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Long-Term Effects on Clinical Outcomes of Aggressive Lowering of Low-Density Lipoprotein Cholesterol Levels and Low-Dose Anticoagulation in the Post Coronary Artery Bypass Graft Trial

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Background—The Post Coronary Artery Bypass Graft Trial, designed to compare the effects of 2 lipid-lowering regimens and low-dose anticoagulation versus placebo on progression of atherosclerosis in saphenous vein grafts of patients who had had CABG surgery, demonstrated that aggressive lowering of LDL cholesterol (LDL-C) levels to <100 mg/dL compared with a moderate reduction to 132 to 136 mg/dL decreased the progression of atherosclerosis in grafts. Low-dose anticoagulation did not significantly affect progression.

Methods and Results—Approximately 3 years after the last trial visit, Clinical Center Coordinators contacted each patient by telephone to ascertain the occurrence of cardiovascular events and procedures. The National Death Index was used to ascertain vital status for patients who could not be contacted. Vital status was established for all but 3 of 1351 patients. Information on nonfatal events was available for 95% of surviving patients. A 30% reduction in revascularization procedures and 24% reduction in a composite clinical end point were observed in patients assigned to aggressive strategy compared with patients assigned to moderate strategy during 7.5 years of follow-up, $P=0.0006$ and 0.001 , respectively. Reductions of 35% in deaths and 31% in deaths or myocardial infarctions with low-dose anticoagulation compared with placebo were also observed, $P=0.008$ and 0.003 , respectively.

Conclusions—The long-term clinical benefit observed during extended follow-up in patients assigned to the aggressive strategy is consistent with the angiographic findings of delayed atherosclerosis progression in grafts observed during the trial. The apparent long-term benefit of low-dose warfarin remains unexplained. (*Circulation*. 2000;102:157-165.)

Key Words: bypass ■ grafting ■ anticoagulation ■ lipids ■ follow-up studies

The Post Coronary Artery Bypass Graft Trial (Post CABG) was a multicenter, randomized, double-blind clinical trial designed to compare the effects of 2 lipid-lowering strategies and low-dose anticoagulation versus placebo on progression of atherosclerosis in saphenous vein grafts, as documented by assessment of angiograms obtained before entry and 4 to 5 years after entry. Patients were enrolled between March 1989 and August 1991; 1351 patients were randomized. Follow-up of patients was completed in December 1995.¹

See p 144

Angiographic changes in coronary arteries have been shown to predict clinical outcomes,²⁻⁴ as have changes in

bypass grafts.⁵ Additional follow-up of patients who were enrolled in Post CABG was undertaken to ascertain whether the angiographic findings in grafts evaluated in the trial predicted subsequent clinical events and to evaluate the long-term effects of the treatment strategies on clinical outcomes. This report is limited to the second objective.

Design, Methods, and Results of the Post CABG Trial

Patient Selection

Eligible patients were 21 and 74 years of age and had undergone bypass surgery 1 to 11 years before screening.

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*Investigators and centers participating in the trial are listed in a previous publication.¹

Guest Editor for this article was David D. Waters, MD, San Francisco General Hospital, San Francisco, Calif.

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Patients had to have LDL cholesterol (LDL-C) levels of 130 to 175 mg/dL (3.4 to 4.5 mmol/L) and triglyceride levels <300 mg/dL (3.4 mmol/L) after initiation of a step 1 diet,⁶ 2 patent grafts (stenosis <75%) in men (1 in women), and ejection fraction \geq 30%. Exclusion criteria have been described previously.¹

Study Treatments

Patients were randomized (2×2 factorial design) to either an aggressive or moderate strategy to lower LDL-C and either warfarin or placebo. Patients assigned to aggressive LDL-C lowering received 40 or 80 mg/dL of lovastatin (and 8 g cholestyramine/d, if needed) to achieve 60 to 85 mg/dL (1.6 to 2.5 mmol/L). Patients assigned to moderate LDL-C lowering were treated with 2.5 or 5 mg/dL of lovastatin (and 8 g cholestyramine/d, if needed) to achieve 130 to 140 mg/dL (3.4 to 3.6 mmol/L). Patients assigned to warfarin received 1 to 4 mg/d of warfarin to maintain international normalized ratios <2.0; patients assigned to placebo received 1 to 4 mg/d of matching placebo.

Angiographic Data

Baseline and follow-up angiograms were obtained with catheterization techniques that would permit computer-assisted quantitative assessment.⁷ Follow-up angiograms were obtained on average 4.3 years after study entry. If only an interim angiogram was available, the latter was used for the follow-up status of grafts. Surviving patients who did not have follow-up or interim angiograms were excluded from the primary analyses (n=95).

