ORIGINAL INVESTIGATION

Effective Lipid Modification by Partial Ileal Bypass Reduced Long-term Coronary Heart Disease Mortality and Morbidity: Five-Year Posttrial Follow-up Report From the POSCH

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Background: In 1990, when the Program on the Surgical Control of the Hyperlipidemias (POSCH) reported its in-trial results strongly supporting the conclusion that effective lipid modification reduces progression of atherosclerosis, the differences for the end points of overall mortality and mortality from atherosclerotic coronary heart disease (ACHD) did not reach statistical significance.

Methods: The Program on the Surgical Control of the Hyperlipidemias recruited men and women with a single documented myocardial infarction between the ages of 30 and 64 years who had a plasma cholesterol level higher than 5.69 mmol/L (220 mg/dL) or higher than 5.17 mmol/L (200 mg/dL) if the low-density lipoprotein cholesterol level was in excess of 3.62 mmol/L (140 mg/dL). Between 1975 and 1983, 838 patients were randomized: 417 to the diet control group and 421 to the diet plus partial ileal bypass intervention group. Mean patient follow-up for this 5-year posttrial report was 14.7 years (range, 12.2-20 years).

Results: At 5 years after the trial, statistical significance was obtained for differences in overall mortality ($P = .049$) and mortality from ACHD ($P = .03$). Other POSCH end points included overall mortality (left ventricular ejection fraction ≥50%) ($P = .01$), mortality from ACHD (left ventricular ejection fraction ≥50%) ($P = .05$), mortality from ACHD and confirmed nonfatal myocardial infarction ($P<.001$), confirmed nonfatal myocardial infarction ($P<.001$), mortality from ACHD, confirmed and suspected myocardial infarction and unstable angina ($P<.001$), incidence of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty ($P<.001$), and onset of clinical peripheral vascular disease ($P = .02$). There were no statistically significant differences between groups for cerebrovascular events, mortality from non-ACHD, and cancer. All POSCH patients have been available for follow-up.

Conclusion: At 5 years after the trial, all POSCH mortality and atherosclerosis end points, including overall mortality and mortality from ACHD, demonstrated statistically significant differences between the study groups.

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THE PROGRAM on the Surgical Control of the Hyperlipidemias (POSCH) was a multiclinic, randomized, prospective, secondary intervention trial designed to ascertain whether the effective reduction of plasma total cholesterol and low-density lipoprotein (LDL) cholesterol levels and the increase of the plasma high-density lipoprotein (HDL) cholesterol levels induced by the partial ileal bypass operation had a favorable impact on overall mortality and the mortality and morbidity attributable to atherosclerotic coronary heart disease (ACHD). The Program on the Surgical Control of the Hyperlipidemias was both a clinical and arteriographic end points trial, the first atherosclerosis intervention trial to correlate changes observed on sequential coronary arteriograms with clinical atherosclerotic events.

Between 1975 and 1983, 838 survivors of a single myocardial infarction documented by electrocardiograms and changes in enzyme values were entered into this study: 417 patients were randomly assigned to treatment with diet instruction only (control group) and 421 to diet instruction plus partial ileal bypass surgery (intervention group). The formal trial ended July 19, 1990, with a mean patient follow-up of 9.7 years (range, 7.0-14.8 years). Partial ileal bypass effected a 23.3% reduction in total plasma cholesterol and a 37.7% reduction in LDL cholesterol at 5 years in the intervention group compared with the control group.[1] These findings were accompanied by a 35.0% lower mortality rate from ACHD combined with confirmed nonfatal myocardial infarction ($P<.001$), a 36.0% lower overall mortality rate in the surgery subgroup with a

PATIENTS AND METHODS

TRIAL PROTOCOL

Three hundred seventy-eight patients were entered into the study at the University of Minnesota, Minneapolis, 135 at the University of Arkansas Medical Center, Little Rock, 141 at the University of Southern California, Los Angeles, and 184 at the Lankenau Hospital and Research Center, Philadelphia, Pa. The first patient was enrolled in September 1975 and the last in July 1983.

