Antithrombotic Therapy in Patients With Saphenous Vein and Internal Mammary Artery Bypass Grafts Following Percutaneous Transluminal Coronary Angioplasty

Paul D. Stein, M.D., F.C.C.P., Chairman
James E. Dalen, M.D., F.C.C.P.
Steven Goldman, M.D.
Leonard Schwartz, M.D.
A. G. G. Turpie, M.D.
Pierre Thérioux, M.D.

Saphenous Vein Bypass Grafts

Over one half of the randomized prospective studies of anticoagulants or antiplatelet agents on saphenous vein graft closure have shown a beneficial effect of therapy (Table 1). This applies to studies of aspirin alone in various doses, aspirin plus dipyridamole, sulfinpyrazone, ticlopidine, and warfarin. Studies in which aspirin was administered before operation or within one day after operation showed a beneficial effect, irrespective of the dose of aspirin. Also, all studies in which aspirin or dipyridamole was administered before operation or within one day after operation showed a beneficial effect. No studies in which aspirin or aspirin plus dipyridamole was started two or more days after surgery showed a beneficial effect. Almost immediately after harvesting the saphenous vein, the endothelium is lost, and the raw surface is vulnerable to platelet aggregation.

Table 1 — Saphenous Vein Graft Patency

<table>
<thead>
<tr>
<th>Drug/Daily Dose</th>
<th>Graft Patency Treated, %</th>
<th>Graft Patency Untreated, %</th>
<th>Study Duration, mo</th>
<th>Treatment Onset, Days Postop</th>
<th>Evidence Level</th>
<th>p</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>36 of 40 (90)</td>
<td>36 of 53 (66)</td>
<td>4</td>
<td>1</td>
<td>I</td>
<td>0.012</td>
<td>Lorenz et al, 1984</td>
</tr>
<tr>
<td>325</td>
<td>347 of 371 (94)</td>
<td>327 of 384 (85)</td>
<td>&lt;2</td>
<td>-1</td>
<td>I</td>
<td>&lt;0.01</td>
<td>Goldman et al, 1986</td>
</tr>
<tr>
<td>600</td>
<td>65 of 81 (80)</td>
<td>54 of 74 (72)</td>
<td>24</td>
<td>3-4</td>
<td>II</td>
<td>NS</td>
<td>McEnany et al, 1982</td>
</tr>
<tr>
<td>975</td>
<td>313 of 339 (92)</td>
<td>327 of 384 (85)</td>
<td>&lt;2</td>
<td>-1</td>
<td>I</td>
<td>&lt;0.05</td>
<td>Goldman et al, 1986</td>
</tr>
<tr>
<td>975</td>
<td>87 of 111 (78)</td>
<td>76 of 95 (80)</td>
<td>12</td>
<td>3-5</td>
<td>II</td>
<td>NS</td>
<td>Sharma et al, 1983</td>
</tr>
<tr>
<td>975</td>
<td>101 of 115 (88)</td>
<td>116 of 147 (79)</td>
<td>12</td>
<td>3-5</td>
<td>II</td>
<td>NS</td>
<td>Brown et al, 1981</td>
</tr>
<tr>
<td>Aspirin + Dipyridamole, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,300 + 100</td>
<td>69 of 75 (92)</td>
<td>72 of 93 (77)</td>
<td>3-6</td>
<td>1</td>
<td>I</td>
<td>&lt;0.02</td>
<td>Mayer et al, 1981</td>
</tr>
<tr>
<td>975 + 225</td>
<td>425 of 478 (89)</td>
<td>364 of 486 (75)</td>
<td>12</td>
<td>-2*, 0</td>
<td>I</td>
<td>&lt;0.05</td>
<td>Chesebro et al, 1984</td>
</tr>
<tr>
<td>975 + 225</td>
<td>27 of 38 (72)</td>
<td>50 of 61 (82)</td>
<td>6</td>
<td>3</td>
<td>II</td>
<td>NS</td>
<td>Pantely et al, 1979</td>
</tr>
<tr>
<td>975 + 225</td>
<td>113 of 135 (84)</td>
<td>116 of 147 (79)</td>
<td>12</td>
<td>3-5</td>
<td>II</td>
<td>NS</td>
<td>Brown et al, 1981</td>
</tr>
<tr>
<td>975 + 225</td>
<td>61 of 74 (83)</td>
<td>76 of 95 (80)</td>
<td>12</td>
<td>3-5</td>
<td>II</td>
<td>NS</td>
<td>Sharma et al, 1983</td>
</tr>
<tr>
<td>990 + 225</td>
<td>87 of 95 (92)</td>
<td>88 of 118 (75)</td>
<td>6</td>
<td>-1</td>
<td>I</td>
<td>&lt;0.01</td>
<td>Rajah et al, 1985</td>
</tr>
<tr>
<td>975 + 225</td>
<td>300 of 359 (82)</td>
<td>327 of 384 (85)</td>
<td>&lt;2</td>
<td>-2, -1†</td>
<td>I</td>
<td>&lt;0.05</td>
<td>Goldman et al, 1988</td>
</tr>
<tr>
<td>990 + 225</td>
<td>100 of 133 (75)</td>
<td>91 of 133 (68)</td>
<td>12</td>
<td>2 or 3</td>
<td>II</td>
<td>NS</td>
<td>Brooks et al, 1985</td>
</tr>
<tr>
<td>Sulfinpyrazone, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td>204 of 212 (96)</td>
<td>199 of 219 (91)</td>
<td>&lt;1</td>
<td>1</td>
<td>I</td>
<td>0.025</td>
<td>Baur et al, 1987</td>
</tr>
<tr>
<td>800</td>
<td>296 of 328 (90)</td>
<td>327 of 384 (85)</td>
<td>&lt;2</td>
<td>-2</td>
<td>I</td>
<td>NS</td>
<td>Goldman et al, 1986</td>
</tr>
<tr>
<td>Ticlopidine, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>185 of 220 (84)</td>
<td>153 of 207 (74)</td>
<td>12</td>
<td>2</td>
<td>I</td>
<td>0.01</td>
<td>Limet et al, 1987</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT 1.5-2.0 (N Am)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 of 65 (84)</td>
<td>54 of 74 (72)</td>
<td>24</td>
<td>3-4</td>
<td>II</td>
<td>NS</td>
<td>McEnany et al, 1982</td>
<td></td>
</tr>
<tr>
<td>PT 1.7-2.3 (N Am)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 of 37 (78)</td>
<td>50 of 61 (82)</td>
<td>6</td>
<td>3</td>
<td>II</td>
<td>NS</td>
<td>Pantely et al, 1979</td>
<td></td>
</tr>
<tr>
<td>PT 2.2-2.7 (N Am)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>227 of 251 (90)</td>
<td>199 of 238 (84)</td>
<td>2</td>
<td>4-7</td>
<td>I</td>
<td>&lt;0.015</td>
<td>Gohle et al, 1981</td>
<td></td>
</tr>
</tbody>
</table>

