Postscripts From the Post Coronary Artery Bypass Graft Trial
The Sustained Benefit of More Aggressive Cholesterol Lowering and the Enigma of Low-Dose Anticoagulation

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How Valid Are Post-Trial Results?
Properly designed and executed clinical trials provide the foundation for the evidence-based practice of cardiology. The key features of clinical trials that ensure their validity are randomization and blinding and, to a lesser degree, predefined end points, adherence to assigned therapy, careful follow-up and ascertainment of events, and a sufficient number of end point events. The level of certainty that we can assign to the conclusion depends on prior evidence plus the trial results.

Post-trial follow-up exhibits some, but not all, of the features of a clinical trial. Randomization occurs at the outset, but unblinding patients and their physicians at the end of the trial introduces potential confounding. This may take the form of intergroup differences in ongoing medical treatment, in referrals for revascularization (an end point), or in follow-up and outcome ascertainment. Stopping the study medication would obviously progressively attenuate any benefit of therapy. Perhaps the major limitation of post-trial results is that they tend to be more post hoc than a priori. If the follow-up period is going to yield crucial results, why wasn’t it included as part of the original trial? If the results are totally unexpected (low prior probability), shouldn’t another trial be performed to confirm them?

In summary, post-trial follow-up is more akin to a very good cohort study than to a clinical trial. The reader should focus on the potential for confounding and on prior evidence, as well as on the specific results. How does the Post-CABG Trial measure up to these criteria?

How Valid Are the Post-CABG Results for Cholesterol Lowering?
There are precedents for post-trial follow-up with older interventions to lower cholesterol. For example, between 1966 and 1975, the Coronary Drug Project randomized 8341 men with previous infarction to 1 of 4 cholesterol-lowering treatments or to placebo.4 When the trial ended, after a mean follow-up of 6.2 years, none of the interventions had reduced the primary end point of total mortality; however, niacin was associated with a significant reduction in nonfatal infarction. After a total of 15 years of follow-up, 8.8 years after the termination of the study, a survival advantage was seen for niacin-treated patients ($P=0.0004$).

The follow-up of patients enrolled in coronary angiographic trials clearly indicates that progression during studies is a potent predictor of coronary events thereafter. In one report, the relative risk during 44 months of post-trial...
follow-up was 7.3 for cardiac death ($P<0.001$) and 2.3 for cardiac death or nonfatal infarction ($P=0.009$) when comparing progressors to nonprogressors. The Cholesterol Lowering Atherosclerosis Study (CLAS) is quite comparable to Post-CABG: both included only patients with previous saphenous vein bypass graft surgery. Progression in native arteries and progression or new lesions in vein grafts were strongly predictive of coronary events over the 7 years after the end of CLAS.

Given this background, the result of the post-CABG follow-up with respect to the cholesterol-lowering interventions is expected (high prior probability). The angiographic benefit seen with the aggressive strategy at the end of the trial translated into a reduction in clinical events during the subsequent 3 years of follow-up. As pointed out by the investigators, the difference in events was not due to revascularization procedures driven by the findings on the end-of-study angiogram, which would be one potential source of confounding. The post-CABG postscript on aggressive cholesterol lowering can be accepted with a high degree of certainty.

**Can Results in Saphenous Bypass Graft Patients Be Generalized to All Coronary Patients?**

Saphenous vein bypass grafts represent a human model of accelerated atherosclerosis. Within the first year after surgery, intimal hyperplasia develops in all vein grafts and thrombotic occlusion occurs in up to 20%, primarily as a consequence of poor distal runoff. Thereafter, atherosclerosis progresses rapidly, such that by 10 years, approximately half of venous grafts are severely stenotic or occluded. The intimal surface of venous grafts releases less prostacyclin, nitric oxide, and tissue plasminogen activator compared with that of arteries; thus, the vein graft is less resistant to thrombus deposition. Vein grafts also have weaker defenses against lipid uptake.

The pathological features of vein graft atherosclerosis differ somewhat from native coronary atherosclerosis. Vein grafts have less calcification and more diffuse, friable, concentric lesions (as opposed to focal, fibrotic, eccentric lesions), and thrombosis is a more prominent feature in vein grafts. The Glagov phenomenon, compensatory arterial enlargement to preserve lumen size in response to atherosclerosis, does not occur in vein grafts.

Despite these differences, hypercholesterolemia seems to be at least as important a risk factor for vein graft atherosclerosis as it is for native arterial disease. In the Montreal Heart Institute series, total cholesterol, triglycerides, and HDL cholesterol levels were powerful predictors of vein graft disease 10 years after surgery. CLAS and Post-CABG demonstrate marked clinical benefit from LDL cholesterol reduction.

