THE EFFECT OF AGGRESSIVE LOWERING OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS AND LOW-DOSE ANTICOAGULATION ON OBSTRUCTIVE CHANGES IN SAPHENOUS-VEIN CORONARY-ARTERY BYPASS GRAFTS

THE POST CORONARY ARTERY BYPASS GRAFT TRIAL INVESTIGATORS*

Abstract

Background Obstructive changes often occur in aortocoronary saphenous-vein bypass grafts because of atherosclerosis and thrombosis. We studied whether aggressive lowering of low-density lipoprotein (LDL) cholesterol levels or low-dose anticoagulation would delay the progression of atherosclerosis in grafts.

Methods We studied 1351 patients who had undergone bypass surgery 1 to 11 years before baseline and who had an LDL cholesterol level between 130 and 175 mg per deciliter and at least one patent vein graft as seen on angiography. We used a two-by-two factorial design to assign patients to aggressive or moderate treatment to lower LDL cholesterol levels (with lovastatin and, if needed, cholestyramine) and to treatment with warfarin or placebo. Angiography was repeated an average of 4.3 years after baseline. The primary angiographic outcome was the mean percentage per patient of grafts with a decrease of 0.6 mm or more in lumen diameter.

Results As measured annually during the study period, the mean LDL cholesterol level of patients who received aggressive treatment ranged from 93 to 97 mg per deciliter; with moderate treatment, the range was from 132 to 136 mg per deciliter (P < 0.001). The mean international normalized ratio was 1.4 in the warfarin group and 1.1 in the placebo group (P < 0.001). The mean percentage of grafts with progression of atherosclerosis was 27 percent for patients whose LDL cholesterol level was lowered with aggressive treatment and 39 percent for those who received moderate treatment (P < 0.001). There was no significant difference in angiographic outcome between the warfarin and placebo groups. The rate of revascularization over four years was 29 percent lower in the group whose LDL cholesterol level was lowered aggressively than in the group receiving moderate treatment (6.5 percent vs. 9.2 percent, P = 0.03).

Conclusions Aggressive lowering of LDL cholesterol levels to below 100 mg per deciliter reduced the progression of atherosclerosis in grafts. Low-dose warfarin did not reduce the progression of atherosclerosis. (N Engl J Med 1997;336:153-62.)

©1997, Massachusetts Medical Society.

Address reprint requests to the Post CABG Coordinating Center, Maryland Medical Research Institute, 600 Wyndhurst Ave., Baltimore, MD 21210.

*The manuscript was prepared by the following investigators, who assume responsibility for the overall content: Lucien Campeau, M.D., Genell L. Knatterud, Ph.D., Michael Domanski, M.D., Donald B. Hunninghake, M.D., Carl W. White, M.D., Nancy L. Geller, Ph.D., and Yves Rosenberg, M.D. Investigators and centers participating in the trial are listed in the Appendix.
the risk of illness and death from cardiovascular causes as the serum LDL cholesterol level rises from 60 mg per deciliter to 200 mg per deciliter (from 1.6 mmol per liter to 5.2 mmol per liter)\textsuperscript{21,22} and on the initial recommendations of the National Cholesterol Education Program.\textsuperscript{23}

**METHODS**

**Study Design**

There were seven clinical centers, a coordinating center, an angiogram-reading center, an apolipoprotein core laboratory, and a hematology core laboratory. The data and safety monitoring board and the institutional review boards of the individual centers approved the protocol, and the patients gave written, informed consent. Enrolled patients were seen by study staff every 6 weeks for 15 months and every 3 months thereafter.

**Selection of Patients**

Patients were identified who were 21 to 74 years of age, had LDL cholesterol levels of no more than 200 mg per deciliter, and had had at least two saphenous-vein coronary bypass grafts placed 1 to 11 years before the start of the study. Of these patients, we deemed eligible those who had LDL cholesterol levels of 130 to 175 mg per deciliter (4.3 mmol per liter) and triglyceride levels below 300 mg per deciliter (3.4 mmol per liter), as measured at any visit to a study physician after the initiation of a Step 1 diet\textsuperscript{24}; two patent saphenous-vein grafts (with stenosis of less than 75 percent) in men (one in women); and an ejection fraction of no less than 30 percent. Major exclusion criteria included a likelihood of revascularization or death in five years, unstable angina or myocardial infarction within six months before the start of the trial, severe angina, heart failure, and contraindications to treatment with any of the study medications. Eligible patients were randomly assigned by the coordinating center to receive either aggressive or moderate treatment to lower the LDL cholesterol level and to receive either warfarin or placebo.