During the screening visit, eligibility was determined and most of the baseline values for the study variables were obtained. Before randomization, all patients received instruction in the American Heart Association phase 2 diet, according to which less than 25% of total daily calories is consumed as fat (⅓ as saturated, ⅓ as monounsaturated, and ⅓ as polyunsaturated fat) and no more than 250 mg of cholesterol is consumed daily. All patients taking hypocholesterolemic drugs were asked to discontinue this treatment at least 6 weeks before baseline plasma lipid measurement, and all patients were encouraged not to resume or start taking hypocholesterolemic medications during their participation in the trial. Immediately after the baseline coronary arteriogram was obtained and while the patient remained in the hospital, randomization was performed by the coordinating center. Patients in the control group were discharged from the hospital. Patients in the intervention group remained in the hospital and underwent partial ileal bypass. This operative procedure has been described previously in detail.[11-17] The operation involves bypass of either the distal 200 cm or the distal one third of the small intestine, whichever length is greater, with restoration of bowel continuity by an end-to-side ileocecostomy. At each clinic, 1 surgeon performed all partial ileal bypass procedures.

Patients were eligible for our study if they were between the ages of 30 and 64 years and had survived a single myocardial infarction, documented by electrocardiographic and enzymatic changes, that had occurred between 6 and 60 months before the date of randomization. They were required to have a total plasma cholesterol level of at least 5.69 mmol/L (220 mg/dL), or an LDL cholesterol level of at least 3.62 mmol/L (140 mg/dL) if their total plasma cholesterol level was between 5.17 and 5.66 mmol/L (200 and 219 mg/dL), after they had followed the American Heart Association phase 2 diet for a minimum of 6 weeks. Most of the potentially confounding major risk factors for atherosclerosis were criteria for exclusion: hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥105 mm Hg), a body weight 40% above the ideal weight, and the presence of diabetes mellitus. Patients with the risk factor of cigarette smoking and other potential atherosclerosis risk factors were distributed by the randomization process. In addition, patients with certain impairments of the cardiovascular system or other major organ systems (eg, cancer occurring within 5 years of randomization) that could potentially influence the study outcome were excluded. Patients who had previously undergone cardiac surgery or the implantation of a permanent cardiac pacemaker were ineligible, as were patients with stenosis of the left main coronary artery that was more than 75% or with no measurable coronary artery stenosis on the arteriogram obtained before randomization.

The primary end point of the trial was overall mortality. Secondary end points included cause-specific mortality, in particular mortality from ACHD, a determination based on blinded review of all available records by the POSCH Mortality Review Committee. A key secondary end point was mortality from ACHD and confirmed nonfatal myocardial infarction combined. Other secondary

left ventricular ejection fraction of 50% or more ($P = .05$), a 60.1% lower incidence of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty ($P<.001$), and a consistently lower rate of disease progression on comparison of the baseline coronary arteriograms with those obtained at 3, 5, 7, and 10 years after randomization in the intervention group ($P<.001$ for each time interval compared with baseline).[1] In 1990, overall mortality and mortality from ACHD were reduced, but not significantly: deaths overall (control vs intervention), 62 vs 49 ($P = .16$); deaths attributable to ACHD, 44 vs 32 ($P = .13$).

Subsequent POSCH publications have reported that coronary arteriography changes can be used in atherosclerosis intervention trials as surrogate end points for certain clinical coronary events, in particular for overall mortality and mortality from ACHD[2]; that the POSCH arteriographic findings demonstrated not only a statistically significant decrease in coronary lesion progression but statistically significant lesion regression as well[3]; that there was little change in the perception of quality of life before and after disclosure of the trial's results to the patients[4]; that the use of aspirin in POSCH decreased the incidence of overall mortality and recurrent myocardial infarction in current and former cigarette smokers[5]; that subgroup analyses of the major POSCH end points were consistent with the total group results and seemed to indicate that reductions in the risk of ACHD, comparable with increases in risk of ACHD, are a function of the number of risk factors modified[6]; that disease-free intervals can be determined in atherosclerosis intervention trials, comparable with the design of cancer intervention studies[7]; that effective lowering of cholesterol levels reduces the incidence of and improves survival after myocardial infarction following coronary revascularization[8]; that POSCH was the first major trial to demonstrate improvement in the clinical prognosis of peripheral arterial disease[9]; and that in POSCH, as well as in a meta-analysis of lipid/atherosclerosis intervention trials, beneficial clinical results for women have not been documented.[10]

