Starting Aspirin Therapy After Operation
Effects on Early Graft Patency

Steven Goldman, MD; Jack Copeland, MD; Thomas Moritz, MS; William Henderson, PhD; Karen Zadina, RN, MA; Theron Ovitt, MD; Karl B. Kern, MD; Gulshan Sethi, MD; G.V.R.K. Sharma, MD; Shukri Khuri, MD; Kent Richards, MD; Fred Grover, MD; Douglass Morrison, MD; Glenn Whitman, MD; Elliot Chesler, MD; Y. Sako, MD, PhD; Ivan Pacold, MD; Alvaro Montoya, MD; Henry DeMots, MD; Storm Floten, MD; James Doherty, MD; Raymond Read, MD; Stewart Scott, MD; Ted Spooner, MD; Zaki Masud, MD; Clair Haakenson, RPh, MS; Laurence A. Harker, MD; and the Department of Veterans Affairs Cooperative Study Group

Background. Although aspirin therapy started before operation improves vein graft patency after coronary artery bypass grafting, it also causes bleeding. The objective of this prospective, centrally directed, randomized, double-blind, placebo-controlled trial was to compare the effects of aspirin therapy started before operation with aspirin started 6 hours after operation on early (7–10-day) graft patency.

Methods and Results. Patients were randomized to receive either aspirin 325 mg or placebo the night before surgery; after operation, all patients received aspirin 325 mg daily, with the first dose administered through the nasogastric tube 6 hours after operation. Angiography was performed in 72% of the analyzed patients an average of 8 days after operation, and the primary end point was saphenous vein graft patency in 351 patients. Internal mammary artery graft patency was also assessed in 246 patients because many individuals received both internal mammary artery and vein grafts. In the patients given preoperative aspirin, the vein graft occlusion rate was 7.4±1.3% compared with 7.8±1.5% in those who received preoperative placebo (p=0.871). In the subgroup of patients receiving Y grafts, 0.0% of the grafts were occluded in the preoperative aspirin group compared with 7.0±3.6% in the preoperative placebo group (p=0.066). The internal mammary artery occlusion rate was 0.0% (0 of 131) in the aspirin group compared with 2.4±1.4% (three of 125) in the placebo group (p=0.081). Patients in the aspirin group received more transfusions than those in the placebo group (median, 900 versus 725 ml, p=0.006). The reoperation rate for bleeding in the aspirin group was 6.3% compared with 2.4% in the placebo group (p=0.036). Median chest tube drainage within the first 6 hours after operation was 500 ml in the aspirin group compared with 448 ml in the placebo group (p=0.011).

Conclusions. Thus, preoperative aspirin is associated with increased bleeding complications and offers no additional benefit in early vein graft patency compared with starting aspirin therapy 6 hours after operation. There was a trend, although not significant, toward improved early patency for Y grafts and internal mammary artery grafts with preoperative aspirin. (Circulation 1991;84:520–526)
gastric tube. Although these investigations were interpreted to demonstrate that preoperative treatment was necessary to improve vein graft patency, the importance of starting treatment before or immediately after surgery was not specifically addressed. These studies focused on vein grafts. The effect of aspirin on internal mammary artery (IMA) graft patency was not addressed.

During cardiopulmonary bypass, the pump oxygenator activates platelets and results in consequent platelet dysfunction during surgery and early in the postoperative period. This transient decrease in platelet function may protect grafts from early thrombosis. An alternative consequence of platelet activation by the pump oxygenator may be enhanced risk of intraoperative thrombosis. Mural thrombosis begins as soon as the first blood begins to flow through the graft, but whether this is extensive enough to make a difference in graft patency is uncertain. Thus, determining whether any preoperative treatment is required to improve vein graft or IMA patency is important for our understanding of the pathophysiology of graft occlusion.