**Treatment**

**Lowering of Lipid Levels**

In the aggressive-treatment group, lovastatin was initially given in doses of 40 mg per day, as compared with 2.5 mg per day in the moderate-treatment group. Lipid levels were measured in clinical-center laboratories certified by the Centers for Disease Control and Prevention; results were transmitted to the coordinating center by staff members who did not have responsibility for patient care. The staff of the coordinating center issued recommendations to double the lovastatin doses, if deemed necessary, in order to reach a target LDL cholesterol level of less than 85 mg per deciliter in the aggressive-treatment group and a target of less than 140 mg per deciliter in the moderate-treatment group. If a patient’s LDL cholesterol level fell below 60 mg per deciliter in the aggressive-treatment group or 130 mg per deciliter in the moderate-treatment group, the lovastatin dose was reduced. Cholestyramine, in a dose of 8 g per day, was added to the regimen if a patient’s LDL cholesterol level at two consecutive visits remained above 95 mg per deciliter (2.5 mmol per liter) in the aggressive-treatment group or at or above 160 mg per deciliter (4.1 mmol per liter) in the moderate-treatment group. Patients given cholestyramine continued to receive 80 mg of lovastatin per day in the aggressive-treatment group and 5 mg per day in the moderate-treatment group (that is, double the initial dosage).

**Anticoagulation**

The dose of warfarin or placebo was 1 mg at entry. After the dosage of lipid-lowering medications given to a patient was stabilized, the patient was instructed to increase the daily dose of warfarin (or placebo) by 1 mg, starting two weeks before the next scheduled study visit. This 1-mg increase occurred for each of three consecutive visits (up to a total dose of 4 mg per day) unless the patient’s international normalized ratio was 2.0 or higher. Biotrack machines (Boehringer Mannheim, Fremont, Calif.), which provided clinical-center staff with coded readings, beeped if an international normalized ratio was 2.0 or higher. If the machine beeped, the patient’s daily dose of warfarin or placebo was reduced by 1 mg. If a review by the coordinating center indicated that the international normalized ratio of a patient receiving warfarin was 1.8 or more, but less than 2.0, notice was sent to the physician to keep the medication at the last dosage given before the international normalized ratio was determined. Similar notices were also sent out for a random sample of patients given placebo. All patients in the study were encouraged to take 81 mg of aspirin per day.

**Angiographic Methods**

Base-line angiograms and follow-up angiograms (performed four to five years after enrollment) were obtained with catheterization techniques that permitted computer-assisted quantitative measurement (CAAS System, PIE Medical, Maastricht, the Netherlands).\textsuperscript{24} Nitroglycerin was given to all patients, with the same route of administration, during both base-line and follow-up studies. All grafts were visualized in at least two orthogonal projections. If the graft could not be injected, aortic-root injection was performed. At follow-up, the same views and film sequences were repeated.

After the initial qualitative evaluation by the angiogram-reading center, the single pair of matched end-diastolic frames were selected from the base-line and follow-up angiograms in which any graft lesions were best seen. Quantitative assessments of the angiograms were then performed by personnel blinded to other patient information. The following information was obtained: the mean and minimal diameter of each graft, the minimal diameter and percentage of stenosis at the site of any lesion, and the diameter of the lumen at the lesion site showing the greatest change (progression or regression) from base line. In 40 study patients, the standard deviation of repeated measurements of the diameter of the graft at the site of the lesion after injections of contrast material separated by 20 minutes was 0.2 mm. A substantial change was defined as a change of 0.6 mm or more (3 SD). Similar measurements of variation (SD = 0.2 mm) have been found for repeated readings of both native coronary arteries\textsuperscript{25} and grafts.\textsuperscript{26,27} Unscheduled interim angiography, performed because patients had symptoms, often did not permit accurate computer-assisted quantitative measurement, but did allow for a less precise qualitative classification of lesions into prespecified categories, according to the degree of stenosis (0, 1 to 24, 25 to 49, 50 to 74, 75 to 89, and 90 to 100 percent). A substantial change was defined as a change of two categories for lesions with stenosis of less than 50 percent at base line, and a change of one category for lesions with stenosis of 50 percent or more.