To date, no POSCH patient has been lost to follow-up. Patient contact, on at least a yearly basis, has been uninterrupted since the first patient entered the POSCH trial in 1975. Since the end of the formal POSCH trial, the telephone interview process in effect and the confirmation of end points has taken up to 1 year for error-free database entry. The POSCH database for this 5-year posttrial follow-up report was analyzed up to September 30, 1995, with the entered information updated and

end points were overall mortality and mortality from ACHD as a function of the left ventricular ejection fraction (<50% vs ≥50%) determined by the method of Sandler and Dodge[18]; recurrent myocardial infarction, whether confirmed or suspected; the occurrence of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; the development of peripheral vascular disease; and the documentation of other atherosclerosis events.

All patients were followed up by means of clinic visits and telephone calls according to a uniform protocol. In-trial lipid analyses were performed at baseline, 3 months after randomization, and at every clinic visit (annual visits during the first 5 years and 1 visit at 7 or 10 years), and discontinued in 1990. Sequential lipid profiles consisted of measurement of the total plasma cholesterol, total plasma triglycerides, LDL cholesterol, very low-density lipoprotein cholesterol, HDL cholesterol, and lipoprotein phenotyping.[19-21] Detailed descriptions of the design and methods of the POSCH trial,[11] as well as the enrollment of patients,[22] have been presented elsewhere.

FOLLOW-UP PROTOCOL

Following completion of the formal POSCH trial on July 19, 1990, all surviving patients underwent scheduled closeout interviews at their home clinic, during which the trial results and each patient's individual data were reviewed with the patient and subsequently sent to the patient's physician. All patient records were consolidated at the Minnesota clinic and the other 3 clinics were closed. Each living patient was contacted by the Minnesota clinic and signed an informed consent form indicating his/her willingness to participate in the long-term follow-up protocol.

All surviving POSCH patients have been contacted annually, preferably within a 60-day window of the anniversary of his/her randomization, for an extended telephone interview. During this structured interview, a medical history update designed to identify all health changes within the past year is completed. Arrangements are made for the documentation of reported events from hospital records and outpatient office files. The patient's medication record, smoking history, bowel habits, and quality of life are recorded. The cholesterol level and other lipid parameters, weight, and blood pressure are requested from the patient's personal physician. All deaths are documented by death certificates, hospital records, autopsy reports, and statements from the physician and family members. The cause of death is determined by the POSCH Mortality Review Committee, blinded as to the control or intervention group assignment of the patient. Quality control and quality assurance procedures have been in place since the initiation of the POSCH trial and allow the coordinating center to oversee patient follow-up.

STATISTICAL ANALYSIS

All analyses were based on randomization assignment (intention-to-treat), whether or not the treatment was actually carried out. Relative risks and their confidence intervals were calculated,[23] adjusting for baseline covariates by Cox regression.[24] The baseline covariates in POSCH have previously been defined.[6] In the Kaplan-Meier life-table analyses,[25] the date of randomization was used as the starting point. To account for differences in the lengths of time to events, both the Mantel-Haenszel statistic[26] and the Gehan statistic[27] were calculated. The Mantel-Haenszel statistic, having greater power to detect differences in the Kaplan-Meier curves at later times, is the one used throughout this article in determining the cited *P* value. A 2-sided $P<.05$ was used to define statistical significance.

corrected up to April 30, 1996, and reviewed and approved by the POSCH Data Monitoring Committee July 18, 1996. Mean patient follow-up for this report was 14.7 years (range, 12.2-20 years).

RESULTS

OVERVIEW

The average age of the patients at randomization was 51 years. Of 838 patients, 90.7% were men and 97.9% were white. The mean interval between the qualifying myocardial infarction and entry into the trial was 2.2 years. The characteristics of the population at baseline have been presented in detail elsewhere.[28] There were 355 patients in the control group and 372 in the intervention group alive at formal trial closure (July 19, 1990).