The objective of this prospective, centrally directed, randomized, double-blind, placebo-controlled trial was to compare the effects of aspirin therapy started before operation with aspirin therapy started early after operation. Patients were randomized to receive either aspirin 325 mg or placebo the night before surgery. After operation, all patients received aspirin 325 mg daily, with the first dose administered through the nasogastric tube 6 hours after operation. Cardiac catheterization was performed an average of 1 week after surgery, and the primary end point was graft patency. We tried to determine 1) whether aspirin therapy started in the early postoperative period is as effective as aspirin started before operation with respect to patency of vein grafts 1 week after surgery and 2) whether the bleeding complications of aspirin are obviated by starting therapy 6 hours after operation. Because many of the patients receiving saphenous vein grafts also received IMA grafts, we analyzed the effects of preoperative aspirin on early IMA graft patency as well.

Methods

Study Population

This trial, organized by the Cooperative Studies Program of the Department of Veterans Affairs Medical Research Service, consisted of data from 489 male patients entered into the study at 10 participating hospitals from July 1986 to September 1988. The exclusion criteria, definition of the study population, and stratification techniques have been previously described.1

These 489 patients represent 20% of all the patients undergoing elective CABG at these institutions during the study period. Of the 823 patients eligible according to the protocol, 489 (59%) patients consented and were enrolled. Of the 2,471 patients undergoing CABG at the 10 institutions, the predominant

Treat protective factors for eliminating 1,982 patients were emergency operations and scheduling problems that precluded the administration of study medications before operation, refusal to participate, other diseases requiring the long-term use of aspirin or other prostaglandin inhibitors, previous CABG, and need for concomitant valve replacement.

Treat Regimens

To be eligible for the study, patients were required to be off of aspirin therapy a minimum of 5 days before operation. The randomization was carried out for preoperative aspirin or placebo with either aspirin 325 mg administered as a single dose 12 hours before operation or placebo. All patients were given aspirin after operation, with the first dose of aspirin (325 mg) administered 6 hours after operation through a nasogastric tube, which was clamped for 1.5 hours. Therapy was continued by nasogastric tube until regular oral administration could be substituted. The aspirin and matching placebo were provided by Glenbrook Laboratories, New York. All medications were provided in individualized patient kits.

Surgery

CABG was performed by the usual protocol for each of the study institutions. The decision to use the IMA or saphenous vein as a conduit was made by the attending surgeon. If the surgeon decided before operation to use only IMA grafts in certain patients, these patients were not randomized because the primary objective of the study was to assess the effect of starting aspirin 6 hours after surgery on the early patency of saphenous vein grafts. However, because many patients received both saphenous vein grafts and IMA grafts, we were able to determine the effect of early postoperative aspirin on IMA graft patency. The saphenous vein and IMA grafts were included in separate analyses.

Although no attempt was made to establish a uniform technique for performing surgery, those institutions chosen to participate in the study were selected on the basis of experience and competence as documented by yearly statistics compiled by the Department of Veterans Affairs Central Office. Detailed data forms covering technical aspects of the perfusion, cardioplegic solutions, time of operation, arrest period, technical considerations regarding vessel and graft size, postoperative support, and bleeding were maintained for each patient.

Angiographic Analysis

The angiographic analysis used in this study was identical to that in our earlier trial. Briefly, the left IMA and each aortic anastomosis were selectively engaged and injected. If the status of a vein graft could not be determined by graft or stump injection, aortic root angiography was performed. Selective angiography of the native coronary arteries was performed only when a graft was occluded. All angiograms were interpreted at both the participating
institution and the central angiographic laboratory. The data from the central angiographic laboratory were used for this report. At the central angiographic laboratory, each angigram was interpreted independently by two cardiovascular radiologists unaware of the patients' treatment regimen. The analysis was performed with a system developed for this study, which included a projector and high-resolution television camera (Vanguard Instrument Corp., Melville, N.Y.) to record the images. The images were digitized, and the information was entered into an integrated image processor-computer system. Images were then redisplayed on the integrated memory plane; absolute measurements were made, and stenoses were calculated for all vessels 1 mm or greater in diameter. The number, type, and size of all grafts were recorded using an interactive computer program. Images of the cineframes, with the measurements superimposed, were filmed for storage in hard copy format. The angiographic analysis used in this study was prospective. The size of the distal vessel was analyzed by measuring the lumen of the vessel from the cinefilm. To determine the absolute lumen diameter of the distal vessel, the diameter of the catheter was measured. The appropriate magnification factor was calculated by knowing the actual diameter of the catheter. Actual vessel size was reported with this correction factor.

