Role of platelets and platelet inhibitors in aortocoronary artery vein-graft disease

Valentin Fuster, M.D., and James H. Chesebro, M.D.

ABSTRACT To study the prevention of occlusion of aortocoronary-artery bypass grafts, we conducted a prospective, randomized, double-blind trial comparing long-term administration of dipyridamole (begun 2 days before operation) plus aspirin (begun 7 hr after operation) with placebo in 407 patients. Results at 1 month and at 1 year showed a reduction in the rate of graft occlusion in patients receiving dipyridamole and aspirin. On the basis of our clinical trial and our experimental studies in dogs and pigs, we describe four consecutive phases of aortocoronary artery bypass vein-graft disease: (1) an early postoperative phase of platelet thrombotic occlusion, which is significantly prevented by platelet inhibitor therapy when started in the perioperative period; in addition, occlusion rates are presently decreasing, perhaps related to better surgical and technical experience; (2) an intermediate phase of platelet-related intimal hyperplasia, within the first postoperative year, which is not prevented with platelet inhibitor therapy; (3) a late phase of occlusion, toward the end of the first postoperative year, in which intimal hyperplasia or complicating platelet thrombi superimposed on the intimal hyperplasia may contribute to occlusion; platelet inhibitor therapy is of significant benefit in the prevention of this thrombotic type of occlusion; (4) a phase of atherosclerotic disease, after the first postoperative year, in which the role of platelets and of platelet inhibitor therapy is under investigation. Circulation 73, No. 2, 227–232, 1986.

CORONARY VEIN-GRAFT DISEASE is an important contributor to the morbidity after coronary artery bypass surgery. It may be responsible for return of angina pectoris, myocardial infarction, and compromised left ventricular function. The natural history of vein-graft disease, its pathogenesis, and its prevention with drug therapy have been illuminated by recent experimental and clinical studies.

Natural history of vein-graft disease (Figure 1). Coronary vein grafts may be individual, sequential, or branched Y and are usually placed in three or more arteries. Hence, in interpreting data on the natural history of vein-graft disease, occlusion rates should be specifically expressed per distal anastomosis, per graft, or per patient, and this is not always stated. Another difficulty is that studies of consecutive patients are needed for accurate determination of occlusion rates, but such studies are few. There is a wide variation also in occlusion rates, depending on time after operation and risk factors for occlusion.

Early phase of occlusion. Cumulative overall risk of occlusion per distal anastomosis is greatest during the first year and increases more slowly thereafter. The postoperative occlusion rate at one month is 8% to 18%, but the occlusion rate per patient, with one or more distal anastomosis occluded, in the same period ranges from 21% to 38%. Analysis of risk factors for early occlusion is essential in drug trials, since randomization does not ensure equality of treatment groups, and therapy should be analyzed in subsets at equal risk. In our study, two important risk factors that increased the early occlusion rate of bypass grafts were low vein-graft blood flow and a small luminal size of the grafted artery (Table 1); such factors mainly result from decreased distal runoff or severe arterial disease. Other risk factors of vein-graft occlusion are endarterectomy, bypass to the left circumflex or right coronary artery, local atheromas at the arteriotomy site, or extension of the arteriotomy into a branch vessel, postoperative elevated serum lipids, and smoking. Currently, there is an overall impression that the early postoperative occlusion rates are decreasing, perhaps related to...
better surgical and technical experience as well as to wider use of circular sequential grafts and internal mammary artery grafts.

**Intermediate phase of intimal hyperplasia.** All patent grafts develop some intimal hyperplasia within the first year after operation. \(^{12,13}\) This produces an angiographically detectable diffuse reduction in the caliber of the vein graft averaging 25% to 30% compared with the diameter of the graft early after operation. \(^{14,15}\) By 12 months, 5% to 10% of the patent grafts show at least a 50% segmental luminal narrowing, often at the site of the anastomosis between the graft and the recipient artery.\(^ {15}\)

**Late phase of occlusion.** The overall occlusion rate per distal anastomosis is about 16% to 26% in the first postoperative year.\(^ {4,5,15-17}\) About 41% to 47% of patients will have one or more distal anastomoses occluded in that time. The same risk factors that affect early occlusion rates also affect the late occlusion rates.\(^ {18}\) As previously mentioned, because the early postoperative occlusion rates are decreasing, it is reasonable to think the overall occlusion rates observed in the first postoperative year will also be lower.

