Antiplatelet Therapy to Prevent Coronary Artery Bypass Graft Occlusion

Julie E. Buring, DSc, and Charles H. Hennekens, MD, DrPH

Oclusion rates after coronary artery bypass surgery rise from about 10–15% per distal anastomosis in the first month to approximately 16–26% at 1 year, 2% per year in the next 5 years, and 5% per year for the remainder of the decade. Rates are thus about 37% at 5–7 years and 55% at 12 years. As a result, the identification of a safe and effective medical therapy to prevent occlusion, such as the antiplatelet regimens reported in this issue of Circulation by Sanz and colleagues, could enhance the efficacy of this surgical technique.

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Antiplatelet therapy following bypass surgery, with aspirin alone or in combination with dipyridamole, has been studied extensively. The first trial to find a positive result for antiplatelet treatment was the Mayo Clinic trial. This double-blind, placebo-controlled randomized trial tested a combined regimen of aspirin and dipyridamole on 407 subjects. Angiography was obtained on 360 (88%) subjects within the first 6 months and again on 343 (84%) after an average of 12 months of treatment. Treatment consisted of preoperative dipyridamole (100 mg q.i.d.) for 2 days and, after immediate postoperative treatment with 100 mg dipyridamole by nasogastric tube, a combined regimen of aspirin (325 mg t.i.d.) and dipyridamole (75 mg t.i.d.) for 12 months. Occlusion rates within 1 month of surgery were significantly lower in those patients assigned antiplatelet therapy: 8% of the patients in the treated group had occlusion compared with 21% in the placebo group (p=0.003). There was also a benefit noted in occlusion rates observed after 1 year: 22% of the treated patients compared with 47% of the placebo patients (p=0.048) had occlusion.

In the subsequent Wadsworth Veterans Administration trial of 147 bypass patients, there was a trend for benefit for the subgroup of patients treated less than 60 hours after surgery. In this subgroup, the percentage of patients with vein graft occlusion was 8% for aspirin compared with 23% in placebo (p<0.05). These findings of a benefit of aspirin are consistent with those in all trials that initiated treatment within 24 hours postoperatively. In earlier trials reporting null results, treatment was started more than 72 hours postoperatively.

Several trials have compared antiplatelet and anticoagulant therapies. In a trial of 50 patients randomized 3 days postoperatively to a combined antiplatelet regimen of aspirin (325 mg t.i.d.) and dipyridamole (75 mg t.i.d.), anticoagulant therapy with warfarin, or placebo. No benefit was found for either the antiplatelet or anticoagulant regimens. In another trial of 207 patients randomized to aspirin (600 mg b.i.d.), warfarin, or placebo beginning 3–4 days postoperatively, there was an apparent but nonsignificant benefit in graft patency with both treatments in those who underwent angiography less than 24 months after surgery (80% in aspirin, 83% in warfarin, 69% in placebo), but this was no longer evident in those who underwent angiography 25–48 months after surgery.

More recently, 249 patients were randomized to 25 mg b.i.d. aspirin and 200 mg b.i.d. dipyridamole, or standard anticoagulant therapy, and to either 3 months or 1 year of treatment. When angiography was performed within 2 weeks of surgery, there was no significant difference between the two active-treatment groups: 16% of those treated with dipyridamole and aspirin and 19% of the patients treated with anticoagulants had occlusion. Extended treatment with both regimens, however, suggested a greater but still nonsignificant benefit: 22% of all patients treated with either active therapy for an additional 9 months had late graft occlusion compared with 32% in all those who received placebo for those 9 months (p=0.08). Further, the difference in number of individual grafts occluded (6% treated, 13% placebo) was statistically significant (p=0.01).

Aspirin has also been compared with other antiplatelet agents. A recent trial randomized 209 patients to aspirin (50 mg t.i.d.) and dipyridamole (75 mg t.i.d.), triflusal (300 mg t.i.d.) and dipyridamole (75 mg t.i.d.), or placebo. Although no significant differences were found 9 days postoperatively, angiography at 6 months showed a significant benefit.
Graft occlusion rates at 6 months were 24% for placebo, 16% for aspirin and dipyridamole, and 12% for triflusal and dipyridamole ($p=0.027$). However, the analyses were based on the subgroup of those who had both follow-up angiograms (66% of all randomized subjects), so the possibility of bias cannot be excluded when interpreting these findings.