A single vein or IMA graft was defined as patent when the origin was visualized and when contrast material opacified the graft and the distal vessel, either by selective injection or by aortic root angiography. When analyzing sequential or Y vein grafts, a distal anastomosis (either side to side or end to side) was defined as patent when the contrast material was seen to flow from the vein graft into the graft artery. If the graft was occluded at its origin, all associated distal anastomoses were considered occluded. If one distal anastomosis of a Y or sequential vein graft was occluded, that site was defined as an occluded graft. When there was a difference of opinion regarding patency, the films were reviewed, and a consensus opinion was reported.

Statistical Analysis

Data are presented as mean±SD unless otherwise specified. Comparability of treatment groups was tested with the χ² statistic on qualitative variables. Quantitative variables were evaluated with the Student’s t test for normally distributed data and the Wilcoxon’s rank-sum test for non-normally distributed data. The patency data for saphenous vein grafts were analyzed in two ways: 1) comparison of grafts that were occluded, assuming grafts to be dependent and 2) comparison of the proportion of patients with one or more occluded grafts. Because our previous data showed that there was a dependency of graft patency among individual patients, a cluster sampling approach was used to define the variance for the first type of analysis.

Results

Patient Data

Of the 489 patients entered into the study, catheterization was not performed in 121 patients because of patient refusal in 85, death in 13, and other medical problems in 19. Catheterization was deferred in four patients secondary to technical difficulties. The remaining 368 (75%) patients underwent the postoperative catheterization. This report contains the data on 351 of 489 (72%) patients with vein grafts who underwent catheterization within 60 days of surgery and whose data were available in the central angiographic laboratory. Seventeen of these patients were not included in the primary results of this report because nine of the angiograms were obtained later than 60 days after surgery, the data on two patients were not available in the central laboratory, and six patients ultimately received only an IMA graft at surgery even though the decision was originally made before randomization to use at least one saphenous vein graft. The angiographic data on these six individuals are included only in the IMA analyses. The median time from surgery to catheterization was 8 days with a range of 4 to 58 days for the 351 patients in this report. Eighty-seven percent of the catheterizations were performed within 21 days after surgery.

The baseline clinical characteristics for the patients having at least one saphenous vein graft are shown in Table 1. There were no differences between the treatment groups for any of the clinical characteristics. Similarly, when clinical characteristics for the subset of patients with IMA grafts were analyzed (Table 2), no differences between treatment groups were observed. Only one difference in clinical characteristics was observed when patients who underwent the postoperative catheterization were compared with those who did not. The patients who had angiography were 60±8 years of age compared with 62±8 years of age for those who did not (p=0.025).

Vein Graft Occlusion Data

The vein graft occlusion rates for the two treatment groups are shown in Table 3. There were 659 single, 184 sequential, and 65 Y grafts.

The vein graft occlusion rate for the distal anastomoses in the aspirin group was 7.4±1.3% compared with 7.8±1.5% in the placebo group (p=0.871, with a 95% confidence interval of −3.6% to 4.2%). When patients and not grafts were considered as the units of observation, 17.0% of the patients in the aspirin group had one or more occluded grafts compared with 15.4% in the placebo group (p=0.682).

