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Lipid-lowering therapy after coronary artery bypass surgery: the Post-CABG trial

ABSTRACT: The Post Coronary Artery Bypass Graft trial is an important milestone that documents the benefits of treating hypercholesterolemia in patients with severe coronary atherosclerosis who have had bypass surgery. In the present article, we highlight the rationale, study design, and results of the Post-CABG study, which was recently published in the *New England Journal of Medicine.*

In a major study, aggressive LDL-lowering protected saphenous vein coronary bypass grafts

Aggressive lipid-lowering therapy after coronary artery bypass grafting (CABG)—with a goal of achieving a low-density lipoprotein (LDL) concentration of less than 85 mg/dL—reduces the incidence and rate of progression of atherosclerosis in the grafts and, perhaps, the need for repeat revascularization procedures. Anticoagulant therapy with low doses of warfarin, on the other hand, has no effect on these outcomes. These were the principal results of the milestone Post-CABG study, recently published in the *New England Journal of Medicine*.[1]

STUDY RATIONALE

Several previous clinical trials demonstrated that cholesterol-lowering therapy can reduce coronary artery disease events and all-cause mortality in patients both with and without established coronary artery disease.[2–7] In addition, a number of angiographic trials demonstrated that aggressive cholesterol-lowering therapy slows progression of coronary artery disease, and in some cases even causes it to regress.[8–16]

Atherosclerotic lesions develop at an accelerated rate in saphenous vein coronary bypass grafts compared with native coronary arteries, and thrombosis also contributes to occlusion.[17–21] Up to now, not all physicians have accepted that lipid-lowering therapy is beneficial in bypass graft patients.

However, Blankenhorn et al[22] reported beneficial effects of cholesterol-lowering on atherosclerosis in saphenous vein grafts in a randomized intervention trial in 162 men, all younger than 60 years, who took either niacin and colestipol or placebo for 2 years. However, no large-scale trial had been undertaken. The Post-CABG trial used more carefully defined measures of quantitative angiography, included older patients, included women, and was carried out over a longer period of time than the Blankenhorn study.

Furthermore, it had not been demonstrated that lowering LDL cholesterol to less than 100 mg/dL would reduce progression in saphenous vein grafts when compared to more moderate (130 mg/dL) lipid-lowering therapy.

POST-CABG STUDY DESIGN

The purpose of the Post-CABG trial was to assess the effect of two different intensities of lowering LDL cholesterol and the effects of low-dose anticoagulation therapy on angiographically determined narrowing or occlusion of saphenous vein coronary bypass grafts. The trial was sponsored by the National Heart, Lung, and Blood Institute and was carried out in seven clinical centers in the United States and Canada.

Aggressive cholesterol lowering appears beneficial even if it is started several years after the CABG procedure

The study used a two-by-two factorial design with double-blind treatment. Participants and study personnel were blinded to the treatment regimens, lipid levels, and international normalized ratio (INR) determinations throughout the trial. Medication adjustments were determined by a central coordinating center. A total of 1351 patients were randomized, 92% of them men. The mean age at entry was 61.5 years.

Patients underwent angiography at baseline and at the end of the trial, a mean of 4.3 years. Clinical follow-up data were obtained about coronary artery disease events, revascularization procedures, vital status, and the occurrence of other major medical problems.

Eligibility

The study included only patients who:

- Had undergone coronary bypass procedures that included placement of one or more saphenous vein grafts 1 to 11 years before the start of the study.
- Had a left ventricular ejection fraction of at least 30%.
- Had no coronary instability.
- Had at least one measurement of LDL cholesterol of 130 to 175 mg/dL in the prerandomization phase.
- Were 21 to 74 years old at entry.

Lipid-lowering treatment

All patients were instructed in a step-one diet as outlined by the National Cholesterol Education Treatment Program.[23] In addition, the patients were randomly assigned to receive one of two different lipid-lowering regimens:

Aggressive (goal LDL level 60 to 85 mg/dL), starting with lovastatin at 40 mg/day, or

Moderate (goal LDL level 130 to 140 mg/dL), starting with lovastatin at 2.5 mg/day.

Lovastatin doses were doubled if these LDL cholesterol target levels were not met. Cholestyramine (8 g/day) was added if LDL cholesterol levels at two consecutive visits remained greater than 95 mg/dL for patients assigned to the aggressive strategy, or greater than 160 mg/dL for patients assigned to the moderate lipid-lowering strategy.

Anticoagulation treatment

In addition, half the patients were randomly assigned to receive warfarin in low doses (1 to 4 mg/day) to achieve a targeted INR less than 2.0, and half received a corresponding placebo. The actual INR achieved at the end of the dosage adjustment period was 1.4 in the warfarin group and 1.05 in the placebo group.