End Points

The primary end point of substantial progression in bypass grafts was defined as a decrease of \geq 0.6 mm in lumen diameter at the site of greatest change at follow-up compared with baseline. A secondary composite clinical outcome was defined as death from cardiovascular or unknown causes or any of the following nonfatal events: myocardial infarction, stroke, bypass surgery, or angioplasty.

Major Results

At the first annual visit after enrollment (after titration was completed for most patients), the mean LDL-C level of patients assigned to aggressive strategy was 93 mg/dL (2.4 mmol/L), a 40% reduction from baseline, and the mean LDL-C level of patients assigned to moderate strategy was 136 mg/dL (3.5 mmol/L), a 13% reduction.¹ Mean levels at subsequent annual visits were similar to the means at the first annual visit in each strategy.

After titration, the annual mean international normalized ratio for patients assigned to warfarin was \approx 1.4, and for patients assigned to placebo, \approx 1.1.

Of the 1351 patients enrolled, 1192 (88%) had follow-up or interim angiographic data. Sixty-four patients died before follow-up angiography could be performed; for those patients, all patent grafts at baseline were considered occluded at follow-up. The modified ratio estimate statistic⁸ was used to compare the mean per-patient percentage

of initially patent major grafts that had substantial progression of atherosclerosis.⁹

The mean per-patient percentage of grafts with substantial progression was 39% with the moderate strategy and 27% with the aggressive strategy, a 31% difference ($P<0.001$). A 29% reduction in occurrence of revascularization procedures (angioplasty or bypass surgery) was observed for patients assigned to the aggressive strategy compared with the moderate strategy (6.5% versus 9.2%, $P=0.03$); this difference was not considered significant by study criteria ($P\leq 0.01$) for secondary outcomes.¹

No statistically significant differences in angiographic outcomes or clinical outcomes were observed for warfarin versus placebo patients.

Extended Follow-Up Study Methods

Design

Each patient who completed the close-out visit was asked to provide permission to be contacted later. Beginning in August 1997, Clinical Center Coordinators attempted to contact each patient by telephone for a brief interview. If the patient was not able to participate in a telephone interview or could not be contacted, a relative and/or the patient's physician (contacts obtained during the close-out visit) was interviewed. If these efforts were not successful, coordinators sent a letter with a request that the patient call the Clinical Center.

Patients were asked about nonfatal cardiovascular events and procedures: myocardial infarction, PTCA, repeat bypass surgery, stroke, and any peripheral vascular procedure. Questions concerning cancer, other serious medical events, and prescribed medications were also asked. Patients who reported cardiovascular events were requested to give permission to release medical records for central review. For patients who had died, information about cause of death was obtained from hospital records or the patient's physician.

Cause-of-death forms and event forms were reviewed by a physician in the Coordinating Center or NHLBI Project Office to classify the event and/or the cause of death; the reviewers did not know the patients' treatments. If the reviewer agreed with the classification, this was recorded on the appropriate study form. If not, the Clinical Center was notified and/or additional documentation was requested before the event could be classified. There was agreement for all but 2 events; the diagnosis made by the central reviewer was later confirmed by the Clinical Center physician.

Ascertainment of Vital Status

For patients enrolled in Clinical Centers in the United States, the National Death Index and Social Security Death Index (includes deaths only for individuals who received benefits) were searched for death reports for patients who could not be contacted. Mortality records for the years 1990 to 1997 were included for these searches. The causes of death for 5 patients enrolled in the Montreal Clinical Center were obtained from the Quebec Provincial Health Ministry.

Statistical Methods

Event rates for clinical outcomes were estimated with the Kaplan-Meier method¹⁰ and compared by the log-rank statis-

TABLE 1. Data Available by Treatment Group

	Aggressive Strategy		Moderate Strategy		Total
	Warfarin	Placebo	Warfarin	Placebo	
Vital status, all patients					
Number of patients enrolled in trial	337	339	337	338	1351
Number of patients who did not complete close-out visit or did not give consent to be contacted later	9	4	11	6	30
Number who could not be contacted during extended follow-up	8	12	10	10	40
Number submitted to National Death Index	17	16	20	14	67
Total deaths	40	47	40	66	193
Deaths reported before end of study*	17	15	11	24	67
Deaths reported in extended follow-up	21	28	23	39	111
Deaths reported from National Death Index†	2	4	6	3	15
Vital status unknown‡	0	0	1	2	3
Follow-up of patients enrolled in extended follow-up					
Number enrolled in extended follow-up study	311	320	315	308	1254
Number of deaths	22	31	28	39	120
Number of patients interviewed	259	250	252	235	996
Number of interviews of other sources	23	30	30	24	107
Incomplete follow-up for nonfatal events	7	9	5	10	31

*Includes 3 deaths that occurred after follow-up angiography was performed but before the close-out visit was completed.