There were no differences in patency rates between aspirin and placebo regimens when comparisons were based on type of vein graft or location (Table 3). It is also important to note that there were no differences in patency rates to the left anterior descending coronary artery. The only subset in which there was a trend toward a benefit from aspirin was in
TABLE 1. Characteristics of Patients With at Least One Saphenous Vein Graft

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>176</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Age (yr) (mean±SD)</td>
<td>60±8</td>
<td>60±7</td>
<td>0.932</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>97</td>
<td>98</td>
<td>0.527</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>56</td>
<td>50</td>
<td>0.263</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>62</td>
<td>60</td>
<td>0.711</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past (%) (pack yr)</td>
<td>52 (40)</td>
<td>55 (39)</td>
<td>0.484</td>
</tr>
<tr>
<td>Current (%) (pack yr)</td>
<td>29 (45)</td>
<td>26 (51)</td>
<td>0.493</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl) (mean±SD)</td>
<td>219±53</td>
<td>218±51</td>
<td>0.903</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl) (median)</td>
<td>191</td>
<td>183</td>
<td>0.293</td>
</tr>
<tr>
<td>Serum HDL (mg/dl) (median)</td>
<td>32</td>
<td>33</td>
<td>0.793</td>
</tr>
<tr>
<td>Canadian functional class (I-IV) (mean±SD)</td>
<td>3.4±0.9</td>
<td>3.3±0.8</td>
<td>0.865</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; HDL, high-density lipoprotein.
There were no differences between the two treatment groups for any of these variables.

Y grafts in which the occlusion rate was 0.0% (0 of 22) in the aspirin group compared with 7.0±3.6% (three of 43) in the placebo group (p=0.066).
Prospective stratification for the size of the recipient vessel did not affect the outcome (Table 3). For example, there were no differences in patency in the vein grafts to distal vessels less than or equal to 1.5 mm in diameter (183 grafts), with an occlusion rate of 24.7% in the aspirin group compared with 27.6% for placebo (p=0.709). Similar results were seen in vein grafts to distal vessels less than or equal to 2.0 mm in diameter (406 grafts), with an occlusion rate of 15.6% for the aspirin group compared with 15.0% for placebo (p=0.870). There were no differences in the results when the diameter of the recipient vessel was greater than 1.5 mm in diameter (725 grafts), with an occlusion rate of 3.5% for the aspirin group compared with 2.3% for placebo (p=0.333). The results were similar in vessels greater than 2.0 mm in diameter (502), with an occlusion rate of 1.5% for the aspirin group compared with 1.3% for placebo (p=0.815).

IMA Graft Occlusion Data

The occlusion rates for the two treatment groups for all IMA grafts are shown in Table 4. The IMA occlusion rate in the aspirin group was 0.0% (0 of 131) compared with 2.4±1.4% (three of 125) in the placebo group (p=0.081, with a 95% confidence interval of -0.3% to 5.1%). After only single IMA grafts to the left anterior descending coronary artery were considered, the occlusion rate in the aspirin group was 0.0% (0 of 116) compared with 2.8±1.6% (three of 108) in the placebo group (p=0.110). Moreover, prospective stratification for vessel size revealed that there was no significant difference with aspirin in the vessels less than or equal to 2.0 mm in diameter.

Surgical Data

There were no differences in median operative time (261 compared with 260 minutes, p=0.646) or median cardiopulmonary bypass time (111 compared with 107 minutes, p=0.442) between the aspirin and placebo groups. Within the first 6 hours after surgery, the median chest tube drainage in the aspirin group was 500 ml (lower 5%, 155 ml; upper 5%, 1,899 ml) compared with 448 ml (lower 5%, 115 ml; upper 5%, 1,576 ml) in the placebo group (p=0.011). Within the first 35 hours after surgery, the median value for chest tube drainage in the aspirin group was 1,150 ml (lower 5%, 499 ml; upper 5%, 3,182 ml) compared with 1,045 ml (lower 5%, 331 ml; upper 5%, 2,736 ml) with placebo (p=0.148). The patients in the aspirin group received more transfusions (median, 900 compared with 725 ml, p=0.006). In the patients receiving aspirin, 42±3% received platelet transfusions compared with 33±3% of the patients who received placebo (p=0.043). There were no differences in fresh frozen plasma replacement between the aspirin and placebo groups; that is, 55±3% of the aspirin group received fresh frozen plasma compared with 50±3% of the placebo group (p=0.283). Preoperative aspirin increased the reoperation rate for bleeding at a rate of 6.3±1.6% compared with a rate of 2.4±1.0% with placebo (p=0.036). Operative mortality was 2.7% with no difference between groups.