**Phases of atherosclerotic disease.** The overall occlusion rate per distal anastomosis at 5 to 7 years is 25% to 35%\(^ {15,19}\) and at 10 years is about 50%.\(^ {19,20}\) In addition, of the grafts patent at 10 years, about 45% have some atherosclerotic narrowing of the lumen.\(^ {19,20}\)

**Role of platelets in the pathogenesis of vein-graft disease.** The pathogenesis of vein graft occlusion appears to have some similarities to the development and progres-

### FIGURE 1

Scheme of the phases of vein-graft disease leading to occlusion within the first year postoperatively: (1) early thrombotic occlusion (high in panel, left), (2) intermediate phase of intimal hyperplasia (low in panel, middle), and (3) late phase of occlusion related to intimal hyperplasia (low in panel, right), or to complicating thrombotic occlusion superimposed on the intimal hyperplasia and fibrotic organization of thrombus (high in panel, right). The phase of atherosclerotic disease, after the first postoperative year, is not represented in the scheme. (From Advances in Prostaglandin, Thromboxane and Leukotriene Research 3: 286, 1985. Copyright 1985, Raven Press, New York. Reprinted with permission.)

### TABLE 1

Frequency of occlusion in all individual vein grafts within 6 months of operation according to blood flow and coronary arterial lumen diameter

<table>
<thead>
<tr>
<th>Blood flow (ml/min)</th>
<th>No. of grafts occluded/total No. (%) occluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>22/64 (34)</td>
</tr>
<tr>
<td>41–80</td>
<td>23/131 (18)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>4/70 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>49/265 (18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lumen diameter (mm)</th>
<th>No. of grafts occluded/total No. (%) occluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>6/16 (38)</td>
</tr>
<tr>
<td>&gt;1.0–1.5</td>
<td>28/130 (22)</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>15/94 (16)</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>0/21 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>49/261 (19)</td>
</tr>
</tbody>
</table>
sion of atherosclerosis, except that during the first year the process is accelerated and very thrombotic.

Early phase of occlusion (figure 1). Vein grafts are vulnerable to endothelial damage, which may occur when the vein is harvested, by handling during the operation, by delay between procurement and placement, and by the sudden exposure to the high-pressure, pulsatile arterial system.21, 22 Platelet deposition occurs in areas of endothelial damage as soon as blood begins to flow through the vein graft.21 This adherence and the consequent release of platelet factors together initiate mural or occlusive thrombus formation that begins during the operation.22, 23 Thus vein-graft occlusion within the first month of operation is mainly thrombotic in origin,23, 24 with an important platelet component. New approaches for the preventing damage to venous endothelium during harvesting and manipulation should decrease this early phase of occlusion.25

Intermediate phase of intimal hyperplasia (figure 1). Smooth muscle cell proliferation and intimal hyperplasia of the vein graft may appear within 30 days after operation.24 The process tends to progress in two forms within the first postoperative year24, 26: There is a primary proliferation of smooth muscle cells with both migration from media to intima and mitogenesis in the intimal region most likely caused by platelet-derived growth factors.27-29 This accelerated process of intimal hyperplasia, an early stage of atherosclerotic plaque formation, probably results from long-term mild endothelial damage and the interaction between platelets and the vessel wall.30 The endothelial damage occurs perhaps as a response of the vein graft to the long-term high-pressure pulsatile stress. If this primary hyperplasia is severe and localized, as frequently occurs at the site of the distal anastomosis,16 a total occlusion may result within the first year; if the proliferation is less severe an diffuse, as occurs in most grafts, overall narrowing results. A secondary proliferation of smooth muscle cells associated with the organization of the early mural thrombus28 may also occur postoperatively.