*Dipyridamole was started 2 days before operation; ASA was started on the day of operation.
†Dipyridamole was started 2 days before operation; ASA was started 12 h before operation.
‡Phenprocoumon. PT estimated from Hirsh et al. 1980.
may explain the need for early treatment. Meta-
alysis showed that all antiplatelet agents as a group
were more beneficial in comparison to no treatment,
and aspirin alone was more effective than no therapy.10

Pfisterer and associates,11 in a level I study, com-
pared antiplatelet agents with anticoagulants. Patients
who received antiplatelet agents alone were adminis-
tered dipyridamole 400 mg/day for two days before
surgery. On the morning of surgery and thereafter,
they received dipyridamole, 400 mg/day, and aspirin,
50 mg/day, in divided doses. Those who received
anticoagulants were administered phenprocoumon,
starting the first postoperative day. Phenprocoumon
was administered in a dose sufficient to maintain a
prothrombin ratio 1.4 to 1.8 times control using North
American thromboplastin. There was no difference in
the effectiveness of antiplatelet agents vs anticoagu-
lants on graft patency at two weeks: 356 of 381 (93
percent) vs 344 of 369 (93 percent) (NS). At the end
of one year, we calculated from the authors' data that
graft patency was lower among patients treated with
antiplatelets than anticoagulants: 137 of 175 (78 per-
cent) vs 130 of 148 (88 percent) (p<0.05). After one
year, among patients treated with antiplatelet agents
or anticoagulants vs patients whose antiplatelet agents
or anticoagulants were discontinued after three
months, graft patency was 270 of 323 (84 percent) vs
243 of 315 (77 percent) (p = 0.08).