**Angiographic Changes**

The primary end point of the study was the per-patient percentage of initially patent major grafts that had substantial progression of atherosclerosis (a decrease of 0.6 mm or more in lumen diameter) at the site of greatest change at follow-up.\textsuperscript{28} Our definition of substantial changes included new lesions in grafts with no preexisting lesion of more than 15 percent stenosis, the progression of one or more lesions present at base line, and new occlusions. Major grafts, for study purposes, included single grafts, the initial segment (from the aortic anastomosis to first insertion site) of continuation grafts, and the graft stem and one limb (selected randomly) of inverted-Y grafts. Predefined secondary angiographic outcomes\textsuperscript{29}

Interim angiograms were used to ascertain the status of grafts if the follow-up angiography called for in the study protocol was not performed. If death occurred before follow-up angiography
could be performed, all grafts were considered to be occluded. Surviving patients who did not have follow-up or interim angiograms and who did not undergo repeated bypass surgery or angioplasty were excluded from the primary analyses. One secondary analysis included only the patients who had interim or follow-up angiograms. An additional secondary analysis included all patients, with an assumption that all grafts were occluded in patients who had died and that surviving patients without follow-up or interim angiograms who were assigned to aggressive treatment to lower lipid levels had the same percentage of major grafts with substantial progression of disease as was actually observed in patients assigned to moderate treatment (and, conversely, that surviving patients without observed outcomes who were assigned to moderate treatment had the same pattern of outcomes actually observed in the aggressive-treatment group).

Clinical Outcomes

A composite clinical outcome, defined before the trial, included death from cardiovascular or unknown causes, nonfatal myocardial infarction, stroke, bypass surgery, or angioplasty. We also assessed these events individually.

Statistical Analysis

We used the modified-ratio-estimate statistic to compare the mean per-patient percentage of grafts with the primary angiographic end point (a decrease of 0.6 mm or more in lumen diameter), as well as with other angiographic outcomes, in the treatment groups. The modified ratio estimate is a weighted average of the percentage per patient of grafts with a specified angiographic outcome in each stratum (strata are defined by the number of vein grafts per patient) that takes into account the differences among strata in the number of patients in the stratum, the percentage per patient of grafts with the outcome under study, and the degree to which the outcome in one graft correlates with the outcome in other grafts in the same patient. The modified-ratio-estimate statistic is calculated as the weighted average of the differences between the treatment groups in each stratum divided by the variance of those differences. This analytic procedure uses all the information available for each patient, adjusting for the number of grafts per patient (one to five) and the correlation of outcomes among the grafts in each patient.

The study's recruitment goal of 1200 patients was based on an estimated 33 percent rate of substantial progression of disease (the estimated rates were 7 percent for the combined outcome of reoperation, myocardial infarction, or death; 13 percent for occlusion; and 15 percent for substantial nonocclusive progression) in the patients in the moderate-treatment group (or, for anticoagulation, in the placebo group). Under these assumptions, the study's power to detect a 35 percent reduction in the progression of disease associated with either aggressive lipid-lowering therapy or with warfarin was 85 percent. The design had a 97 percent power of detecting a difference in the modified ratio estimates for the rate of substantial progression of 20 percent in one treatment group versus 14 percent in the other, with an assumption of a correlation of 0.21 among the outcomes in the grafts within a single patient.

Comparisons between treatment groups with respect to the primary end point were made with a two-sided alpha of 0.05; all other comparisons were made at an alpha level of 0.01. A test for the homogeneity of the effects of lipid-lowering treatment in the warfarin and placebo groups was performed for each angiographic end point. The results were pooled to provide single comparisons of treatment effects, since no interactions between the two factors of treatment were detected.

Cumulative event rates for specified clinical outcomes were estimated with the Kaplan–Meier method. Likelihood ratios were calculated in a Cox model, in which the type of treatment to lower the LDL cholesterol level, therapy with warfarin or placebo, and the interaction of treatments were the independent variables. If interactions were not found, a Cox model in which the interaction of treatments was the independent variable was calculated in a Cox model, in which the type of treatment to lower the LDL cholesterol level and therapy with warfarin or placebo were the independent variables was devised and likelihood ratios were calculated to assess each treatment effect. Comparisons of categorical variables and continuous variables were performed with chi-square tests and t-tests, respectively.

Regardless of treatments actually received, in all analyses data were grouped according to the treatment groups to which patients were randomly assigned (intention-to-treat analysis). The study's data and safety monitoring board reviewed reports of clinical outcomes according to study group to monitor the efficacy and safety of treatment but did not consider early termination of the study on the basis of reviews of the angiographic data.