A recent overview of all trials of survivors of myocardial infarction, stroke, transient ischemic attack, and unstable angina to prevent reinfarction, stroke, or vascular death indicated no additional benefit when dipyridamole was added to aspirin. Several trials of coronary artery bypass graft occlusion have also attempted to compare these agents directly. In a randomized trial of 176 patients, aspirin (325 mg t.i.d.) was compared with aspirin (325 mg t.i.d.) and dipyridamole (225 mg q.d.) as well as placebo. Treatment was begun 3–5 days after surgery, and there was no apparent benefit for either active treatment when angiography was performed at 1 year. In the Wadsworth Veterans Administration trial of aspirin alone (325 mg t.i.d.), aspirin (325 mg t.i.d.) and dipyridamole (75 mg t.i.d.), and placebo, there were large and statistically significant reductions in both active groups: 49% ($p=0.04$) for aspirin alone versus placebo and 50% ($p=0.04$) for aspirin and dipyridamole versus placebo.

In a trial of 555 patients comparing treatment with aspirin alone at two dosages (325 mg q.d. and 325 mg t.i.d.), aspirin (325 mg t.i.d.) and dipyridamole (75 mg t.i.d.), sulfinpyrazone (267 mg t.i.d.), and placebo, all active treatments significantly decreased occlusion 2 months postoperatively: graft patency was 93.5% in the aspirin 325 mg q.d. group, 92.3% in aspirin 325 mg t.i.d., 91.9% in aspirin 325 mg t.i.d. and dipyridamole 75 mg t.i.d., 90.2% in sulfinpyrazone, and 85.2% in placebo. At 1 year, the graft occlusion rate in all the aspirin groups combined was 15.8% compared with 22.6% in placebo ($p=0.029$). This 1-year benefit appeared confined to vessels ≤2.5 mm in diameter, where the graft occlusion rate in all aspirin groups combined was significantly ($p=0.008$) lower: 20.1% in aspirin compared with 32.3% in placebo. The graft occlusion rate in the subgroup of aspirin patients taking 325 mg aspirin a day (13.2%) was also significantly lower than the rate in the placebo group ($p=0.05$). Thus, aspirin seemed clearly to be of benefit at both dosage levels and in combination with dipyridamole, but there did not seem to be any material differences between the active therapies, and no additional benefit to therapy continued after the first 3 months.

The current trial by Sanz and colleagues randomized 1,112 patients, a sample twice as large as any previous trial. All patients received dipyridamole (100 mg q.i.d.) for 48 hours before surgery. Aspirin (50 mg t.i.d.) plus dipyridamole (75 mg t.i.d.) yielded a significant benefit when administered postoperatively, and aspirin alone (50 mg t.i.d.) also showed an apparent but nonsignificant trend toward benefit. Whether this represents a true difference in the efficacy of the two regimens or whether the sample size simply was not adequate to compare the efficacy of the two treatments directly is not clear.

In addition to the comparative efficacy of the various postoperative antiplatelet regimens, a number of other important research questions remain: What is the optimal dose of aspirin when given alone? What is the optimal dose for aspirin when given with dipyridamole? What is the optimal duration of therapy? What is the benefit of preoperative versus postoperative treatment? What are the best drugs to use preoperatively; that is, how does aspirin compare with dipyridamole preoperatively? Will the findings on the benefit of antiplatelet therapy, all of which have been derived from saphenous vein grafts, be applicable to internal mammary artery grafts?

In the meantime, the fact that a number of questions remain unanswered should in no way detract from the clear evidence of a benefit of antiplatelet therapy in the prevention of coronary artery bypass occlusion. In that regard, the trial by Sanz and colleagues reported in this issue has added important information to that growing body of evidence.

**References**


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J E Buring and C H Hennekens

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