In a level I study, aspirin in small doses (100 mg/
day) was shown to be associated with greater graft
patency at four months than in untreated patients1
(Table 1). Only 68 percent of grafts (36 of 53) in control
subjects were patent compared to 90 percent (36 of
40) in patients treated with aspirin (p = 0.012).1 Larger
doses of aspirin (500 mg/day or 975 mg/day) have also
been employed.10-12 These level II studies that em-
ployed larger doses of aspirin also started treatment
later (three to five days after operation rather than one
day after operation). No significant improvement in
graft patency compared with control subjects was
shown in these studies after one to two years.10-12

Additional information regarding the effect of anti-
platelet therapy on graft patency was derived from the
Veterans Administration (VA) Cooperative Study
(level I study). Postoperative arteriograms were ob-
tained within 60 days of surgery. The drug regimens
employed included the following: (1) aspirin, 325 mg/
day; (2) aspirin, 975 mg/day; (3) aspirin, 975 mg/day
combined with dipyridamole, 225 mg/day; and (4)
sulfipyrazone, 800 mg/day. Aspirin therapy was
started 12 h before surgery. Other drugs (dipyridamole
and sulfipyrazone) were begun two days before
surgery. Among 555 patients (1,781 grafts), there was
greater graft patency (92 to 94 percent) with drug
regimens that included aspirin rather than placebo (85
percent patency) (p<0.05). A disadvantage, however,
was a greater rate of reoperation (6.5 percent) among
treatment groups that included aspirin compared with
treatment groups that consisted of either sulfipyra-
zone or placebo (1.7 percent, p<0.01).

Aspirin, given in combination with dipyridamole,
served a beneficial effect only when antiplatelet
therapy was begun before the operation or within one
day after operation (Table 1). In investigations that
showed no beneficial effect, antiplatelet therapy was
begun two to five days after operation. Most investi-
gators administered aspirin in a dose of approximately
1 g/day in combination with dipyridamole, 225 mg/
day, although one group was administered aspiri-
in, 1,300 mg/day, and dipyridamole, 100 mg/day.6 A
greater incidence of saphenous vein bypass graft
patency was found by some at three to six months (92
vs 77 percent) (p<0.02) and 92 vs 75 percent
(p<0.01).6 One group reported improved graft patency
in patients at one month (97 vs 90 percent patency)
and again at one year (89 vs 75 percent patency).1,16
Some studies, however, failed to show beneficial
results of aspirin given in combination with dipyrida-
 mole.11-14

The risks and benefits of beginning aspirin, 325 mg,
the night before surgery, in comparison to 6 h after
surgery have been evaluated19 (level II). The occlusion
rate at eight days was similar among both control
subjects and treated patients, 34 of 457 grafts (7
percent) vs 35 of 451 grafts (8 percent). Early occlusion
of Y-grafts, however, showed a trend in favor of
preoperative aspirin, 0 of 22 grafts (0 percent) vs 3 of
43 grafts (2 percent) (p = 0.08). A trend also showed a
lower rate of early occlusion of internal mammary
artery bypass grafts with preoperative aspirin, 0 vs 2
percent (p = 0.08). Reoperation for bleeding was more
frequent among patients who received aspirin before
surgery: 8 of 126 (6 percent) vs 3 of 120 (2 percent)
(p = 0.04). Chest tube drainage at 6 h was also more
frequent among those who received aspirin before
surgery: 500 ml vs 448 ml (p = 0.01).

In a randomized level I study, sulfipyrazone was
reported to be associated with greater graft patency
at one to two weeks after bypass among treated
patients, 96 percent graft patenty (204 of 212) vs 91
percent graft patency (199 of 219) (p<0.025).7 This
was not confirmed, however, in the VA Cooperative
Study.3 On the other hand, ticlopidine (an antiplatelet
agent) has been shown to increase graft patency (level
I studies).8,10

Warfarin was reported by some to have no effect on
graft patency at six months14 or at one to two years,10
but a larger group of patients at two months showed a
significant difference, in comparison to untreated
patients (90 percent graft patenty vs 85 percent graft
patency) (p<0.015) (Table 1).