†Six of these deaths were among the patients who were not enrolled in the Extended Follow-up Study.

‡Identifying information not provided by the Clinical Center for 2 patients; 1 patient was enrolled in the Canadian Clinical Center. These patients were censored at the date of last contact in all analyses.

tic.¹¹ Likelihood ratios were calculated with a Cox model to evaluate the effects of the lipid-lowering strategies, the effects of warfarin versus placebo, and the interaction of the LDL-C-lowering and warfarin strategies.^{12,13} If the interactions were not significant ($P \leq 0.05$), the results for the lipid-lowering strategies were compared by pooling the results for patients assigned to warfarin or placebo, and the effects of warfarin were evaluated by pooling the results for the lipid-lowering strategies. For other secondary analyses in Post CABG, comparisons between treatment groups were considered to show some evidence of a difference at a level of $\alpha = 0.01$ and strong evidence at a level of $\alpha = 0.001$.

Analyses were based on all enrolled patients, even though some patients were not in the Extended Follow-up Study. All patients were included in the treatment groups to which they were randomly assigned (intention-to-treat analysis). If a patient had >1 event, the patient was counted only once in the composite outcomes. In life-table analyses, the date of the first event was used. Patients who were not contacted and not reported to have died were censored at the date of last contact for nonfatal events.

Results

Completeness of Follow-up

The status of follow-up for all 1351 patients in the Post CABG Trial and for patients who were enrolled in the Extended Follow-up Study is summarized in Table 1. A search of the National Death Index was made for 67 patients

with vital status unknown and for 23 patients who were reported by Clinical Center staff to have died but for whom documentation was not available. The National Death Index provided date and cause(s) of death for each of these 23 patients and identified 15 deaths among the other 67 patients. All these deaths were included in all analyses. The Social Security Death Index identified all but 1 of the deaths reported by the National Death Index. The 52 patients who were not identified as having died were considered to have been alive as of December 31, 1997, in the analyses for mortality. Follow-up during the main trial averaged 4.3 years; extended follow-up added another 3 years.

Of the 1103 patients known to be alive, 996 patients (90%) were interviewed. Information was obtained from a relative or physician for 107 patients (Table 1).

Total Mortality

The percent dead during all follow-up ranged from 12% in the aggressive strategy/warfarin and moderate strategy/warfarin groups to 20% in the moderate strategy/placebo group (Figure 1). The percent dead during the trial ranged from 3% to 7%.

As shown in Figure 2, top, there was no significant difference between aggressive and moderate lipid-lowering strategies in the occurrence of death during the trial or during extended follow-up. No statistically significant difference between warfarin and placebo groups was observed during the trial, although the curves started to separate at 3 years (Figure 2, bottom). At the end of follow-up, the reduction in

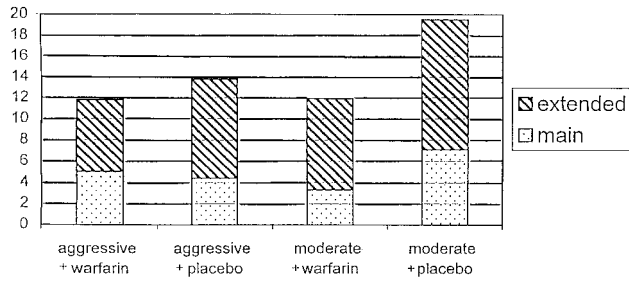


Figure 1. Percent dead by treatment group. Percent dead during trial are shown at bottom of each bar (stippled), and percent dead during period of extended follow-up at top of each bar (hatched).

mortality in the warfarin group was $\approx 35\%$ ($P=0.008$ for comparison of curves through 7.5 years, Table 2).

Myocardial Infarction

The occurrence of fatal or nonfatal myocardial infarction during the trial and during extended follow-up was not significantly different for the comparison of the lipid-lowering strategies. During the trial, the comparison of warfarin versus placebo was not significantly different; how-

ever, the 7.5-year rate was 9.1% in the warfarin group and 13.8% in the placebo group, a 34% reduction, $P=0.01$ (Table 2). Similar findings were noted for death or myocardial infarction (Table 2 and Figure 3). Comparison of the warfarin and placebo curves for all follow-up yielded a value of $P=0.003$, a 31% reduction with warfarin.