Complications of Angiography

There were no reports of bleeding at the catheterization site, ventricular fibrillation, myocardial infarction, cerebral vascular accident, or death during the postoperative catheterization. The only significant complications were an occluded femoral artery after catheterization that required thrombectomy, an asymptomatic localized subintimal aortic dissection secondary
TABLE 3. Frequency of Vein Graft Occlusion According to Type and Location of Graft

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occluded grafts</td>
<td>Distal anastomoses</td>
</tr>
<tr>
<td>All grafts</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>LAD</td>
<td>7.4</td>
<td>457</td>
</tr>
<tr>
<td>RCA</td>
<td>5.9</td>
<td>135</td>
</tr>
<tr>
<td>Cx</td>
<td>5.1</td>
<td>138</td>
</tr>
<tr>
<td>Single vein grafts</td>
<td>10.3</td>
<td>184</td>
</tr>
<tr>
<td>Sequential vein grafts</td>
<td>7.2</td>
<td>333</td>
</tr>
<tr>
<td>Y grafts</td>
<td>9.8</td>
<td>102</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>0.0</td>
<td>22</td>
</tr>
</tbody>
</table>

|                  | ≤1.5   | 24.7   | 85      | 27.6    | 98 | 0.709 |
|                  | 1.5    | 3.5    | 372     | 2.3     | 353 | 0.333 |
|                  | ≤2.0   | 15.6   | 192     | 15.0    | 214 | 0.870 |
|                  | >2.0   | 1.5    | 265     | 1.3     | 237 | 0.815 |

LAD, left anterior descending coronary artery; 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.

This study is the first controlled clinical trial to compare preoperative with postoperative aspirin with respect to IMA and vein graft patency and bleeding after CABG. Previous studies established that vein graft patency is improved when antiplatelet therapy is started before operation.1-5 Indeed, meta-analysis reveals that there is an inverse relation between postoperative vein graft patency and the number of days after operation before starting treatment; that is, the earlier the treatment, the greater the effects on patency.9 The previous studies have been interpreted to indicate that the greatest benefit is achieved when treatment is begun before surgery, thereby ensuring that the antiplatelet effects of the treatment are present during the operation.

The vein graft patency rates in the present study are similar to data we and other investigators reported previously with either preoperative aspirin or dipyridamole.1,4 In a group of patients studied under a separate protocol, we observed an increased rate of reoperation for bleeding and increased transfusions that were related to preoperative aspirin.1 In that study, we found an increased 35-hour chest tube drainage after CABG in patients receiving aspirin before operation. One explanation of why we did not find a similar difference in the present study may be that the preoperative placebo group in this trial received aspirin 6 hours after surgery, whereas the placebo group in the previous trial continued on placebo after surgery. Even this relatively late administration of aspirin may possibly increase postoperative bleeding if hemostasis is not complete. The more frequent use of the IMA as a graft in the present study may be another explanation for the increased chest tube drainage, particularly in the group not receiving preoperative aspirin.

The therapeutic recommendations from this study are clear. The administration of preoperative aspirin results in no significant improvement in either saphen-
ous vein or IMA graft patency. Moreover, by avoiding preoperative aspirin, it is possible to eliminate potential bleeding complications. Although the appropriate duration of aspirin treatment has not yet been established, we recommend that aspirin (325 mg daily) be continued for 1 year because our study group has previously shown that aspirin improves vein graft patency to native vessels less than 2.0 mm in diameter for at least 1 year after surgery.2 A 3-year follow-up study is currently underway to determine the efficacy of aspirin on long-term vein graft and IMA patency.