At 1, 5, 7, and 10 years of follow-up, 5.3%, 16.4%, 25.1%, and 31.5% of patients in the control group, respectively, were taking at least 1 cholesterol-lowering medication. In the intervention group, the corresponding figures were 0.5%, 3.0%, 6.2%, and 3.7%. Five years after formal trial closure, 145 patients (34.8%) in the control group and 51 patients (12.1%) in the intervention group were taking at least 1 cholesterol-lowering medication.

The baseline mean total plasma cholesterol level was 6.49 mmol/L (251 mg/dL), with an average LDL cholesterol level of 4.62 mmol/L (179 mg/dL) and an average HDL cholesterol level of 1.04 mmol/L (40 mg/dL); the baseline mean triglyceride level was 2.30 mmol/L (419 mg/dL). At 5 years after randomization, the intervention group compared with the control group had a 23.3% ± 1.0% (mean ± SE) lower total plasma cholesterol level ($P<.001$), a 37.7% ± 1.2% lower LDL cholesterol level ($P<.001$), a 4.3% ± 1.8% higher HDL cholesterol level ($P = .02$), an 18.3% ± 7.5% higher very low-density lipoprotein cholesterol level ($P = .02$), a 19.8% ± 6.5% higher triglyceride level ($P = .003$), a 37.8% ± 2.8% higher ratio of HDL cholesterol to total plasma cholesterol ($P<.001$), and a 71.8% ± 4.3% higher ratio of HDL cholesterol to LDL cholesterol ($P<.001$). Detailed reports of the in-trial changes in the lipid and lipoprotein concentrations, as well as an analysis of the predictors of the 5-year in-trial changes in total plasma cholesterol and LDL cholesterol, have been published.[29-32] The 5-year posttrial lipid data, as provided by the patients' physicians, include total plasma cholesterol levels for 203 (65.3%) of the surviving patients in the control group and 188 (55.8%) of the surviving patients in

the intervention group. In this cohort, the average total plasma cholesterol level was 5.66 mmol/L (219 mg/dL) in the control group and 4.9 mmol/L (189 mg/dL) in the intervention group for a difference of 14.0% ($P<.003$).

Of 421 patients assigned to surgery, 22 refused to undergo the operation and 23 underwent reversal of the partial ileal bypass procedure up to July 1990, primarily for intolerable diarrhea or recurrent nephrolithiasis. Subsequently, 4 additional patients have undergone reversal. No patient in the control group underwent a partial ileal bypass up to July 1990, and 1 patient in the control group has had a partial ileal bypass after July 1990. Endpoint analyses excluding patients who refused or reversed their randomization assignment do not reveal statistically significant differences from the intention-to-treat analyses. Therefore, results of all clinical analyses, except the left ventricular ejection fraction analyses, are based on the total POSCH randomization numbers of 417 patients in the control group and 421 patients in the intervention group.

OVERALL MORTALITY

There were 106 deaths in the control group (25.4%) compared with 84 in the intervention group (20%) at 5-year posttrial follow-up. The relative risk in the intervention group was 0.75 (95% confidence interval [CI], 0.56-1.00). Using the Mantel-Haenszel statistic, the difference between the control and the intervention groups was statistically significant ($P = .049$) (**Table**; **Figure**, A; the Table includes a comparison with the in-trial results). In the subgroup with a left ventricular ejection fraction of 50% or more, 67 (22.9%) of 292 patients in the control group had died and 42 (14.9%) of 281 patients in the intervention group had died at the 5-year posttrial follow-up. The relative risk in the intervention group was 0.61 (95% CI, 0.41-0.89) ($P = .01$) (Table; Figure, B). Overall mortality in the subgroup with an ejection fraction of less than 50% was 33 (30.8%) of 107 patients in the control group and 41 (32.3%) of 127 patients in the intervention group ($P = .75$).