Revascularization

During the trial, 29% more patients in the moderate strategy than in the aggressive strategy had revascularization, $P=0.03$ (Figure 4). This difference between moderate and aggressive strategies increased to 42% during extended follow-up (Table 2). Of the 73 revascularizations in the aggressive strategy, 13 (18%) occurred within 60 days of follow-up angiography, and of the 97 procedures in the moderate strategy, 22 (23%) were within 60 days of follow-up angiography.

There was no difference in the occurrence of revascularization in the warfarin and placebo groups during the trial or extended follow-up.

Composite Clinical Outcome

At the end of the trial, 18% more patients in the moderate strategy than in the aggressive strategy had ≥ 1 of the events

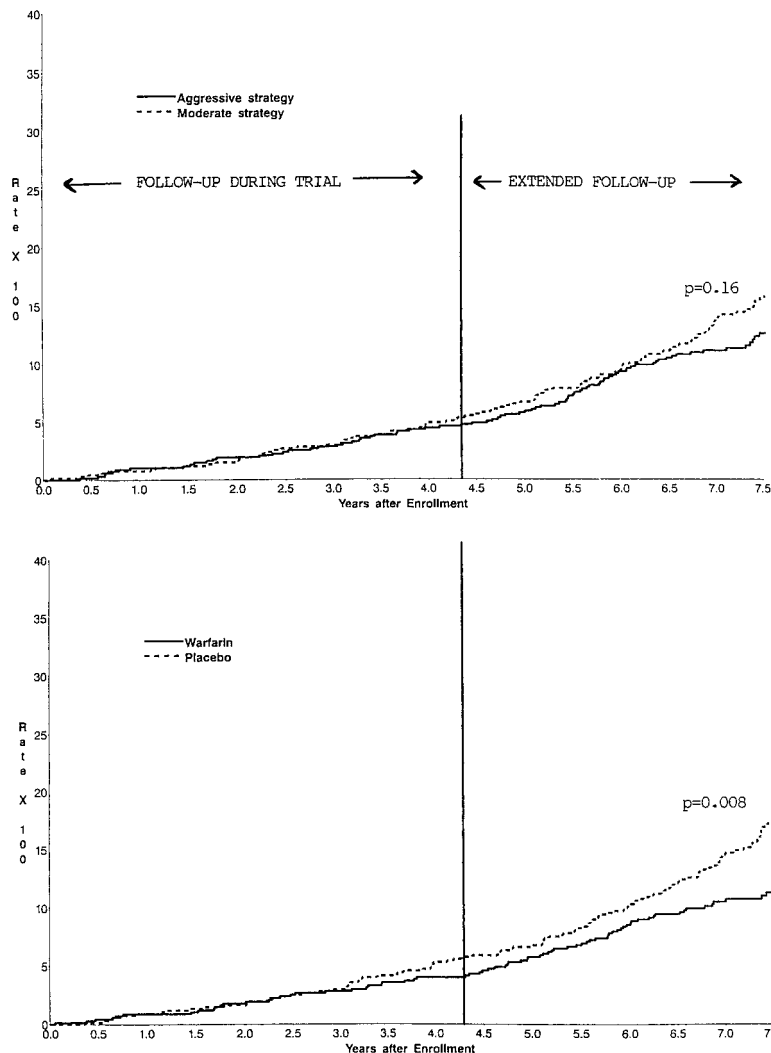


Figure 2. Cumulative life table rates for death by treatment group. Top, Lipid-lowering strategies; bottom, warfarin and placebo groups.

TABLE 2. 7.5-Year Life Table Event Rates by Assigned Treatment

Event	Aggressive Strategy (n=676)	Moderate Strategy (n=675)	<i>P</i> *	Warfarin (n=674)	Placebo (n=677)	<i>P</i> *
Death from all causes	12.7	15.8	0.16	11.2	17.3	0.008
Fatal and nonfatal MI	10.2	12.7	0.23	9.1	13.8	0.01
Nonfatal MI	9.1	11.3	0.24	8.8	11.6	0.12
Death or nonfatal MI	20.3	24.3	0.13	18.2	26.3	0.003
CV death or nonfatal MI	15.1	20.3	0.03	14.3	21.2	0.009
CV death	7.4	11.3	0.03	7.1	11.6	0.03
PTCA or CABG	19.2	27.3	0.0006	21.8	24.7	0.35
One or more of above	32.0	40.4	0.003	32.9	39.4	0.05
Stroke	5.1	5.6	0.68	4.5	6.2	0.14
Composite†	30.6	40.2	0.001	32.1	38.6	0.04
Fatal or nonfatal cancer	14.7	10.7	0.14	13.0	12.6	0.42
Cancer death	3.7	2.5	0.31	2.3	3.9	0.09
Peripheral vascular procedure	6.7	7.3	0.99	6.3	7.8	0.24