Among patients who received dipyridamole, 400

CHEST / 102 / 4 / OCTOBER, 1992 / Supplement 509S
mg/day, beginning two days prior to coronary artery bypass grafting, the additive effects of aspirin, 150 mg/day, with or without dipyridamole, 225 mg/day, beginning one day after operation were compared to aspirin alone or placebo (level I).21 Graft patency was 87 percent among those who received aspirin and dipyridamole compared to 82 percent among those who received no antiplatelet agents after surgery (p = 0.017). Those who received only aspirin after surgery had a graft patency of 96 percent (p = 0.056 vs no postoperative antiplatelet therapy). Mediastinal drainage was somewhat higher among those who received aspirin and dipyridamole vs no postoperative treatment (713 ± 451 ml vs 670 ± 437 ml (p = 0.04). The risk of early reoperation was similar in both groups.

**Internal Mammary Artery Bypass Grafts**

Regarding the use of antiplatelet agents in patients with internal mammary artery bypass grafts, information is limited. Among 45 patients with left internal mammary artery to left anterior descending coronary artery bypass grafts, 18 received aspirin, 1,300 mg/day, as well as dipyridamole, 100 mg/day, beginning one day after operation.6 Following three to six months of observation, graft patency was similar in the control and treatment groups: 26 of 27 (96 percent) vs 18 of 18 (100 percent) (NS) (Table 2). Goldman and associates22 (level II) also showed that internal mammary graft patency after one year with various doses of aspirin, with or without dipyridamole (aspirin started the evening before surgery), was similar among untreated and treated groups. The respective patency rates were 23 of 23 (100 percent) vs 197 of 214 (92 percent) (NS) (Table 2).

**Bleeding Complications: Coronary Artery Bypass Grafts**

Information regarding bleeding complications of various regimens of antithrombotic therapy following saphenous vein bypass surgery is sparse. In a retrospective study, the estimated odds ratio for reoperation for bleeding following coronary artery bypass grafting was 1.82 among patients who received aspirin (dose unstated) within seven days prior to surgery (level IV).23 Among patients in whom chest tube drainage was measured, those who received aspirin prior to surgery had more chest tube drainage than control subjects (p < 0.02) (Table 3).3 Patients who received aspirin, 975 mg/day, had more drainage than those who received 325 mg/day (1,175 ml vs 965 ml). Among patients who received aspirin one to four days after surgery, there was no more bleeding than in control subjects.1,10 In these studies, data on chest tube drainage were not reported, but presumably, the chest tubes were removed before aspirin therapy was started. The duration of drainage in patients who received no antithrombotic therapy or heparin was 20 ± 1 h, and in patients who received aspirin or warfarin, it was 34 ± 4 h (p < 0.001).24 Patients who received aspirin and dipyridamole before surgery in one study had more chest drainage,3 but in another study, the difference was not significant6 (Table 2). Among patients who received aspirin plus dipyridamole starting two to three days after surgery, total bleeding complications (major plus minor) were more frequent than in control subjects.14

There are no comparative studies of bleeding complications following the administration of dipyridamole alone before surgery vs control subjects. Bleeding, however, with dipyridamole alone seems not to be excessive.6 Sulfinpyrazone, administered before surgery, did not result in more bleeding than in control subjects. Warfarin, beginning three to four days after operation, was associated with increased bleeding.10 Severe bleeding, including perioperative tamponade, was more frequent among patients treated with anticoagulants started on the first postoperative day prothrombin ratio 1.4 to 1.8 with North American thromboplatin (INR = 2) than among patients treated with aspirin plus dipyridamole starting on the morning of surgery.17

**Summary: Coronary Artery Bypass Grafts**

1. Aspirin alone may be as effective as aspirin in combination with dipyridamole when both are started before operation,3 but aspirin plus dipyridamole is more effective than aspirin alone, when dipyridamole is started before surgery and aspirin is started after operation.21

2. Aspirin, 325 mg/day, is as effective as aspirin, 975 mg/day, or aspirin, 975 mg/day, plus dipyridamole,
Table 3—Bleeding Complications With Antithrombotic Therapy in Patients With Saphenous Vein Bypass Grafts*