Angiographic studies at baseline and 4 to 5 years

All 1351 patients underwent quantitative angiography at baseline. Of these, 1192 (88.2%) underwent follow-up studies after 4 to 5 years of treatment. Because of symptoms that occurred in the interval, 139 patients had angiograms before the end of the treatment period. Sixty-seven patients died before the end of the trial; angiographic data were available on 93% of the remaining subjects. All angiograms were read at a central reading center.

A modified-ratio-estimate (MRE) statistic[24] was used to calculate the mean percentage of grafts per patient showing progression (defined as a decrease in lumen diameter of at least 0.6 mm), which was the primary endpoint. The test statistic uses all the information available for each patient by adjusting for the number of grafts per patient.

RESULTS

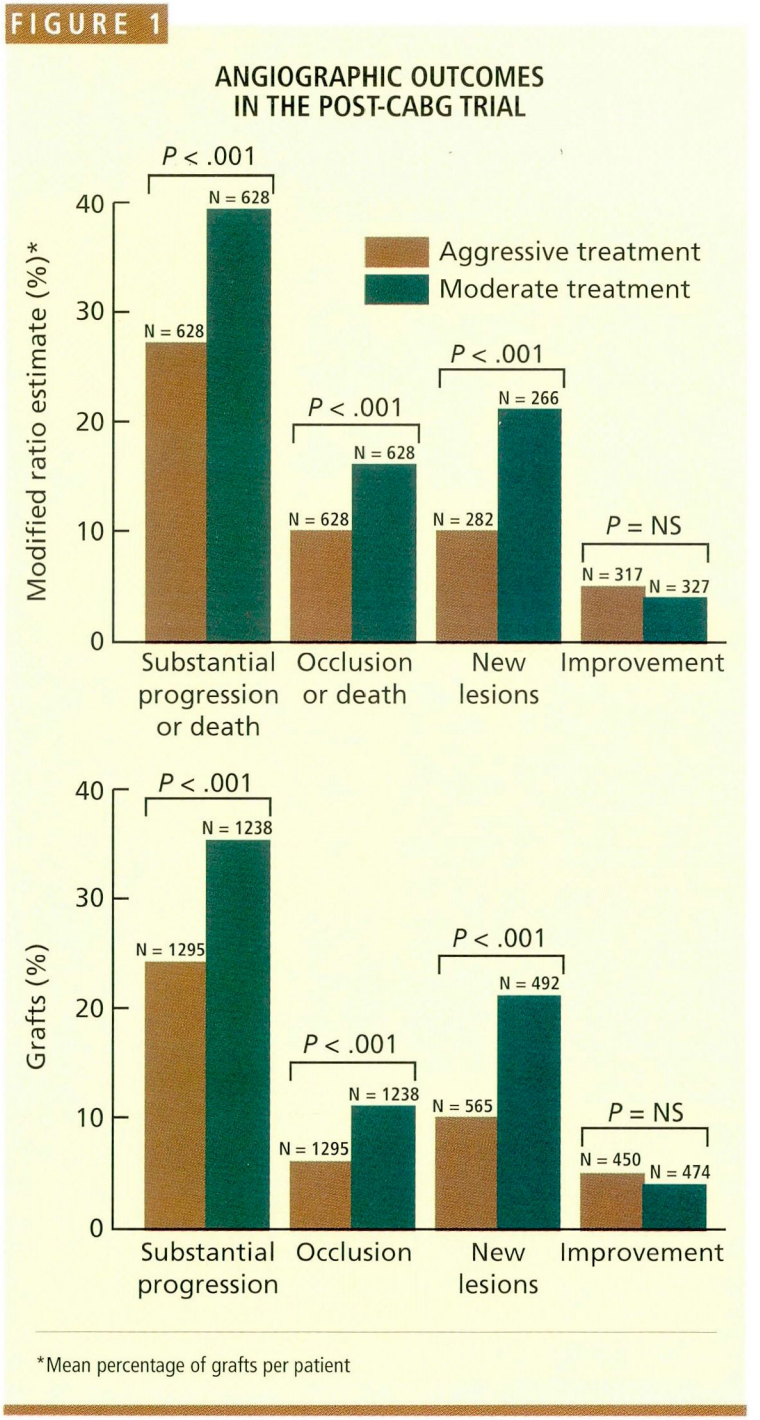
There were no significant differences among the four study groups in baseline characteristics such as age, gender, medical history, medication use, or cholesterol values.

The mean LDL cholesterol concentrations at annual visits ranged between 93 to 97 mg/dL in the aggressive treatment group and 132 to 136 mg/dL in the moderate treatment group.