Appendix

The Department of Veterans Affairs Study Group

Chairman’s Office. Study co-chairmen: Steven Goldman, MD, and Jack G. Copeland, MD. Study coordinator: Karen Zadina, RN, MA. Secretaries: Katherine Handley and Patricia Pettijohn (past).

Participants. Department of Veterans Affairs Medical Centers, participating investigators, nurses, and physician assistants. Asheville, N.C.: Stewart Scott, MD; Mary Basch, PA; and Bill Cogswell, PA (past). Denver: Douglass Morrison, MD; Glenn Whitman, MD; Michael Johnston, MD (past); and Amy Cohan, RN, MN. Buffalo, N.Y.: Ted Spooner, MD; Zaki Masud, MD; and Michelle Lewis, RN. Hines, Ill.: Ivan Pacold, MD; Alvaro Montoya, MD; and Judy Callahan, RN, MSN. Little Rock, Ark.: James Doherty, MD; Raymond Read, MD; and Marilyn Levinson, LPN. Minneapolis: Elliot Chesler, MD; Y. Sako, MD, PhD; Judi Causier, RN; and Caroline Skokun, RN (past). Portland, Ore.: Henry DeMots, MD; Storm Floten, MD; and Becky Leikam, PA. San Antonio, Tex.: Kent Richards, MD; Fred Grover, MD; and Susan Langston, RN, BSN. Tucson: Karl Kern, MD; Gulshan Sethi, MD; Larry-enth Lancaster MD (past); and Deborah Carroll, RN, BS. West Roxbury, Mass.: G.V.R.K. Sharma, MD; Shukri Khuri, MD; and Diane Lapsley, RN, MS, CS.

Executive Committee. Steven Goldman, MD (co-chairman); Jack G. Copeland, MD (co-chairman); Thomas Moritz, MS; Laurence Harker, MD; Gulshan Sethi, MD; G.V.R.K. Sharma, MD; Tim Takaro, MD; Clair Haakenson, RPh, MS; Karen Zadina, RN, MA; and William G. Henderson, PhD (ex-officio).

Biostatistics and Research Data Processing. Hines Cooperative Studies Program Coordinating Center. Chief: William G. Henderson, PhD. Study biostatistician: Thomas Moritz, MS. Administrative officer: Jean Rowe. Programmers: Tai Sook Kim, BS; Raslan Othman; MS; Yui-Li Hsu, RN, MS (past); and Kwan Hur, MS (past). Statistical assistant: Sharon Urbsanski.


Central Angiography Laboratory. Director: Theron Ovitt, MD, University of Arizona, Tucson.

Central Electrocardiographic Laboratory. Director: Karl Kern, MD, Department of Veterans Affairs Medical Center, Tucson.

Data Monitoring Board. Chairman: Joel S. Karriner, MD. Members: Valentin Fuster, MD; Nicholas T. Kouchoukos, MD; and Prof. Michael Gent.

Human Rights Committee. Chairpersons: Eileen Collins, RN; Eileen Hagarty, RN, MS (past). Members: Martin W. Feldbush, DD, MA; Patrick J. Moran, JD; Barbara Harvey, RN; Mr. Robert Lee; Walter Dorus, MD; Nicholas Emanuele, MD; Donna Franklin, PhD; Reverend Jeffrey Stinehelfer; Thomas M. Schmid, PhD; Elizabeth Butler, MS; and Janice Hutchinson, MD.

Cooperative Studies Program Central Administration (Department of Veterans Affairs Central Office, Washington, DC). Chief: Daniel Deykin, MD. Staff assistant: Ping C. Huang, PhD. Administrative officer: Janet Gold.

Acknowledgments

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

References


**KEY WORDS** • graft, vein • coronary artery bypass graft surgery • internal mammary artery • antiplatelet therapy