<table>
<thead>
<tr>
<th>Drug, mg/day</th>
<th>No. Patients</th>
<th>Treat Onset, Days Postop</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Palients</td>
<td>Onset, Mo</td>
</tr>
<tr>
<td>Aspirin, mg</td>
<td>100</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>325</td>
<td>154</td>
<td>153</td>
<td>&lt;2</td>
</tr>
<tr>
<td>600</td>
<td>71</td>
<td>77</td>
<td>24</td>
</tr>
<tr>
<td>975</td>
<td>155</td>
<td>153</td>
<td>&lt;2</td>
</tr>
<tr>
<td>975</td>
<td>64</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>975</td>
<td>37</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>ASA + DIP, mg</td>
<td>1,300 + 100</td>
<td>47</td>
<td>66</td>
</tr>
<tr>
<td>975 + 225</td>
<td>151</td>
<td>172</td>
<td>12</td>
</tr>
<tr>
<td>975 + 225</td>
<td>13</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>975 + 225</td>
<td>49</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>975 + 225</td>
<td>48</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>975 + 225</td>
<td>49</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>975 + 225</td>
<td>162</td>
<td>153</td>
<td>&lt;2</td>
</tr>
<tr>
<td>990 + 225</td>
<td>166</td>
<td>166</td>
<td>12</td>
</tr>
<tr>
<td>Sulfinpyrazone, mg</td>
<td>800</td>
<td>130</td>
<td>125</td>
</tr>
<tr>
<td>800</td>
<td>148</td>
<td>153</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Tiroliptide</td>
<td>500</td>
<td>87</td>
<td>96</td>
</tr>
<tr>
<td>Coumarin derivative</td>
<td>PT 1.5-2**</td>
<td>68</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>PT 1.7-2.3**</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>PT 2.3-2.7††</td>
<td>89</td>
<td>84</td>
</tr>
</tbody>
</table>

*DUR = duration of treatment; DIP = dipyridamole; cont, control subjects; maj, major; min, minor.
†Chest tube drainage, ml.
‡Dipyridamole was started 2 days before operation; ASA was started on the day of operation.
§Dipyridamole was started 2 days before operation; ASA was started 12 h before operation.
¶Recovery for early postoperative hemorrhage.
#Late tamponade.

25 mg/day, and both are more effective than sulfinpyrazone. Bleeding may be less with the lower dose of aspirin.

3. Aspirin administered on the day of operation may be associated with less bleeding than when it is administered before operation (level II).

4. Anticoagulants were effective when the prothrombin ratio was 1.4 to 1.8 times control using North American thromboplastin or higher, but postoperative bleeding was more frequent than in patients who received aspirin and dipyridamole on the day of surgery.

Table 4—Antiplatelet Agents and Periprocedural Events Associated With PTCA*

<table>
<thead>
<tr>
<th>Drug, Mg/Day</th>
<th>Start Time, Days Event</th>
<th>Placebo, E/n (%)</th>
<th>Treated, E/n (%)</th>
<th>p</th>
<th>Ev</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA, 990</td>
<td>−0.3</td>
<td>Q-MI</td>
<td>13/189 (7)</td>
<td>3/187 (2)</td>
<td>0.01</td>
</tr>
<tr>
<td>DIP, 225</td>
<td>−4</td>
<td>MI, CABG</td>
<td>15/110 (14)</td>
<td>6/111 (5)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ASA, 650</td>
<td>−4</td>
<td>MI, CABG</td>
<td>15/110 (14)</td>
<td>2/112 (2)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>DIP, 225</td>
<td>−4</td>
<td>MI, CABG</td>
<td>15/110 (14)</td>
<td>2/112 (2)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

*ASA = aspirin; DIP = dipyridamole; n = number of patients; E = number of events; MI = myocardial infarction; CABG = coronary artery bypass graft; EV = evidence level.

CHEST / 102 / 4 / OCTOBER, 1992 / Supplement 511S
PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)

Antiplatelet agents, when started before the procedure, have been shown to be beneficial in the prevention of periprocedural events associated with PTCA (level I, II studies)\(^{38,37}\) (Table 4). Fewer patients had myocardial infarctions and fewer required emergency coronary artery bypass grafts when aspirin plus dipyridamole or ticlopidine was administered prior to PTCA\(^{38,37}\) (Table 4).

Patients who, starting before the procedure, were administered aspirin alone or in combination with dipyridamole, had fewer significant acute coronary thromboses (100 percent occlusion, emergency coronary artery bypass graft, or emergency thrombolysis) than patients who received either no antiplatelet agents or only dipyridamole (level IV).\(^{38}\) The percentage of patients who suffered acute infarctions was the same among those who received aspirin, 80 mg/day, vs those who received 1,500 mg/day starting one day before PTCA, 9 of 242 (4 percent) vs 10 of 253 (4 percent) (level II).\(^{38}\) This percentage of acute complications was similar to the acute complication rate among patients treated with aspirin plus dipyridamole\(^{38,37}\) (Table 4).