Analyses of the 1192 follow-up angiograms showed less progression of atherosclerosis in the saphenous vein grafts of patients who underwent aggressive vs moderate LDL-lowering therapy (FIGURE 1): the MRE statistic for the combined endpoint of progression or death was 27% in the aggressive treatment group vs 39% in the moderate treatment group ($P < .001$). New lesions occurred in 10% of patients in the aggressive treatment group, and in 21% of patients in the moderate treatment group. Occlusion occurred in 6% of patients in the aggressive treatment group and in 11% of patients in the moderate treatment group. Low-dose warfarin treatment showed no statistically significant benefit over placebo in any of the angiographic or clinical measures.

Although the trial was not designed to detect differences in clinical events, the rate of revascularization procedures (repeat bypass surgery or angioplasty) was 6.5% in the aggressive cholesterol treatment group—29% lower than the 9.2% incidence in the moderate treatment group ($P = .03$, FIGURE 2). There were no differences among the treatment groups in the rates of either cardiovascular death or death from any cause. Cancer risk was no different among the treatment groups.

FIGURE 1



RECOMMENDATIONS AND CONCLUSIONS

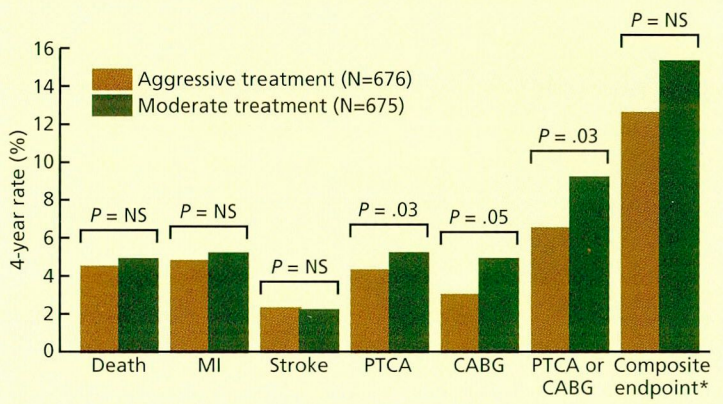
These findings indicate that, in patients with saphenous vein grafts, aggressive LDL-lowering can reduce progression of atherosclerotic narrowing in the grafts, occlusion of the grafts, and the need for repeat coronary bypass surgery or balloon angioplasty.

These results provide a new impetus for preventive treatment in patients with coronary artery disease. The data have broad applicability to patients undergoing coronary artery bypass graft procedures using saphenous vein graft conduits, because the study included both men and women, permitted entry of subjects older than 70 years, and did not exclude participants because of pre-existing illnesses such as diabetes or hypertension.

Moreover, aggressive cholesterol lowering appears beneficial even if it is started several years after the CABG procedure. This study had the power to show the effectiveness of aggressive cholesterol lowering after more than 4 years of therapy, mainly because of the use of quantitative angiography, with which the changes in the lumen diameter of each

FIGURE 2

CLINICAL OUTCOMES IN THE POST-CABG TRIAL



*Death, nonfatal MI, stroke, CABG, or PTCA

portion of each vein graft could be compared using the same technique.

Although the study was not designed to have sufficient power to evaluate clinical outcomes, it is of great clinical interest—albeit of borderline statistical significance—that aggressive lipid lowering seemed to reduce the need for revascularization procedures. This effect may result from stabilization of the atherosclerotic plaque, a change in cholesterol content of the intimal layer, or some other mechanism. If this finding is borne out in larger studies, it implies that cholesterol-lowering has much greater benefits than just reducing the amount of encroachment of the lumen of the grafts.

The absence of any observed benefit from low doses of warfarin also deserves comment. Thrombotic events are now well known to be a part of the occlusive process in both native vessels and surgically placed conduits. The Post-CABG trial data suggest that anticoagulation with warfarin doses that raise INR no higher than 2.0 does not modify this risk. This strategy was used because values in this range were deemed to be safe. In fact, no adverse effects resulted from these low doses of warfarin. Concomitant aspirin use was recommended during the trial and may have modified some possible effects of low-dose warfarin.

Questions remain about how to manage coronary artery disease after CABG:

- Would a greater percent reduction in LDL cholesterol be associated with greater benefit? The Post-CABG trial did not address this question.
- Would other strategies to modify the risk of thrombosis reduce the risk? The absence of beneficial effects of low-dose warfarin reduces enthusiasm for that strategy, but not for warfarin therapy altogether. Warfarin strategies with a goal of a higher INR (eg, 2 to 3) are used in clinical practice and may be considered in a future research project. It is of interest that no significant increases in side effects, death, or complications were seen in the subjects receiving anticoagulation. For the present, it is still advisable to give aspirin to patients who have coronary saphenous vein grafts.
- Does the benefit of aggressive LDL-lowering continue in the longer term and translate into clinical benefit? Long-term follow-up studies will be needed.

Nevertheless, the results of the Post-CABG study give renewed support for lowering LDL cholesterol concentrations to less than 100 mg/dL in all patients with coronary atherosclerosis, including those patients who have had saphenous vein grafts. ■

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