimates of patency rates but the internal mammary grafts were not included in the analysis. The vein graft patency rate defined for distal anastomoses in each treatment group was: daily aspirin, 93.5%; aspirin three times daily, 92.3%; aspirin plus dipyridamole, 91.9%; and sulfinpyrazone, 90.2%, compared with the placebo value of 85.2%. By cluster analysis (figure 1), the three aspirin-containing groups had improved graft patency (daily aspirin, p = .008; aspirin three times daily, p = .036; aspirin plus dipyridamole, p = .047), while the group receiving sulfinpyrazone did not (p = .167). By independent analysis, the same trend was observed (daily aspirin, p = .001; aspirin three times daily, p = .005; aspirin plus dipyridamole, p = .008; and sulfinpyrazone, p = .077). When patients were considered as the units of observation (figure 2), 16.8% of the patients in the aspirin once daily group had one or more occluded grafts, compared with 30.3% in the placebo group. This result approaches statistical significance (p = .067). There were no statistically significant differences in the other groups compared with placebo: aspirin three times daily, 19.0% (p = .137); aspirin/dipyridamole, 21.1% (p = .222); and sulfinpyrazone, 22.1% (p = .280).

The diameter of the recipient vessel was an important determinant of vein graft patency (table 4). The average diameter in the recipient vessel was 2.0 mm in all but the aspirin plus dipyridamole group, in which it

### TABLE 2
Frequency of vein graft occlusion according to location and type of graft

<table>
<thead>
<tr>
<th>Location</th>
<th>Placebo</th>
<th>Aspirin daily</th>
<th>Aspirin tid</th>
<th>Aspirin/dipyridamole</th>
<th>Sulfinpyrazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>9.0 (156)</td>
<td>3.4 (147)</td>
<td>7.7 (142)</td>
<td>3.5 (143)</td>
<td>6.8 (133)</td>
</tr>
<tr>
<td>RCA</td>
<td>19.6 (102)</td>
<td>8.3 (96)</td>
<td>3.5 (86)</td>
<td>7.2 (97)</td>
<td>12.5 (88)</td>
</tr>
<tr>
<td>CX</td>
<td>18.3 (126)</td>
<td>8.6 (128)</td>
<td>10.8 (111)</td>
<td>14.3 (119)</td>
<td>11.2 (107)</td>
</tr>
<tr>
<td>Single vein grafts</td>
<td>15.4 (228)</td>
<td>6.5 (216)</td>
<td>8.9 (192)</td>
<td>8.2 (208)</td>
<td>7.5 (212)</td>
</tr>
<tr>
<td>Sequential vein grafts</td>
<td>14.2 (148)</td>
<td>6.7 (149)</td>
<td>6.3 (143)</td>
<td>8.5 (141)</td>
<td>14.4 (104)</td>
</tr>
<tr>
<td>Y grafts</td>
<td>12.5 (8)</td>
<td>0.0 (6)</td>
<td>0.0 (4)</td>
<td>0.0 (10)</td>
<td>8.3 (12)</td>
</tr>
</tbody>
</table>

Values are percent of grafts occluded and in parentheses are the number of distal anastomoses.

LAD = left anterior descending; RCA = right coronary artery; CX = circumflex. Grafts to the diagonal and ramus intermedius are included under LAD. Each distal anastomotic site is counted as a single graft.

*p < .05 active treatment vs placebo.

### TABLE 3
Frequency of vein graft occlusion according to location of single-vein grafts

<table>
<thead>
<tr>
<th>Location</th>
<th>Placebo</th>
<th>Aspirin daily</th>
<th>Aspirin tid</th>
<th>Aspirin/dipyridamole</th>
<th>Sulfinpyrazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>11.5 (78)</td>
<td>2.7 (75)</td>
<td>9.5 (74)</td>
<td>5.7 (70)</td>
<td>3.8 (79)</td>
</tr>
<tr>
<td>RCA</td>
<td>16.2 (74)</td>
<td>8.3 (72)</td>
<td>3.2 (62)</td>
<td>7.2 (69)</td>
<td>7.7 (65)</td>
</tr>
<tr>
<td>CX</td>
<td>18.4 (76)</td>
<td>8.7 (69)</td>
<td>14.3 (56)</td>
<td>11.6 (69)</td>
<td>11.8 (68)</td>
</tr>
</tbody>
</table>

Values are percent of grafts occluded and in parentheses are the number of distal anastomoses.