**P* values are for the comparison of event curves through 7.5 years by the log-rank test.

†The composite end point was death from cardiovascular (CV) or unknown causes, nonfatal myocardial infarction (MI), stroke, CABG (bypass surgery), or PTCA (angioplasty).

included in the composite clinical end point (Figure 5); this difference was not significant ($P=0.12$). At the end of follow-up, a reduction of 24% ($P=0.001$) was observed for the aggressive strategy compared with the moderate strategy. A 17% reduction was observed for warfarin versus placebo at the end of follow-up; this reduction was not significant by study criteria ($P=0.04$).

Other Outcomes

No treatment differences were observed for the occurrence of stroke, peripheral vascular procedures, or cancer (Table 2). Of the 1103 patients who had a telephone interview, 975 patients (88%) were taking aspirin, 897 (81%) lipid-lowering medication, and 126 (11%) antithrombotic agents. There were no differences by treatment group.

Discussion

Ascertainment of Events

Ascertainment of vital status of all patients enrolled was obtained for all but 3 (0.2%) of 1351 patients. Information on fatal or nonfatal events was available for 98% of the 1254 patients in the Extended Follow-up Study. Completeness of follow-up compares favorably with other studies with similar follow-up protocols.^{4,5,14,15}

Lipid-Lowering Therapy

Post CABG was designed to have adequate power to detect treatment differences in angiographic outcomes of bypass grafts but not clinical events. Nonetheless, the life-table curves for revascularization began to diverge after 2.5 years, indicating a trend in favor of aggressive strategy. The difference at the end of the trial was not significant by study criteria ($P<0.01$). The curves continued to separate, and after 7.5 years of follow-up, the difference was significant ($P=0.0006$). These results are consistent with changes in grafts for the lipid-lowering strategies. Revascularization did

not seem to be a consequence of the follow-up angiographic findings (the majority of procedures were performed >60 days after follow-up angiography) but rather of symptoms or new coronary events.

At the end of the trial, a nonsignificant trend in favor of the aggressive strategy compared with the moderate strategy was observed in the composite end point. After 7.5 years, the 24% reduction for patients in the aggressive strategy was significant ($P=0.001$). This beneficial trend as a consequence of lowering LDL-C to slow atherosclerosis progression is consistent with reports of recent statin trials that have clearly established the benefit of cholesterol-lowering therapy in both primary and secondary prevention.¹⁶

Post CABG and the Cholesterol and Recurrent Events (CARE) Trial¹⁷ enrolled patients who had normal to moderately elevated LDL-C levels. In CARE, post-myocardial infarction patients (n=4159) with LDL-C baseline levels of 115 to 174 mg/dL (3.0 to 4.5 mmol/L) were eligible. Patients were randomized either to 40 mg/d of pravastatin or to placebo. The 32% reduction in LDL-C is similar to that observed in Post CABG patients assigned to the aggressive strategy. The occurrence of the primary end point (cardiovascular death or nonfatal myocardial infarction) was 10.2% in the pravastatin group and 13.2% in the placebo group, a 24% reduction, $P=0.003$. With extended follow-up in Post CABG, the occurrence of this end point was 15.1% in the aggressive strategy and 20.3% in the moderate strategy, a 26% reduction, which was not significant by study criteria. As reported previously, there was a marked reduction in angiographic changes in bypass grafts with the aggressive strategy. Thus, both CARE and Post CABG established the benefit of treating patients with coronary disease who have moderate hypercholesterolemia.