Patients who received dipyridamole, 225 mg/day, in combination with aspirin, 975 mg/day, had no fewer Q wave infarctions than patients who received only aspirin, 975 mg/day, 5 of 117 (4 percent) vs 2 of 115 (2 percent) (NS) (level II).\(^{38}\) The frequency of emergency coronary artery bypass grafts was also comparable in those who received aspirin plus dipyridamole vs aspirin alone, 7 of 117 (6 percent) vs 3 of 115 (3 percent) (NS). Most patients (87 percent) received at least one dose of an antiplatelet agent prior to PTCA.

Patients participating in these studies on the effects of antiplatelet agents on periprocedural events, also received an intravenous bolus injection of heparin, 10,000 U, followed by various amounts of heparin during the procedure.\(^{38,38,30}\) Heparin is often given empirically with an initial fixed bolus of 10,000 U and subsequent additional heparin.\(^{31}\) Additional heparin may be needed to maintain the activated clotting time greater than 300 s.\(^{31}\) Some investigators observed that acute reocclusion after successful PTCA was temporally related to the loss of effective anticoagulation in most patients, 16 of 22 (73 percent) (level IV).\(^{38}\) The continued administration of heparin for 18 to 24 h, in comparison to 2 to 3 h after angioplasty, however, had no documented beneficial effects upon the rate of acute closure (1.8 vs 2.4 percent, NS) (level II).\(^{38}\) Among treated patients, emergency bypass, emergency angioplasty, or infarction occurred in 4 of 208 (2 percent) and in placebo in 6 of 208 (3 percent) (NS) (level II). (Both groups received heparin during angioplasty). Dextran administered in addition to heparin, 5,000 U, aspirin, 900 mg/day, and dipyridamole, 225 mg/day, had no additional effect in comparison to placebo upon the rate of occlusion, 10 of 96 arteries (10 percent) vs 7 of 76 arteries (9 percent) (level II).\(^{34}\)

Bleeding complications were not reported by most.\(^{38-30,32}\) Among 108 patients with an activated clotting time greater than 300 s, no patient had intracerebral bleeding, severe hemoptysis, or major gastrointestinal bleeding.\(^{31}\) Among patients treated 18 to 24 h with heparin, major bleeding occurred in 2 of 208 (1 percent); there was no major bleeding among 208 control subjects (NS) (level II).\(^{33}\)

**Long-Term Effects and Late Restenosis**

Regarding restenosis, antiplatelet agents have shown inconsistent benefits (Table 5). Schwartz and associates\(^{38}\) showed a similar number of patients with restenosis four to seven months after PTCA among patients treated with aspirin, 990 mg/day, plus dipyridamole, 225 mg/day, vs placebo, 46 of 122 (38 percent) vs 49 of 127 (39 percent) (NS) (level II). The severity of restenosis, however, was less in the 40 segments in the active treatment group than in the 46 segments in the placebo group (mean minimal luminal diameter at the stenosis, 1.03±0.45 mm vs 0.76±0.52 mm, \(p=0.01\) (level II).\(^{38}\) Moreover, Heiss and associates,\(^{38}\) after six months, showed fewer late reclosures among patients treated with the same dose of aspirin plus dipyridamole in comparison to untreated control subjects, 18 of 47 (38 percent) vs 28 of 47 (60 percent) (Table 5).