Late phase of occlusion (figure 1). Vein graft occlusion within the first year after operation seems to be related to the rapid progression of the intermediate phase of primary intimal hyperplasia. Intermittent platelet adhesion to mildly injured endothelial surface, without thrombus formation,30 is associated with long-term smooth muscle cell and connective tissue proliferation.26 This may lead to the late occlusion of the graft with or without a superimposed thrombus.

Phase of atherosclerotic disease. Beyond the first year after operation there is further connective tissue synthesis from smooth muscle cells and fibroblasts. This may be followed by incorporation of lipid into the lesions, first intracellularly and then extracellularly. The histologic picture is then indistinguishable from that of arterial atherosclerotic disease.31 From this point on, histologic changes in the vein grafts usually progress slowly, since the grafts resemble arteries, and what they develop is atherosclerotic disease.28

Role of platelet inhibitor drugs. The decision of when to begin drug therapy, the drugs chosen, and their doses should be based on the capacity of the drugs to forestall the vein-graft occlusive process. Because platelet deposition plays a major role in some of the phases leading to occlusion, platelet inhibitors are preferable to oral anticoagulants because the latter have no significant antiplatelet effects. In addition, use of oral anticoagulants is complicated by the fact that it cannot be started in effective doses until 2 days after operation and must be monitored by laboratory testing. Because platelet deposition begins during operation, therapy for prevention of vein graft occlusion should begin before operation to be fully beneficial.

Platelet inhibitors in the early phases of occlusion. In experiments with dogs, dipyridamole given before, just prior to, and early after operation significantly decreased platelet deposition and formation of mural thrombus early after operation.21, 23, 26 Dipyridamole alone in physiologic doses does not prolong the bleeding time and does not increase bleeding during cardiopulmonary bypass operation in dogs or humans;2, 23, 26, 32 whereas aspirin given before operation increases bleeding in dogs21, 23, 26 but not consistently in humans.33, 34 Thus, administration of aspirin might be avoided for approximately 1 week before operation.

Using the above experimental information and rationale, we designed and conducted a prospective, randomized, double-blind, placebo-controlled clinical trial of dipyridamole (begun 2 days before operation) plus aspirin (begun 7 hr after operation) in 407 patients (table 2).3 Angiographic examination of the vein grafts was done early (median 8 days, range 7 days to 6 months) in 360 patients (88%). Within 1 month of operation, 2% of vein-graft distal anastomoses were occluded in the treated group and 10% were occluded in the placebo group. The proportion of patients with one or more distal anastomoses occluded was 6% in the treated group and 22% in the placebo group (p = .003) (figure 2).

Beginning therapy before and immediately after operation probably accounted for the striking benefit in this trial compared with borderline benefit or no benefit in six previous randomized trials where therapy was
TABLE 2
Platelet inhibitor therapy for aortocoronary vein bypass operations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole</td>
<td>On day</td>
<td>75 mg qid</td>
</tr>
<tr>
<td></td>
<td>6 A.M.</td>
<td>100 mg orally</td>
</tr>
<tr>
<td></td>
<td>7 hrs after operation</td>
<td>75 mg orally</td>
</tr>
<tr>
<td></td>
<td>1½ hrs</td>
<td>325 mg via nasogastric tube</td>
</tr>
</tbody>
</table>

 begun 2 days before operation. On day of operation 6 A.M.: dipyridamole 100 mg orally. One hour after operation: dipyridamole 100 mg via nasogastric tube (clamp, 1½ hr). Seven hours after operation: dipyridamole 75 mg and aspirin 325 mg via nasogastric tube (clamp, 1½ hr). On day after operation Dipyridamole 75 mg and aspirin 325 mg orally tid.

No other aspirin or prostaglandin-inhibitor drugs.

started 1 to 4 days after operation. A small patient population with high occlusion rates 4 months after operation (35% of distal anastomoses) showed decreased occlusion to 19% of distal anastomoses (a rate slightly greater than our placebo group) when therapy with aspirin at the low dose of 100 mg/day was used. The probable role of low-dose aspirin needs to be confirmed in larger trials. One such trial in the United States is the ongoing Veterans Administration Cooperative Study.