LAD = left anterior descending; RCA = right coronary artery; CX = circumflex. Grafts to the diagonal and ramus intermedius are included under LAD.

*p < .05 aspirin tid vs placebo.

![FIGURE 1. Percentage of occluded grafts in each treatment group. P = placebo; A1 = aspirin once daily; A3 = aspirin three times daily; A/D = aspirin/dipyridamole; S = sulfinpyrazone. *p < .05 refers to comparison between each treatment group and placebo by cluster analysis. The 95% confidence intervals (CIs) of the differences are: A1 vs P, difference 1.7, 15.0 CI; A3 vs P, difference 7.2%, 13.8 CI; A/D vs P, difference 6.8%, 13.4 CI; S vs P, difference 5.1% (1.6, 11.8 CI).]
was 2.1 mm. In vessels with a diameter of less than 1.5 mm, aspirin daily and aspirin three times daily improved graft patency. In vessels with a diameter between 1.6 and 2.0 mm, there was a beneficial effect of sulfinpyrazone.

Endarterectomies were done in 30 vessels, which represented 1.7% of all distal sites. There were no differences in the incidence of endarterectomies among the treatment groups (placebo, 1.6%; aspirin once daily, 2.4%; aspirin three times daily, 0.9%; aspirin plus dipyridamole three times daily, 2.0%; and sulfinpyrazone, 1.5%). When distal vessels in which endarterectomies were performed were compared with those in which it was not, there were no differences in occlusion rates (10.0% and 9.3%, respectively).

**Blood loss, replacement therapy, and reoperation.** The surgical blood loss data are presented in figure 3. The 35 hr median chest tube drainage in patients receiving aspirin daily (965 ml), aspirin three times daily (1175 ml), and aspirin with dipyridamole (1000 ml) exceeded (p < .02) that in patients on placebo (805 ml), while drainage in patients on sulfinpyrazone (775 ml) did not (p > .05). The combined blood loss in all three aspirin groups (1035 ml) exceeded (p < .001) that in the placebo group. This blood loss was evenly distributed among all the patients in the aspirin groups and was not due to a few patients who bled heavily. There was no change in the overall pattern of blood loss over the course of the study. The median blood loss for all patients varied between 873 and 926 ml for the 3 years of patient accrual.

Compared with placebo, the aspirin groups received more (p < .005) transfusion replacement of red blood cells and platelets. There were no differences among the treatment groups with respect to fresh frozen plasma or whole blood administered.

There were no differences among the treatment groups with regard to operative times or cardiopulmonary bypass times. The reoperation rates for each of the groups were as follows: aspirin daily, 9.3%; aspirin three times daily, 6.3%; aspirin/dipyridamole, 3.9%; sulfinpyrazone, 2.1%; and placebo, 1.3%. The reoperation rate in the three aspirin-containing groups combined exceeded (p < .01) that in the two nonaspirin-containing groups.

The 30 day surgical mortality was 2.3%. There was no difference in mortality among the individual treatment groups and there was no evidence that periopera-

![Graph showing percentage of patients with at least one occluded graft.](image)

**FIGURE 2.** Percentage of patients with at least one occluded graft. P = placebo; A1 = aspirin once daily; A3 = aspirin three times daily; A/D = aspirin/dipyridamole; S = sulfinpyrazone. The 95% confidence intervals of the differences are: A1 vs P, difference 13.4% (−0.2, 27.1 CI); A3 vs P, difference 11.2% (−2.5, 24.9 CI); A/D vs P, difference 9.2% (−4.5, 22.9 CI); S vs P, difference 8.1% (−5.5, 21.9 CI).