MORTALITY FROM ACHD

The number of deaths from ACHD at 5 years after the trial was 70 (16.8%) in the control group and 49 (11.6%) in the intervention group. The relative risk in the intervention group was 0.66 (95% CI, 0.46-0.96) ($P = .03$) (Table; Figure, C). In the subgroup of patients with a left ventricular ejection fraction of 50% or more, 37 (12.7%) of 292 patients in the control group and 23 (8.2%) of 281

In-Trial vs 5-Year Posttrial Follow-up Results*

Outcomes	No. of Patients		Relative Risk	95% Confidence Interval	Mantel-Haenszel *P*
	Control Group	Intervention Group			
Overall mortality					
In trial	62	49	0.77	0.53-1.12	.16
5 y after trial	106	84	0.75	0.57-1.00	.049
Overall mortality EF ≥50					
In trial	39	24	0.61	0.37-1.01	.05
5 y after trial	67	42	0.61	0.41-0.89	.01
Mortality from ACHD					
In trial	44	32	0.71	0.45-1.12	.13
5 y after trial	70	49	0.66	0.46-0.96	.03
Mortality from ACHD and EF ≥50					
In trial	24	15	0.62	0.32-1.18	.13
5 y after trial	37	23	0.60	0.36-1.02	.05
Mortality from ACHD and confirmed nonfatal MI					
In trial	125	82	0.60	0.45-0.79	<.001
5 y after trial	157	105	0.60	0.47-0.77	<.001
Confirmed nonfatal MI					
In trial	93	56	0.57	0.41-0.79	<.001
5 y after trial	109	68	0.57	0.42-0.77	<.001
Mortality from ACHD, confirmed and suspected MI, and unstable angina					
In trial	222	160	0.62	0.50-0.76	<.001
5 y after trial	279	229	0.68	0.57-0.81	<.001
CABG or PTCA					
In trial	170	67	0.35	0.26-0.46	<.001
5 y after trial	201	106	0.41	0.32-0.53	<.001
Onset of peripheral vascular disease					
In trial	71	52	0.70	0.49-1.00	.04
5 y after trial	93	68	0.68	0.50-0.93	.02

**EF indicates baseline left ventricular ejection fraction; ACHD, atherosclerotic coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.*

patients in the intervention group had died of ACHD at the 5-year posttrial follow-up. The relative risk in the intervention group was 0.60 (95% CI, 0.36-1.02) (*P* = .05) (Table; Figure, D). Mortality from ACHD in the subgroup with an ejection fraction of less than 50% was 28 (26.2%) of 107 patients in the control group and 26 (20.5%) of 127 patients in the intervention group (*P* = .43).

OTHER ACHD AND PERIPHERAL VASCULAR DISEASE EVENTS

The Table presents the in-trial and the 5-year posttrial relative risks, with 95% CI, and the Mantel-Haenszel *P* values for mortality from ACHD and confirmed nonfatal myocardial infarction (Figure, E); confirmed nonfatal myocardial infarction (Figure, F); mortality from ACHD, confirmed and suspected myocardial infarction, and angina pectoris (Figure, G); coronary artery bypass grafting or percutaneous transluminal coronary angioplasty (Figure, H); and onset of peripheral vascular disease.

CEREBROVASCULAR EVENTS

At 5-year posttrial follow-up, a cerebrovascular accident was confirmed in 28 patients in the control group and in 31 patients in the surgery group (*P* = .88). When all cerebrovascular events (cerebrovascular accidents and transient ischemic attacks) were combined, there were 68 events in the control group (16.3%) and 85 in the surgery group (20.2%) (*P* = .24).