No excessive bleeding is caused by preoperative dipyridamole plus early postoperative aspirin therapy. The safety of this therapy has been documented by canine studies and intraoperative infusion of dipyridamole in patients. Furthermore, we have demonstrated the lack of increase in blood loss from the chest tube and the lack of need for transfusion of red cells, frozen plasma, or platelet during or after operation. If future trials with low-dose aspirin alone show benefit in preventing early vein-graft occlusion without increasing perioperative bleeding, then preoperative treatment with this agent might be accepted by cardiothoracic surgeons.

Platelet inhibitors in the intermediate phase of hyperplasia. Our studies in dogs and pigs have shown that antiplatelet therapy does not prevent the single layer of platelet deposition that can stimulate the process of primary proliferation of smooth muscle cells and intimal hyperplasia. Likewise, our preliminary results in humans show no significant difference in vein graft dimensions over the first year between treated and control subjects. That is, patients from our trial who

![Graphs showing cumulative occlusion rates for distal anastomoses and patients.](http://circ.ahajournals.org/)

FIGURE 2. Left. Cumulative percentage of all vein-graft coronary artery distal anastomoses occluded in patients who had vein-graft angiography performed by t days after the operation or sooner. Right. Cumulative percentage of all patients who had one or more distal anastomoses occluded at vein-graft angiography by t days after the operation or sooner. The occlusion rates did not change from 120 to 180 days after operation; only six patients underwent angiography during this period. (From Chesebro et al., N Engl J Med 307: 73, 1983.)

TABLE 3
Vein-graft diameter (mm) early and late postoperatively

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of VG</th>
<th>EPO</th>
<th>LPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>152</td>
<td>5.0 ± 0.07</td>
<td>3.8 ± 0.06</td>
</tr>
<tr>
<td>Placebo</td>
<td>103</td>
<td>5.0 ± 0.09</td>
<td>3.8 ± 0.07</td>
</tr>
</tbody>
</table>

VG = vein grafts; EPO = early postoperatively; LPO = late postoperatively.
had individual grafts patent 1 month after operation were continued in the trial and had repeat angiography 1 year later. Reduction in vein graft mean diameter, which appears to result from intimal hyperplasia,24 was measured from orthogonal spot films. The change in the vein graft for the entire length and for the proximal and distal 2 cm did not differ in the treated and placebo groups (table 3). Thus the benefit of antiplatelet therapy appears to be in the prevention of early thrombus formation but not in prevention of the subsequent discrete platelet deposition, which leads to smooth muscle cell proliferation and intimal hyperplasia.

Platelet inhibitors in the late phase of occlusion. In our trial, the beneficial effect of platelet inhibition in preventing graft occlusion was less striking at 1 year than early after operation.18 Thus all grafts patent up to 1 month after operation, the percentage developing late occlusion was reduced from 14% in the placebo group to 9% in the treated group; of patients with all grafts patent up to 1 month after operation, the percentage developing late occlusion was reduced from 27% in the placebo group to 16% in the treated group (p = .038) (figure 3). This less striking beneficial effect of platelet inhibition late after operation is not unexpected. As we discussed earlier, we cannot expect the primary proliferative process that affects late graft occlusion to be significantly prevented by platelet inhibitors. We believe that the slight therapeutic benefit of these agents late postoperatively results from the prevention of thrombus formation on the intimal hyperplasia rather than to the prevention of the primary occlusive proliferative process.

Platelet inhibitors in the phase of atherosclerotic disease. After the first postoperative year, vein grafts develop atherosclerosis similar to that in the native coronary arteries. Our ongoing 5 year trial of dipyridamole and aspirin19 for prevention of the progression of disease in native coronary arteries should provide further insight concerning the long-term use of this therapy in surgical patients. We expect to report our results by 1987.

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Addendum
References


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