<table>
<thead>
<tr>
<th>Vessel diameter (mm)</th>
<th>Placebo</th>
<th>Aspirin daily</th>
<th>Aspirin tid</th>
<th>Aspirin/dipyridamole</th>
<th>Sulfinpyrazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.5</td>
<td>40.0 (110)</td>
<td>15.9 (107)*</td>
<td>17.1 (117)*</td>
<td>26.1 (92)</td>
<td>31.5 (92)</td>
</tr>
<tr>
<td>1.6–2.0</td>
<td>12.0 (100)</td>
<td>4.8 (105)</td>
<td>4.2 (95)</td>
<td>4.2 (118)</td>
<td>2.1 (96)*</td>
</tr>
<tr>
<td>2.1–2.5</td>
<td>0.9 (107)</td>
<td>1.0 (97)</td>
<td>2.7 (73)</td>
<td>0.0 (79)</td>
<td>1.2 (83)</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>0.0 (67)</td>
<td>1.6 (62)</td>
<td>0.0 (53)</td>
<td>0.0 (70)</td>
<td>0.0 (57)</td>
</tr>
</tbody>
</table>

Values are percent of grafts occluded and in parentheses are the number of distal anastomoses.

*Different from placebo at p < .001.

*Different from placebo at p < .02.
tive bleeding caused the death of any patient. Specifically, there were no patients in whom excessive bleeding was either the immediate cause of death or contributed to death.

Complications. Complications occurred in 27 patients during the early postoperative angiogram. Ventricular fibrillation requiring direct-current countershock occurred in eight patients, cerebral vascular accident in one, uneventful iatrogenic aortic dissection of a graft in one, traumatic dissection of a graft in one, femoral artery embolus in one, and protamine reaction in two. The other complications were minor and did not require treatment or prolong the hospitalization. There were no deaths or permanent sequelae resulting from these postoperative catheterizations.

One major drug complication was the transient renal failure attributed to sulfinpyrazone. There were 10 instances of early increases in blood urea nitrogen and serum creatinine. Nine of these patients were taking sulfinpyrazone and one patient was in the aspirin/dipyridamole group. In each case, the impairment of renal function was noted before the patient was taken to the operating room, the medication was permanently discontinued, and the surgery was postponed until a later date. All patients recovered and nine patients underwent elective coronary artery bypass surgery and had normal blood urea nitrogen and serum creatinine levels at the time of surgery and postoperatively. The tenth patient refused surgery.

Compliance. When patient compliance within 60 days of surgery was assessed by pill counts, it was found that 85% of the study medications were taken. There were no differences among treatment regimens. The following percentages of patients had detectable urine salicylates at the time of the catheterization: aspirin daily, 66%; aspirin three times daily, 92%; aspirin with dipyridamole, 86%; sulfinpyrazone, 14%; and placebo, 20%. Only in the aspirin groups did this represent a significant increase over baseline values (p<.001). Serum uric acid levels in the sulfinpyrazone group decreased from 5.9 ± 1.7 mg/dl before beginning study drug to 2.6 ± 1.2 mg/dl (p<.001) at the time of catheterization. Serum uric acid levels in the three aspirin and placebo groups combined did not change between initiation of study drug (6.6 ± 2.2 mg/dl) and the time of catheterization (6.2 ± 1.7 mg/dl).

Discussion

These results demonstrate that specific antiplatelet therapy with 325 mg aspirin daily, 325 mg aspirin three times daily, and aspirin plus dipyridamole (325 and 75 mg three times daily, respectively) improved early graft patency to a comparable extent after coronary artery bypass surgery. Dipyridamole and sulfinpyrazone were started 2 days before surgery, and aspirin was given 12 hr before surgery. All treatments were resumed 6 hr after surgery. Each of the aspirin-containing preoperative treatment regimens increased the frequency of reoperation and the requirements for transfusion of red blood cells and platelets. Chest tube drainage was also increased in patients receiving aspirin.