MORTALITY FROM NON-ACHD

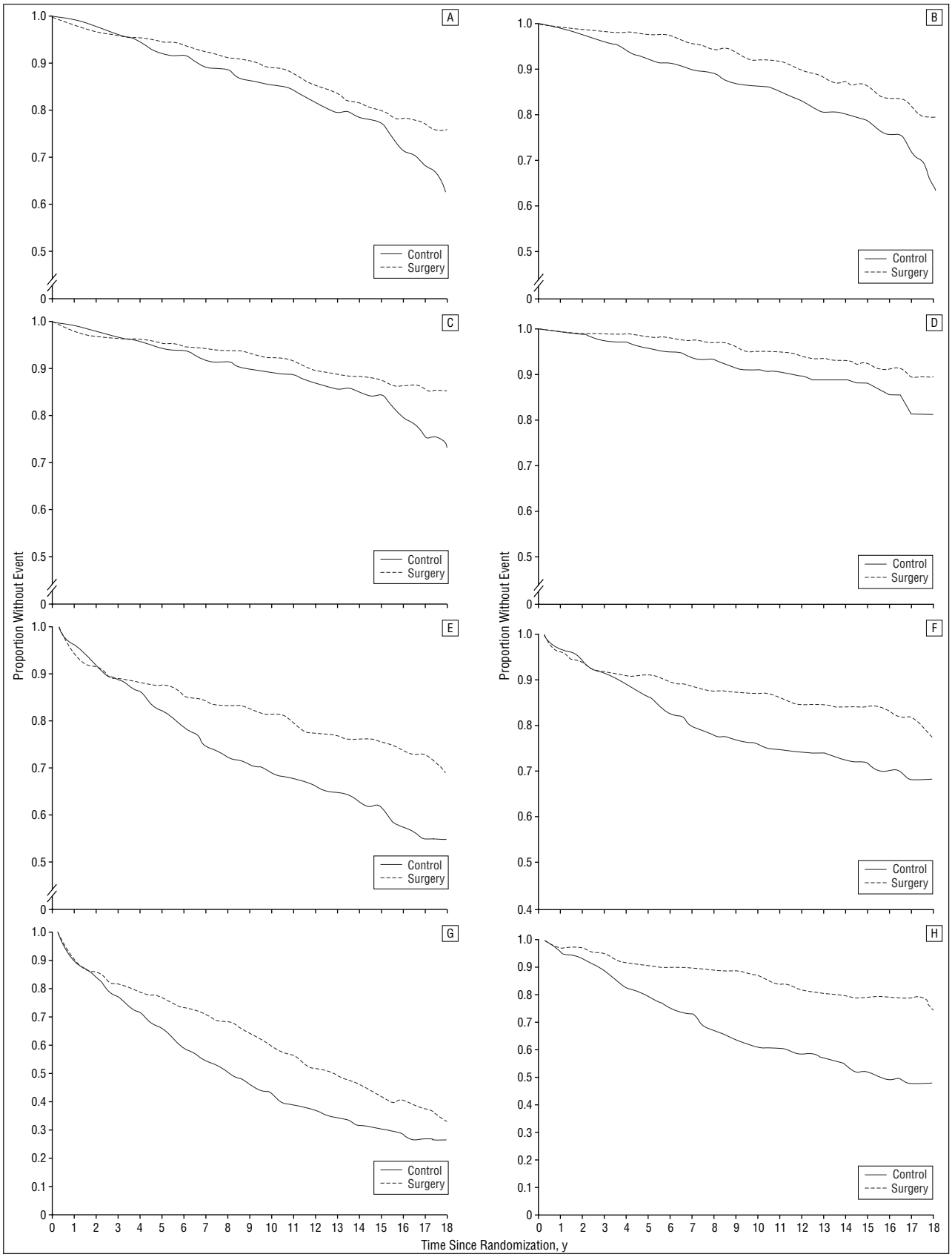
At 5-year posttrial follow-up, deaths from non-ACHD occurred in 36 patients in the control group (8.6%) and in 35 patients in the intervention group (8.3%) (*P* = .73). The significant decrease in overall mortality in POSCH was, therefore, the result of the significant decrease in mortality from ACHD, uninfluenced by mortality from non-ACHD.

INCIDENCE OF CANCER

At 5-year posttrial follow-up, 58 cancers were detected in the control group (13.9%) and 61 in the surgery group (14.5%) (*P* = .99). There were 8 (1.9%) colorectal cancers in the control group and 10 (2.4%) in the surgery group (*P* = .69). Therefore, there was no difference in the incidence of cancer between groups.