These considerations suggest that it would require only a small leap of faith to extrapolate the Post-CABG results to all patients with coronary atherosclerosis.

**Should the Post-CABG Results Influence our Cholesterol Treatment Thresholds?**

The current National Cholesterol Education Panel guidelines have stood up remarkably well considering that they were published in early 1994, before the major statin trials. They recommend that LDL cholesterol be reduced to ≤100 mg/dL in patients with coronary disease and that drug therapy be instituted to attain this goal when LDL cholesterol is ≥130 mg/dL. For LDL cholesterol levels between 100 and 129 mg/dL, the physician is admonished to use clinical judgment as to whether or not drug therapy should be initiated. The guidelines are now under revision.

On the basis of the Post-CABG results, lowering LDL-cholesterol to just 130 mg/dL can no longer be considered adequate therapy, at least for patients with venous bypass grafts. The absolute between-group differences of 5% for cardiovascular death or nonfatal infarction and 8% for revascularization translate to only 20 and 12.5 patients, respectively, who must be treated more aggressively to prevent one of these major end points.

The American Heart Association’s report on the management of patients after coronary revascularization endorsed the National Cholesterol Education Panel’s LDL cholesterol target of 100 mg/dL. However, it could be argued that LDL cholesterol levels should be lower for patients with vein grafts compared with other coronary patients because of the increased susceptibility of vein grafts to cholesterol uptake and accelerated atherosclerosis. However, the reduction in events with more aggressive treatment in Post-CABG strongly implies that aggressive treatment would also be beneficial in other coronary patients.

In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial (COURAGE), which began to recruit patients in 1999, optimal medical therapy has been defined to include a target LDL cholesterol level of 60 to 85 mg/dL. Several large trials are underway to determine whether a target level in this range provides further event reduction compared with a target of 100 mg/dL. Clearly, the momentum is toward lower LDL cholesterol targets for patients with established atherosclerosis, and the Post-CABG results provide an added push in that direction.

**Can the Mortality Reduction After Low-Dose Anticoagulation Therapy Be Explained?**

Put in the simplest of terms, 4.3 years of low-dose warfarin therapy had no apparent effect on either angiographic progression of vein graft disease or clinical events, yet after 3 additional years of follow-up with the study medication discontinued for all but a small minority of patients (11%), overall mortality was 35% lower in the warfarin group ($P=0.008$). Because warfarin has no known long-lasting physiological effects, it is tempting to label this unexpected result as an aberration.

And yet, as the authors point out, The Medical Research Council’s (MRC) General Practice Research Framework Thrombosis Prevention Trial reported similar results. Low-dose warfarin reduced the primary end point, coronary death plus fatal or nonfatal myocardial infarction, from 12.4 to 9.8 events/1000 person-years, which is a 21% decrease (95%
confidence interval, 4% to 35%), and reduced fatal coronary events by 39% (95% confidence interval, 15% to 57%). The main differences between the trials were the patient population, which in the MRC Trial consisted of men with risk factors but without evidence of coronary disease, and the discontinuation of warfarin after 4.3 years in Post-CABG.

The 2 trials also shared important features. The average international normalized ratio (INR) was 1.47 in the MRC trial and 1.4 in Post-CABG. The average duration of follow-up was well beyond 5 years in the 2 studies. The event rate curves begin to diverge at 3 years in Post-CABG and somewhat earlier in the MRC Trial. The Coumadin Aspirin Reinfarction Study tested low-dose warfarin therapy in survivors of myocardial infarction but followed patients for a median of only 14 months and achieved lower INR values. That warfarin had no effect in this trial is compatible with the MRC and Post-CABG results.

High factor-VII levels were associated with increased cardiac risk, particularly for fatal events, in the Northwick Park Heart Study. The low dose of warfarin that corresponds to an INR of 1.5 reduces factor-VII levels from the high-risk to the low-risk stratum. Presumably, factor VII returns to pretreatment levels after warfarin is discontinued, so that this mechanism cannot account for the post-trial event reduction in the Post-CABG patients.

The absence of angiographic differences between the warfarin and placebo groups strongly suggests that the effect of warfarin (if it exists) works through a different mechanism than atherosclerosis progression. The pattern of event reduction with warfarin is also strikingly different than with aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. The MRC Trial consisted of men with risk factors but without evidence of coronary disease, and the discontinuation of warfarin after 4.3 years in Post-CABG.

Should Low-Dose Anticoagulation Be Used in Patients After Bypass Grafting?

On the basis of these considerations, the evidence is not strong enough to treat post-bypass patients routinely with low-dose warfarin. Yet, this conclusion seems vaguely disatisfying. We turn the letter over. There is nothing on the back. We read the postscript again and then the whole letter. We put it down and ponder. Reality leaves a lot to the imagination.

References


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