Warfarin Therapy

In the Post CABG trial, low-dose anticoagulation did not influence the progression of atherosclerosis in vein grafts, nor

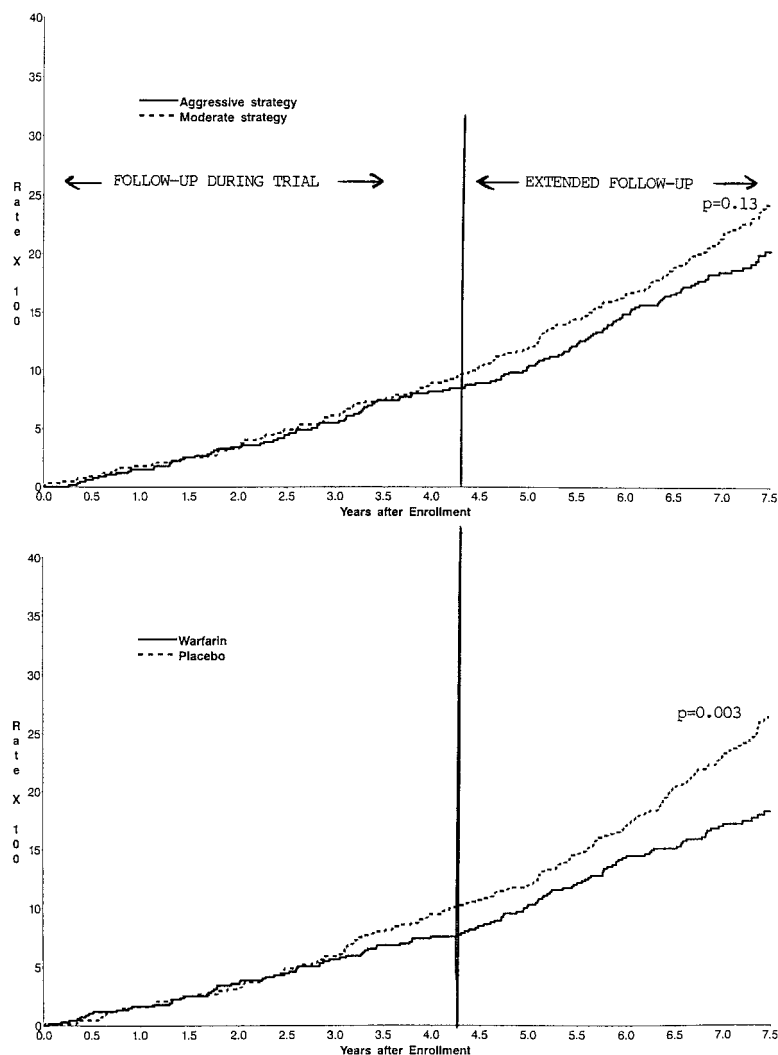


Figure 3. Cumulative life table rates for death and myocardial infarction by treatment group. Top, Lipid-lowering strategies; bottom, warfarin and placebo groups.

were there any significant differences for clinical outcomes. However, differences in total mortality and death or nonfatal myocardial infarction emerged during extended follow-up. The reduction in mortality with warfarin was $\approx 35\%$, $P=0.008$; the reduction for death or nonfatal myocardial infarction was 31% , $P=0.003$.

Post CABG trial results are consistent with the Coumadin Aspirin Reinfarction Study (CARS), which demonstrated that low-fixed-dose warfarin did not provide any clinical benefit during a period of almost 3 years of follow-up.¹⁸ In CARS, 8803 patients after myocardial infarction were randomly assigned to 1 or 3 mg/d of warfarin combined with 80 mg aspirin or to warfarin-placebo and 160 mg aspirin. The primary end point included reinfarction, nonfatal ischemic stroke, or cardiovascular death. After a maximum follow-up of 33 months, there were no differences for this end point among the 3 treatment groups and no differences in all-cause mortality.

The Post CABG long-term results are consistent with the low-intensity anticoagulation trial reported by the Medical Research Councils General Practice Research Framework.¹⁹ In this primary prevention study, 5499 men who were at risk of ischemic heart disease were recruited from 108 practices in

the United Kingdom. Patients were randomly assigned to warfarin and aspirin, warfarin and placebo-aspirin, placebo-warfarin and aspirin, or placebo-warfarin and placebo-aspirin. The primary end point was coronary death and fatal or nonfatal myocardial infarction. The main effect of aspirin was a 20% reduction, primarily in nonfatal events. Warfarin reduced all events by 34%, primarily in fatal events. The investigators concluded that aspirin reduced nonfatal ischemic heart disease and warfarin reduced fatal ischemic heart disease. A beneficial effect on mortality, but not on nonfatal ischemic heart disease, was observed in the long-term follow-up of Post CABG patients.