RESULTS

Base-Line Characteristics

Between March 1989 and August 1991, 2302 patients were screened and 1351 enrolled in the study. The majority were male (92 percent) and white (94 percent); the mean age was 61.5 years. There were no significant differences among the study groups in the distributions of the more than 40 base-line characteristics that were recorded (Table 1). There was also no evidence of significant differences among the four groups with respect to angiographic characteristics at base line (Table 2).

Completeness of Follow-up

During follow-up (mean duration, 4.3 years) 5 percent of the subjects (64 patients) died, 78 percent had scheduled angiography (as part of the study), and 10 percent had angiography because of symptoms. Clinical follow-up was complete for 98 percent of the patients; vital status at the end of follow-up was known for all but three patients.

Effects of Lipid-Lowering Therapy

At the first annual visit after enrollment (which took place after the dose-adjustment period for most patients), patients assigned to the aggressive-treatment group were taking a mean (± SD) of 76±12.6 mg of lovastatin per day; 30 percent of this group were also given 8 g of cholestyramine per day. Patients assigned to the moderate-treatment group were given a mean of 4±1.25 mg of lovastatin per day; 5 percent were also given 8 g of cholestyramine per day. The prescribed doses of lovastatin and cholestyramine remained constant after this visit for most patients.

At the first annual visit, the mean LDL cholesterol level was 93 mg per deciliter (2.4 mmol per liter) for patients assigned to aggressive treatment and 136 mg per deciliter (3.5 mmol per liter) for patients assigned to moderate treatment (Fig. 1). In the aggressive-treatment group, 66 percent of patients had an LDL cholesterol level below 100 mg per deciliter (2.6 mmol per liter) and 6 percent had a level of 130 mg per deciliter or higher; in the moderate-treatment group 5 percent had a level below 100 mg per deciliter and 58 percent had a level of 130 mg
Effects of Warfarin and Placebo

Among the patients assigned to receive warfarin, the mean international normalized ratio was 1.8 to 2.0 in 8 percent and 1.5 to 1.7 in 30 percent at the...
**Table 2. Angiographic Characteristics at Base Line, According to Study Group.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aggressive Treatment</th>
<th>Moderate Treatment</th>
<th>All Patients (N = 1350)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin (N = 337)</td>
<td>Placebo (N = 339)</td>
<td>Warfarin (N = 337)</td>
<td>Placebo (N = 337)</td>
</tr>
<tr>
<td>No. of patent major grafts (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>20</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>53</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>25</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>≥4</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean no. of grafts</td>
<td>2.2</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>No. of grafts with ≥15% stenosis at lesion (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>0</td>
<td>48</td>
<td>43</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>41</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>13</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>≥3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mean percent stenosis</td>
<td>19.2</td>
<td>19.7</td>
<td>21.0</td>
<td>19.7</td>
</tr>
</tbody>
</table>

*Only the results of quantitative or qualitative assessments are included.
†One patient who was not eligible because there was ≥75 percent stenosis in all grafts is not included.
‡P values are from chi-square tests of the distribution of characteristics in the four study groups.

**Figure 1. Mean Lipid Levels According to Study Group.**

To convert cholesterol values to millimoles per liter, multiply by 0.02586. To convert triglyceride values to millimoles per liter, multiply by 0.01129.
end of the dose-adjustment period. Among the patients assigned to placebo, 1 percent had ratios between 1.8 and 2.0 and 3 percent had ratios between 1.5 and 1.7. The mean international normalized ratio at the end of the dose-adjustment period was 1.4 in the warfarin group and 1.05 in the placebo group. Hospitalization because of bleeding or for transfusion (or for both reasons) occurred in 3 percent of the patients in each of the anticoagulation groups. Approximately 93 percent in each group took aspirin; 86 percent of all patients took 81 mg per day.

More patients discontinued warfarin or placebo during follow-up (9 percent) than discontinued lovastatin (2 percent). The rate of patient compliance with therapy was 80 percent in the warfarin group and 85 percent in the placebo group.