COMMENT

The lipid/atherosclerosis theory has been substantially confirmed within the last 5 years. The observational studies starting in the 19th century,[33,34] the experimental



Life and event tables for overall mortality (A); overall mortality with left ventricular ejection fraction of 50% or more (B); mortality from atherosclerotic coronary heart disease (ACHD) (C); mortality from ACHD with left ventricular ejection fraction of 50% or more (D); mortality from ACHD and confirmed nonfatal myocardial infarction (MI) (E); confirmed nonfatal MI (F); mortality from ACHD, confirmed and suspected MI, suspected MI, and unstable angina (G); and coronary artery bypass grafting or percutaneous transluminal coronary angioplasty (H). The difference between the groups was significant for all 8 end-point analyses ($P<.05$ *to* $P<.001$*).*

studies of the early 20th century,[35-37] and the post–World War II epidemiological studies[38-44] gave rise to the concept that for populations, and for their constituent individuals, the higher the plasma cholesterol level, the greater the incidence and severity of ACHD. Since this statement was supported by the majority of the available data, proof of the corollary to this axiom of causation became the goal of innumerable scientists; namely, demonstration that lowering the total plasma cholesterol, or more precisely lowering the LDL cholesterol level and modifying the LDL to HDL cholesterol relationship,[45] would result in a decrease in the incidence of ACHD and favorably alter the outcome of established ACHD. The latter goal was to be manifested by the prevention of, or the extension in time to, death from ACHD, a nonfatal myocardial infarction, or another ACHD event, all resulting in a prolongation of life expectancy. The validity of atherosclerosis retardation, arrest, and even reversal have now been clinically established for men younger than 65 years. The evidence for the benefits of lipid modification after the age of 65 years is also good,[46] although handicapped in achieving undebated determination in controlled clinical trials by the increase in competing mortal diseases after 65 years of age and by the fact that people older than that age are naturally or medically selected survivors and possibly less susceptible to elevated lipid parameters. As previously stated, the issue of proven clinical benefits for women by lipid modification remains an open question.[10]

In actuality, the first 13 lipid/atherosclerosis intervention trials provided little or no evidence to reject the null hypothesis that individuals do not derive clinical benefits from lipid intervention.[47] Then followed the suggestive reports of the 1980s from the Cholesterol Lowering Atherosclerosis Study,[48] the Helsinki Heart Study,[49] the NHLBI Type II Coronary Intervention Study,[50] and the Lipid Research Clinics–Coronary Primary Prevention Trial.[51] In 1990, POSCH reported its in-trial findings and ushered in 5 years of multiple independent reports from controlled clinical trials strongly confirming the validity of the lipid/atherosclerosis theory.[1] In 1990, there followed the affirmative reports from the Familial Atherosclerosis Treatment Study[52] and the Arteriosclerosis Specialized Center of Research Study,[53] both trials of sequential coronary arteriography changes as surrogate end points for clinical events. In 1992, the positive clinical findings of the St Thomas' Atherosclerosis Regression Study[54] were published, as well as the results of a study of the changes in lifestyle by Gould et al.[55] In 1993, the Monitored Atherosclerosis Regression Study[56] provided further arteriographic evidence for a favorable change in prognosis secondary to marked lipid intervention, as did the 1994 Stanford Coronary Risk Intervention Project.[57]

The year 1994 marked the start of the reporting of the statin drugs trials. The first of these was the landmark Scandinavian Simvastatin Survival Study,[46] the first trial ever to demonstrate a statistically significant reduction in overall mortality secondary to lipid intervention. In rapid succession came complementary reports from the Multicentre Antiatheroma Study,[58] the Canadian Coronary Atherosclerosis Intervention Trial,[59] the Asymptomatic Carotid Artery Progression Study,[60] the Regression Growth Evaluation Statin Study,[61] and the West of Scotland Coronary Prevention Study.[62] The West of Scotland study was the first long-term primary prevention trial with statistically significant evidence of clinical benefits from LDL cholesterol lowering. Additional ongoing statin trials include the Cholesterol and Recurrent Events trial[63] and the Long-Term Intervention With Pravastatin in Ischemic Disease megastudy[64] of 9014 patients, including 3516 patients older than 65 years and 1511 women.