Explanation of Warfarin Effects

The finding that warfarin therapy reduced mortality from all causes, which emerged after treatment was discontinued, was unexpected. Warfarin or placebo was discontinued before the performance of follow-up angiography. Only 11% of patients reported taking anticoagulants during extended follow-up. Thus, the benefit could not be attributed to continued anticoagulation. There were also no differences in revascularization rates. Information on other therapies was limited.

One possible explanation is that the differences observed for warfarin represent type I errors and are chance findings.

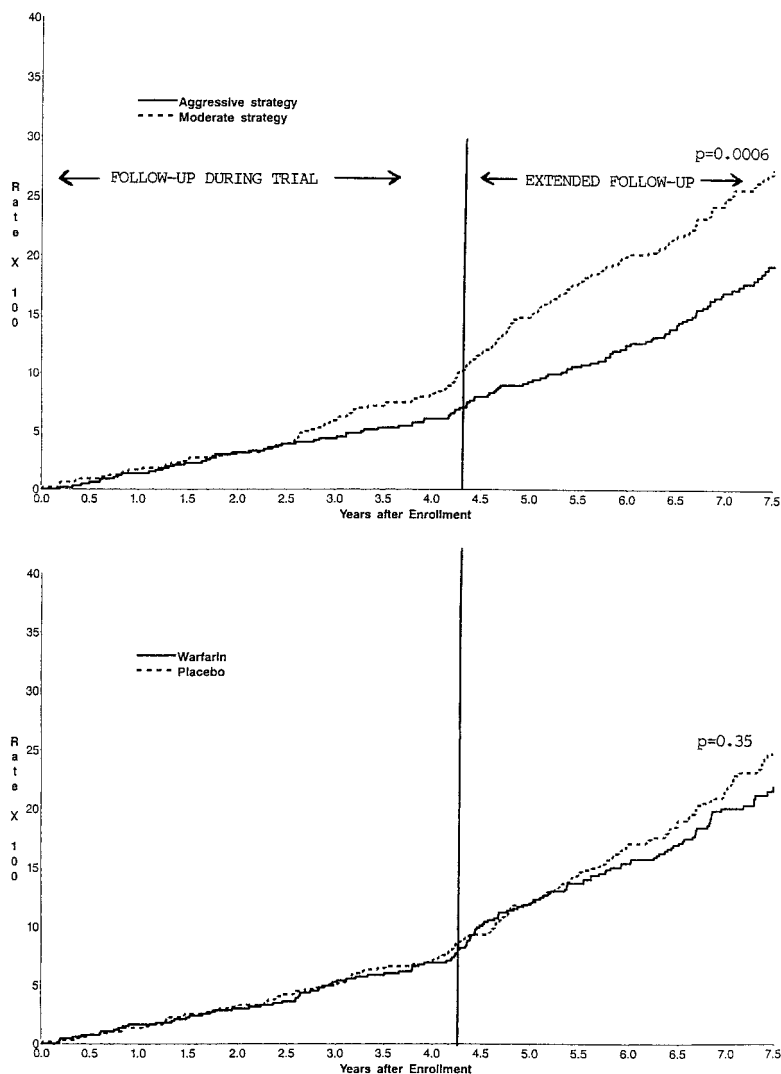


Figure 4. Cumulative life table rates for PTCA or repeat CABG. Top, Lipid-lowering strategies; bottom, warfarin and placebo groups.

We have greater confidence in the mortality findings than in the findings for nonfatal events. Censoring at the time of last contact in the analysis for surviving patients with incomplete follow-up assumes that these data were missing at random. We cannot confirm or refute this assumption.

The CDP Mortality Follow-up Program investigators reported a long-term survival benefit of niacin.¹⁴ They speculated that this effect might be explained in part by reduction in definite nonfatal MI observed during the trial. A nonsignificant difference in nonfatal MI was observed in Post CABG. There was no evidence that low-dose anticoagulation significantly reduced the progression of disease in bypass grafts as assessed by the primary angiographic end point, substantial progression, or a secondary angiographic end point, occlusion. There was a somewhat unfavorable trend for other secondary measures of progression, and there was less improvement in ≥ 1 lesion in patients who had ≥ 1 major grafts with $\geq 15\%$ stenosis at baseline.¹ The treatment effects on the coronary arteries are being evaluated.

A delayed effect of warfarin on either arrhythmias and/or thrombogenesis rather than atherogenesis might explain the long-term findings. In view of the increased understanding of

the importance of thrombosis, endothelial cell function, and plaque stability in the role of clinical events, a durable effect of warfarin on clinical events may be postulated. If small thrombotic events had an adverse effect on the coronary arteries or saphenous vein grafts and if these events were reduced by low-dose warfarin, the Post CABG findings may lend insight in designing studies to evaluate such mechanisms.