### Angiographic Outcomes

The primary analysis included 1192 patients for whom follow-up or interim angiographic data were available and 64 patients who died (in whom all grafts were considered to be occluded). Of the 1192 available pairs of base-line and subsequent films, 119 (10 percent) underwent only qualitative assessment of all major grafts. Modified ratio estimates of the mean percentage per patient of grafts with progression of disease were 80 percent in the warfarin group and 7 percentage points lower in the placebo group.*

### Table 3. Angiographic Outcomes According to Study Group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aggressive Treatment</th>
<th>Moderate Treatment</th>
<th>P Value</th>
<th>Warfarin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Mean % of patients</td>
<td></td>
<td>No. of patients</td>
<td>Mean % of patients</td>
<td></td>
</tr>
<tr>
<td>Grafts with substantial progression</td>
<td>628 27</td>
<td>599 24</td>
<td>&lt;0.001</td>
<td>630 34</td>
<td>602 31</td>
<td>0.48</td>
</tr>
<tr>
<td>Grafts with new lesions‡</td>
<td>317 5</td>
<td>599 6</td>
<td>0.001</td>
<td>325 3</td>
<td>390 28</td>
<td>0.34</td>
</tr>
<tr>
<td>Grafts with occlusion</td>
<td>1295 24</td>
<td>628 16</td>
<td>0.001</td>
<td>1298 31</td>
<td>1235 28</td>
<td>0.007</td>
</tr>
<tr>
<td>Grafts with substantial improvement‡</td>
<td>317 7</td>
<td>599 11</td>
<td>0.001</td>
<td>327 4</td>
<td>390 7</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in lumen diameter‡</td>
<td>557 −0.197</td>
<td>536 −0.379</td>
<td>&lt;0.001</td>
<td>548 −0.310</td>
<td>545 −0.266</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>557 −0.165</td>
<td>536 −0.342</td>
<td>&lt;0.001</td>
<td>548 −0.287</td>
<td>545 −0.219</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>549 0.000</td>
<td>526 −0.004</td>
<td>0.77</td>
<td>540 −0.013</td>
<td>535 0.010</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in percent stenosis</td>
<td>593 7.9</td>
<td>584 13.3</td>
<td>&lt;0.001</td>
<td>597 11.5</td>
<td>580 9.7</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Percentages listed are modified ratio estimates.

†In the primary analysis of treatment effects, for patients who died, all grafts that were patent at base line were considered occluded at follow-up.

‡Only patients who had no major grafts with >15 percent stenosis at base line and who had at least one lesion with substantial progression at follow-up or interim angiography included.

§Substantial improvement is defined as an increase in lumen diameter of 0.6 mm or more at the site of a lesion in patients who had at least one major graft with stenosis of 15 percent or more at base line.

¶Negative numbers denote decreases in lumen diameter.
gression of disease are presented for pooled treatment groups (i.e., moderate vs. aggressive treatment and warfarin vs. placebo) in Table 3, because interactions were not found to be significant (P > 0.05). The modified ratio estimate of the percentage per patient of grafts with substantial progression of disease was 27 percent in the aggressive-treatment group and 39 percent in the moderate-treatment group (P < 0.001). No significant differences in angiographic outcomes were observed between the warfarin and placebo groups.

When data from patients who died were excluded, the pattern of results was similar. When outcomes for all patients were analyzed, with imputed data ascribed to surviving patients for whom angiographic data were unavailable, the pattern of results for the comparison of aggressive and moderate treatment to lower lipid levels and of therapy with warfarin and placebo was substantially unchanged (data not shown).

The mean percentage per patient of grafts with occlusion or new lesions was significantly lower for patients assigned to aggressive treatment than for patients assigned to moderate treatment (Table 3). The analysis of substantial improvement in the condition of grafts included only patients who at baseline had at least one graft with a preexisting lesion; this analysis revealed no significant differences among the study groups.

The analysis of the percentage of all grafts with progression of disease indicated significant differences (P < 0.001) between the two approaches to lipid-lowering treatment. The analyses of the percentage of patients with one or more grafts in which various changes were evident had a similar pattern of results. The decrease in lumen diameter (mean and minimum) was significantly less in the aggressive-treatment group than in the moderate-treatment group (P < 0.001) (Table 3).

Clinical Outcomes

Sixty-four patients died before the scheduled follow-up angiography could be performed, and three died after interim angiography (Table 4). The majority (63 percent) of deaths were from cardiovascular causes. There were no significant differences among the study groups in the incidence of cancer or in deaths from cancer.

An analysis of individual and composite clinical outcomes found no differences due to treatment (Table 5 and Fig. 2). There was a 29 percent lower rate of revascularization procedures in the aggressive-treatment group than in the moderate-treatment group (P = 0.03), but this difference did not meet the study criteria for significance.