The present results are in accord with previous studies reporting improved early graft patency when antiplatelet therapy is started before surgery and then continued in the immediate postoperative period. The major benefit appears to occur when vein grafts are placed into smaller diameter vessels. The difference between our study and that from the Mayo Clinic is that we tested three different aspirin-containing therapies and they tested only the combination of aspirin and dipyridamole. We found that there was no additional benefit when dipyridamole was added to aspirin and that aspirin once a day was as effective as aspirin three times daily.

The discrepancy between our results and those of studies that showed little or no improvement in patency may be explained by the delayed onset of therapy in

FIGURE 3. Blood loss data obtained from 35 hr postoperative chest tube drainage. Values are medians. P = placebo; A1 = aspirin once daily; A3 = aspirin three times daily; A/D = aspirin/dipyridamole; S = sulfinpyrazone. *p<.02 refers to comparison between each treatment group and placebo.
those trials for several days after operation. Since these results have been interpreted to indicate that early graft occlusion is caused by thrombosis in the immediate perioperative period, we began therapy before surgery to ensure the presence of adequate early antiplatelet activity when thrombotic risk was greatest. However, neither our results nor those from the Mayo Clinic study prove that preoperative treatment is necessary since that specific hypothesis was not directly tested. It is of interest to note that cardiopulmonary bypass causes transient platelet dysfunction secondary to oxygenator-mediated activation of platelets and consequent platelet refractoriness. It is possible that this transient platelet dysfunction during bypass surgery may be sufficient to prevent thrombosis for several hours after operation. The actual benefit from treatment regimens in the present report and the Mayo Clinic study may be due to the presence of active therapy early (6 hr) after surgery, with maintenance thereafter. This possibility is consistent with previous reports in which postoperative antiplatelet therapy was more effective if begun within 24 hr after surgery than when started later.

The present study demonstrates that aspirin increased measured blood loss and increased the transfusion requirements of red blood cells and platelets. Moreover, there was an increased frequency of reoperation in all aspirin groups. We do not have an explanation for why there was a difference in the reoperation rates in the aspirin three times daily and aspirin daily groups because each group received the same treatment (325 mg aspirin) before surgery.

Our study was not designed to examine the effects of antiplatelet therapy on internal mammary graft patency. Enthusiasm has increased recently for the internal mammary artery as a graft because it is believed to have a higher long-term patency rate than the vein graft. This conclusion, however, has not been examined in a controlled prospective study. If the internal mammary had been used once in every patient in the present study, there would still have been at least two vein grafts in each case. Thus, increased use of the internal mammary artery does not obviate the use of saphenous vein grafts.

The statistical analysis used in this study deserves comment. The traditional method of analysis in previous studies examining the effects of antiplatelet agents on graft patency assumed that grafts within patients were independent and that the patency rate was not related to any particular patient characteristic. Since that hypothesis has never been tested, we analyzed the data three ways: (1) using a cluster sampling approach in which all the grafts within each patient were grouped together, (2) assuming the grafts were independent, and (3) comparing the proportion of patients manifesting any occluded grafts. A more detailed description of the statistical analysis, including evidence of dependency among grafts, is contained in the Appendix.

This investigation has shown that early graft patency is comparably improved by any one of the three aspirin-containing regimens used in this study. Since there was similar improvement in graft patency with all these treatments we were unable to determine which regimen was most effective. Thus, the optimum choice among these regimens is not clear at present. Since transient renal failure is associated with sulfipyrazone therapy, we believe that it should not be used despite its possible benefit with regard to graft patency. The importance of including dipyridamole, either preoperatively or postoperatively, remains to be established. Moreover, because we observed a modest increase in blood loss and an increased incidence of reoperation in all three aspirin groups, many clinicians may not want to use even a single preoperative dose of aspirin. In this regard, it may be that the administration of aspirin within a few hours after operation with maintenance of dosing thereafter might produce the same benefit on graft patency without bleeding complications.