**Table 5—Restenosis (Late)**

<table>
<thead>
<tr>
<th>Drug, Mg/Day</th>
<th>Start Time, h</th>
<th>Follow Angios, mo</th>
<th>Placebo, E/n (%)</th>
<th>Treated, E/n (%)</th>
<th>p</th>
<th>Ev</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA, 990</td>
<td>-8</td>
<td>4-7</td>
<td>5/140 (37)</td>
<td>53/144 (37)</td>
<td>NS</td>
<td>I</td>
<td>Schwartz et al, 1988(^{38})</td>
</tr>
<tr>
<td>DIP, 225</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA, 990</td>
<td>1-2</td>
<td>6</td>
<td>2/47 (60)</td>
<td>18/47 (38)</td>
<td>0.04</td>
<td>II</td>
<td>Heiss et al, 1990(^{38})</td>
</tr>
<tr>
<td>DIP, 225</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA, 300</td>
<td>1-2</td>
<td>6</td>
<td>2/47 (60)</td>
<td>25/47 (53)</td>
<td>NS</td>
<td>II</td>
<td>Heiss et al, 1990(^{38})</td>
</tr>
<tr>
<td>DIP, 225</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA, 1500</td>
<td>...</td>
<td>4-6</td>
<td>42/111 (38)</td>
<td>49/288 (17)</td>
<td>0.001</td>
<td>IV</td>
<td>Bussman et al, 1987(^{27})</td>
</tr>
<tr>
<td>Warfarin, INR ≥2.5</td>
<td>&lt;12</td>
<td>5</td>
<td>16/43 (37)</td>
<td>12/42 (29)</td>
<td>NS</td>
<td>II</td>
<td>Urban et al, 1988(^{38})</td>
</tr>
</tbody>
</table>

*Abbreviations same as in Table 4.*

5128

**Antithrombotic Therapy after Bypass Grafts and PTCA (Stein et al)**
(p = 0.039) (level I). They did not observe such beneficial effects in comparison to control subjects, however; among patients treated with aspirin, 300 mg/day, plus dipyridamole, 225 mg/day. Bussman and associates, in a retrospective study, observed fewer patients with restenosis among those treated with aspirin, 1,500 mg/day, vs placebo, 49 of 288 patients (17 percent) vs 42 of 111 patients (38 percent) (p<0.001) (level IV). They observed no benefit of a reduced dose of aspirin (dose unstated); 32 percent of these patients had restenosis.

Warfarin, in comparison to placebo, showed no benefit in preventing restenosis, 12 of 42 (29 percent) vs 16 of 43 (37 percent) (NS) (level II). Patients treated with warfarin (North American PT ratio 2 to 2.5) in comparison to aspirin, 325 mg/day, showed no statistically significant difference in the frequency of recurrent stenosis 44 of 122 (36 percent) vs 34 of 126 (27 percent) (NS) (level II). Fish oil has also been evaluated for the prevention of restenosis, but the results have been inconsistent.40-43

SUMMARY: PTCA

1. It is standard practice, in patients undergoing coronary angioplasty, to administer heparin during the procedure. The usual dose is 10,000 U administered intravenously, followed by a continuous infusion or intermittent heparin to maintain therapeutic levels. We found no evidence to indicate that this standard should be modified.

2. There is no evidence that prolonged (18 to 24 h) heparin is of any benefit over a few hours in preventing acute thrombosis in patients who had uncomplicated procedures (level II). Based upon standard practice, heparin for 16 to 24 h is administered for unstable angina, complex lesions, multivessel angioplasty, and a suboptimal result.

3. Antiplatelet agents (in addition to heparin) reduce periprocedural coronary thrombosis and are indicated (level I and II studies).26,27

4. Aspirin alone was as effective as aspirin plus dipyridamole (level II).30

5. The dose of aspirin that was used in most studies was 650 mg/day to 900 mg/day (although sometimes with dipyridamole), and aspirin was started before the angioplasty. Lower doses of aspirin (80 mg/day), started one day before the angioplasty, were also effective (level II).30

6. The evidence that antiplatelet agents may prevent or modify late restenosis is inconsistent (level II). (level IV), (level I).

7. Warfarin, in small size studies, was not effective in preventing late restenosis (level II), but it was not worse than aspirin (level II).30

RECOMMENDATIONS: CORONARY ARTERY BYPASS GRAFTS

1. It is recommended that antiplatelet agents be administered to reduce the frequency of saphenous vein bypass graft closure. This recommendation is based upon several level I and level II studies that showed significant benefits of therapy, as well as meta-analysis that included additional studies, the individual results of which did not reach significance.14

2. Aspirin alone is recommended. The dose of aspirin that has been shown to be beneficial in graft patency in rigorously performed studies is 325 mg/day or higher. Aspirin, 325 mg/day, started 6 h after surgery is safer than aspirin, 325 mg/day, before operation, and the rate of occlusion is similar. If bleeding prevents the administration of aspirin at 6 h after surgery, we recommend starting as soon as possible thereafter.