**DISCUSSION**

This study found that lowering the LDL cholesterol level can retard the progression of atherosclerosis in bypass grafts. Unlike other trials that compared drugs with placebo, this trial compared treatment aimed at two different target levels of reduction in the LDL cholesterol level. The goal for aggressive treatment of a mean level of 85 mg per deciliter was almost achieved; the mean LDL cholesterol level during follow-up ranged from 93 to 97 mg per deciliter (2.4 to 2.5 mmol per liter). This 37 to 40 percent reduction from base-line levels is consistent with the known dose–response effect of lovastatin.33 The failure to attain the target level can be explained by the high LDL cholesterol levels before randomization (more than 175 mg per deciliter in 15 percent of the patients) and by the poor compliance by patients with therapy with cholesterol-lowering treatment.

An analysis of individual and composite clinical outcomes found no differences due to treatment (Table 5 and Fig. 2). There was a 29 percent lower rate of revascularization procedures in the aggressive-treatment group than in the moderate-treatment group (P = 0.03), but this difference did not meet the study criteria for significance.

**TABLE 4. CLINICAL OUTCOMES ACCORDING TO STUDY GROUP.***

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>AGGRESSIVE TREATMENT (N = 676)</th>
<th>MODERATE TREATMENT (N = 675)</th>
<th>WARFARIN (N = 674)</th>
<th>PLACEBO (N = 677)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>35</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>From cardiovascular causes</td>
<td>22</td>
<td>20</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>From other causes</td>
<td>9</td>
<td>15</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>From unspecified causes</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>40</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Fatal</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>29</td>
<td>36</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total†</td>
<td>48</td>
<td>42</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Fatal</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>39</td>
<td>35</td>
<td>50</td>
<td>24</td>
</tr>
</tbody>
</table>

*All events that occurred before the date of follow-up angiography are included. For patients who did not have follow-up angiography, all events that occurred before the follow-up examination completed in the period for scheduled angiography are counted. Events were classified by physicians at the clinical centers.

†Nonmelanoma skin cancers were included.
This study was designed to have adequate power to detect treatment-related differences in angiographic characteristics but not in clinical events. A low-risk population was selected so that a final follow-up angiogram could be obtained after four to five years. Nonetheless, the life-table curves for revascularization procedures (Fig. 2B), which show a nonsignificant trend in favor of aggressive therapy as compared with moderate therapy (P = 0.03), diverge progressively after 2.5 years, a fact that strongly suggests that a significant difference may occur with continued therapy.

A previous study of the effect of lipid-lowering therapy on graft atherosclerosis was a two-year trial that enrolled 162 men at least three months after coronary bypass surgery; they were randomly assigned either to a low-fat diet or to therapy with niacin and colestipol. The serum LDL cholesterol level in the group receiving drug therapy was decreased by 43 percent to a mean level of 97 mg per deciliter (2.5 mmol per liter) during the trial. Adverse changes, as documented with qualitative angiography, were observed in 24 percent of drug-treated patients and in 39 percent of controls (one-tailed P value, 0.03), indicating a trend in favor of aggressive therapy with drugs.

Low-dose anticoagulation did not influence the progression of graft disease in our study. The maximal daily dose of warfarin (4 mg) and the procedure of lowering the dose by 1 mg when the international normalized ratio reached 2.0 (both constraints un-
dertaken for reasons of safety) resulted in a mean international normalized ratio of 1.4 in the patients who received warfarin. Although we found that low-dose anticoagulation did not significantly retard the progression of disease (the primary end point), we cannot conclude that more aggressive anticoagulation would not be beneficial. The unfavorable trend associated with warfarin therapy in the analysis of some secondary measures of progression in all patients and regression (substantial improvement in at least one lesion) in patients who had one or more major grafts with stenosis of at least 15 percent at base line (Table 3) is unexplained and may be the result of chance.

In conclusion, given the very low levels of anticoagulation achieved, there was no beneficial effect observed in association with warfarin therapy. Aggressive reduction of the LDL cholesterol level below 100 mg per deciliter, as compared with moderate lowering to a level near 130 mg per deciliter, significantly reduced the progression of atherosclerosis in grafts. This finding is consistent with the recommendation of the National Cholesterol Education Program that the LDL cholesterol level should be reduced to below 100 mg per deciliter in patients who have coronary artery disease.34

We are indebted to Wanda Ruggie for assistance in the preparation of the manuscript.

APPENDIX

The following institutions and investigators participated in the study (asterisks indicate principal and co-principal investigators):


REFERENCES


MASSACHUSETTS MEDICAL SOCIETY REGISTRY ON CONTINUING MEDICAL EDUCATION

To obtain information about continuing medical education courses in New England, call between 9 a.m. and 12 noon, Monday through Friday, (617) 893-4610, or in Massachusetts, 1-800-322-2303, ext. 1342.