In view of the previous reports showing that preoperative dipyridamole (100 mg daily for 2 days) followed by postoperative aspirin and dipyridamole improved early graft patency without increased blood loss, this preoperative regimen could continue to be used at present until the question of preoperative therapy is resolved by controlled trials.

We acknowledge the important contributions made by the staff cardiologists and cardiovascular surgeons whose names do not appear as authors. We also wish to thank both the medical and surgical housestaff at each hospital. This study could not have been done without the assistance and enthusiastic cooperation of these individuals. We would also like to express our appreciation to the patients who participated in this study.

Appendix

Estimation of the percentage of distal anastomoses occluded and its variance with the ratio estimate as applied to cluster sampling. Since the occlusion or patency of distal anastomoses within the same patient could be a dependent event, an appropriate analysis of vein graft patency data is the ratio estimate as applied to cluster sampling. Patients can be considered to represent clusters of distal anastomoses. These clusters can contain from one distal anastomosis, in the case of a single saphenous vein graft, to multiple distal anastomoses, in the case of several single saphenous vein grafts, sequential or Y grafts, or combinations of these different types of grafts within the same patient.
The estimate of the percentage of distal anastomoses that become occluded is the same as if clusters were ignored. That is, 
\[
\frac{\sum a_i}{n} = \frac{\sum a_i}{m_i} = \frac{p}{m}
\]
where \( p \) = % of occluded distal anastomoses; \( a_i \) = number of occluded distal anastomoses in each individual patient; \( m_i \) = total number of distal anastomoses in each individual patient; \( n \) = total number of patients in the sample.

\( p \) is called a “ratio estimate” because both the numerator and denominator are random variables. That is, both the total number of occluded distal anastomoses and the total number of distal anastomoses are variable.

The variance of the ratio estimate is \( V(p) \)
\[
V(p) = \frac{\sum a_i^2 - 2p \sum a_i m_i + p^2 \sum m_i^2}{nm^2 - n - 1}
\]

where \( m \) = average number of distal anastomoses in the patients.

This variance tends to be somewhat larger than the variance under the assumption that distal anastomoses within patients act independently with respect to patency or occlusion. Therefore, the ratio estimate procedure tends to be somewhat more conservative than the use of a standard chi-square test that assumes independence. That is, the ratio estimate will tend to find fewer statistical significances than the standard chi-square test.

With the use of the data from this VA Cooperative Study, a test of independence was performed. It was found that the patency and occlusion of distal anastomoses within patients are dependent events (\( p = .0004 \)). Therefore, the ratio estimate is an appropriate analysis for these data.

The Veterans Administration Study Group


Executive Committee. Steven Goldman, M.D., Jack G. Copeland, M.D. (Co-Chairmen), Thomas Moritz, M.S., Lawrence Harker, M.D., Gulshan Sethi, M.D., G.V.R.K. Sharma, M.D., Tim Takaro, M.D., Herbert Hultgren, M.D. (past), William G. Henderson, Ph.D. (ex-officio), and Clair Haakenson, R.Ph., M.S.


Central Angiography Laboratory. Theron Ovitt, M.D. (Director), and John Newell, M.D., University of Arizona, Tucson.

Central Electrophysiologic Laboratory. Directors: Laryneth Lancaster, M.D., and Alan Rosenfeld, M.D. (past), VA Medical Center, Tucson.


Operations Committee. Joel S. Karliner, M.D. (Chairman), Valentin Fuster, M.D., Nicholas T. Kouchoskos, M.D., and Professor Michael Gent.


References

Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study.
S Goldman, J Copeland, T Moritz, W Henderson, K Zadina, T Ovitt, J Doherty, R Read, E Chesler and Y Sako

_Circulation_. 1988;77:1324-1332
doi: 10.1161/01.CIR.77.6.1324

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/6/1324

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/