3. Dipyridamole, 225 mg/day, in addition to aspirin, 150 mg/day, has been shown in one study to be more effective than aspirin, 150 mg/day, alone if dipyridamole, 400 mg/day, is administered before surgery and aspirin is started within 7 h after surgery. We recommend this as an alternative to treatment with aspirin alone.

4. Regarding the duration of antithrombotic treatment, aspirin is indicated indefinitely in coronary heart disease, as described elsewhere in this symposium. The benefits of prolonged treatment with aspirin, specifically for graft patency, are uncertain. The evidence for continuing dipyridamole after one month is weak.

5. For patients allergic to aspirin, ticlopidine, 250 mg twice daily, beginning 48 h after surgery, has been reported in one study to be effective and may be considered as an alternative.9

6. There are no studies that show a benefit of antiplatelet agents in patients with internal mammary artery grafts. Treatment of patients with internal mammary artery bypass grafts with antiplatelet agents is considered optional. However, as in recommendation 4, aspirin is indicated in patients with coronary heart disease.

RECOMMENDATIONS: PTCA

1. Heparin, 10,000 U intravenously, followed by a continuous infusion of heparin, or intermittent heparin to maintain the activated partial thromboplastin time 1.5 to 2 times control is recommended on the basis of standard practice.

2. It is recommended that heparin be discontinued 2 to 4 h after the conclusion of an uncomplicated procedure (level II). Based upon standard practice, heparin for 16 to 24 h is recommended for unstable angina, complex lesions, multivessel angioplasty, and a suboptimal result.
3. Aspirin is recommended in addition to heparin. It is recommended that aspirin, 325 mg/day, be administered one day prior to the angioplasty and continued indefinitely after the procedure, although possibly at a lower dose. The use of aspirin before and during the procedure is based upon level I and II studies that showed a reduction of periprocedural coronary thrombosis. The dose of aspirin before and during the procedure is uncertain and is based upon a level II study that showed that aspirin, 1,500 mg/day, was not more effective than aspirin, 80 mg/day, in preventing acute thrombosis in PTCA (level II).

4. Dipyridamole in addition to aspirin and heparin is optional and has been used in trials that showed effectiveness in comparison to placebo (level II), (level I).

5. Long-term aspirin (160 to 325 mg/day) is recommended because of its effect on coronary heart disease, although its effect on restenosis following PTCA is inconsistent.

REFERENCES


occlusion occurring after successful percutaneous transluminal
 coronary angioplasty: temporal relationship to discontinuation
33 Ellis SG, Boubin GS, Wilentz J, et al. Effect of 18- to 24-hour
34 Swanson KT, Vlieutstra RE, Holmes DR, et al. Efficacy of
 adjunctive dextran during percutaneous transluminal coronary
 angioplasty. Am J Cardiol 1984; 54:447-48
35 Schwartz L, Lesperance J, Bourassa MG, et al. The role of
 antiplatelet agents in modifying the extent of restenosis following
 percutaneous transluminal coronary angioplasty. Am Heart J
 1990; 119:232-36
36 Heiss HW, Just H, Middleton D, et al. Reocclusion prophylaxis
 with dipyridamole combined with acetylsalicylic acid following
 PTA. Angiology 1990; 41:263-69
 experience in restenosis after coronary angioplasty. Am J Cardiol
 1987; 60:48-49
38 Urban P, Buller N, Fox K, et al. Lack of effect of warfarin on
 the restenosis rate or on clinical outcome after balloon coronary
39 Thornton MA, Groentzig AR, Hollman J, et al. Coumadin and
 aspirin in prevention of recurrence after transluminal coronary
40 Grigg LE, Kay TWH, Valentine PA, et al. Determinants of
 restenosis and lack of effect of dietary supplementation with
 eicosapentaenoic acid on the incidence of coronary artery
41 Milner MR, Gallino RA, Leffingwell A, et al. Usefulness of fish
 oil supplements in preventing clinical evidence of restenosis
 after percutaneous transluminal coronary angioplasty. Am J
 Cardiol 1989; 64:294-99
42 Dehmer GJ, Popma JJ, Van Den Berg EK, et al. Reduction in
 the rate of early restenosis after coronary angioplasty by a diet
 supplemented with n-3 fatty acids. N Engl J Med 1988; 319:733-
 40
43 Reis GJ, Boucher TM, Sipperly ME, et al. Randomised trial of
 fish oil for prevention of restenosis after coronary angioplasty.
 Lancet 1989; 2:177-81