Conclusions

The late findings in patients who had been assigned to the aggressive LDL-C-lowering strategy were consistent with the findings during the trial, including the observed benefits on angiographic outcomes in bypass grafts. The results are also consistent with other secondary prevention studies, especially the CARE Study, which evaluated patients who had LDL-C levels similar to those of patients enrolled in Post CABG. The Post CABG Trial did not provide clear evidence of a threshold effect but did provide support for the National Cholesterol Education Program recommendation that LDL-C levels should be reduced to <100 mg/dL in patients who have coronary artery disease.

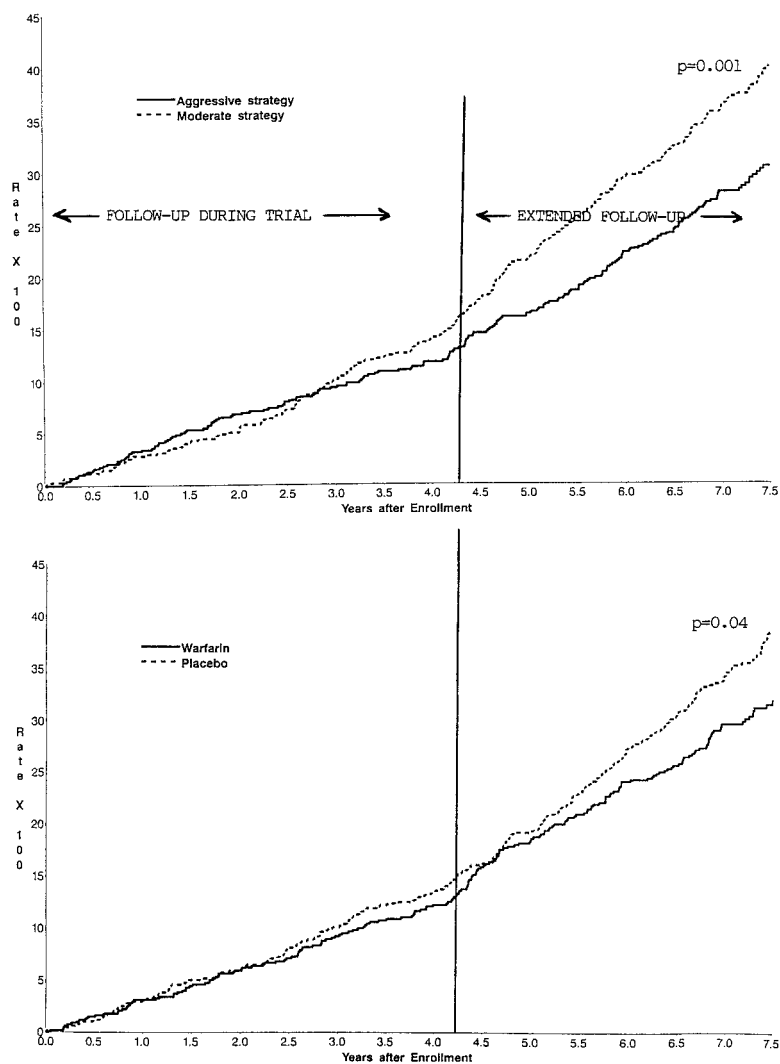


Figure 5. Cumulative life table rates for composite clinical outcome by treatment group. Top, Lipid-lowering strategies; bottom, warfarin and placebo groups.

The apparent late clinical benefit of low-dose warfarin in patients after bypass surgery was unexpected, remains unexplained, and requires confirmation by additional studies.

Appendix

Clinical Center Staff Responsible for Contacting Patients in the Post CABG Trial Extended Follow-Up Study

Baylor College of Medicine—Methodist Hospital and Veterans Affairs Medical Center: Terry Techmanski, RN; Emily Debronner, RN; Melissa Kulkarni, RN; Diane Tanksley, RN. Cedars-Sinai Medical Center: Yara Luptak, RN; Sidney Higgins, RN. Cleveland Clinic Foundation: Fran Yanak, RN. Montreal Heart Institute: Ngo Phong Liem, RN. University of Minnesota: Erving London, RN; Pat Chase, RN; Kristi Wentworth, RN. University of Minnesota—Minneapolis Heart Institute: Connie Baumgard, RN.

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modified Biotrack machines were provided by Biotrack; and aspirin was donated by Bayer.

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