Other reports from long-term follow-up studies include the 15-year mortality report from the Coronary Drug Project[65] that cited an 11% lower overall mortality rate in the group receiving niacin in comparison with the placebo group ($P<.001$), even though niacin therapy had been discontinued for about 9 years; the 3.8-years posttrial Multiple Risk Factor Intervention Trial[66] report demonstrating a 10.6% reduction in mortality from ACHD and a 7.7% reduction in overall mortality, although these differences were not statistically significant; the 6-year posttrial Lipid Research Clinics–Coronary Primary Prevention Trial,[67] which showed no evidence of benefit beyond that presented at the cessation of this trial, with a 0.89 overall mortality risk ratio between the 153 deaths in the control group and the 143 deaths in the intervention group; and the extended follow-up results (3.5 years after trial) from the Helsinki Heart Study[68] that showed no change from the in-trial results of an increase in overall mortality in the treatment group receiving gemfibrozil.

As stated, POSCH was the first of the lipid/atherosclerosis controlled clinical trials to report truly affirmative results in support of marked lipid modification, in particular, lowering of the LDL cholesterol level. The Program on the Surgical Control of the Hyperlipidemias was unique in mandating the inclusion of women, the evaluation of peripheral vascular disease, and the simultaneous evaluation of ACHD by arteriography, as well as by clinical end points. Now, 5 years after closure of the formal POSCH trial, we report the vital status and atherosclerosis clinical events for the original 838 patients in POSCH (417 in the control group and 421 in the intervention group) followed up for a minimum of 12.2 years and a maximum of 20 years (mean, 14.9 years).

The greatest departure from the purity of the original randomization assignment in POSCH has been due to the use of cholesterol-lowering drugs prescribed by the patients' private physicians: 145 patients in the control group and 51 patients in the intervention group were receiving hypocholesterolemic drugs up to September 30, 1995. These agents are statins for the most part. Over time, since most of the hypocholesterolemic drug users are in the control group, the mean lipid levels of the 2 groups have come closer together. However, the impact of the partial ileal bypass performed at trial entry on long-term clinical end points in the intervention group should not, thereby, be impaired.

All the POSCH clinical end points demonstrate beneficial outcomes in the intervention group with a 2-sided Mantel-Haenszel $P<.05$. The last end point to achieve this result was overall mortality. The P value of .049 for the difference in overall mortality will, undoubtedly, fluctuate with time to exceed $P = .05$ or continue

to drop below $P = .05$. The overall mortality difference for those patients who entered the study with a relatively sound heart, despite having sustained a qualifying myocardial infarction (the patients with a left ventricular ejection fraction at the time of trial entry ≥50%), showed a substantial benefit ($P = .01$). Furthermore, the statistically significant results for mortality from ACHD ($P = .03$), for mortality from ACHD combined with confirmed nonfatal myocardial infarction ($P<.001$), and for a recurrent nonfatal myocardial infarction ($P<.001$), as well as those for all the clinical end points combined with overall mortality or mortality from ACHD ($P<.001$), lend additional credibility to the validity of the difference in the POSCH primary end point of overall mortality.

Finally, in evaluating the POSCH data, there was no increase in mortality from non-ACHD or in the incidence of malignancies in the trial population. Of particular note is the absence of an increase in colorectal cancers in the partial ileal bypass group, even though the large intestine of these patients was exposed to an increased concentration of putatively carcinogenic bile acids.

To our knowledge, the POSCH trial is the only controlled clinical trial of lipid modification to use an operative procedure as the intervention modality. When partial ileal bypass was first introduced in 1962,[12] there were no uniformly effective and/or safe and convenient drug protocols for total plasma cholesterol and LDL cholesterol lowering. By offering marked efficacy, lasting results, relative safety, and obligatory therapy, this operation was ideal for use in a controlled clinical trial initiated in the 1970s. With the introduction of the statin compounds, this operative intervention currently has limited clinical applicability. Although there were no in-hospital deaths after partial ileal bypass in the POSCH trial, there were inconvenient and lifestyle compromising adverse effects that were well documented. These included diarrhea, kidney stones, gallstones, gas bloat syndrome, and bowel obstruction attributable to postoperative adhesion formation.[1] Is there, therefore, any clinical role for partial ileal bypass surgery today? We believe this procedure is a therapeutic option to be considered for young patients facing the alternative of many years of expensive, easy-to-neglect drug therapy. Unless undone, operative intervention is obligatory and after 7 years partial ileal bypass surgery becomes cost-effective in comparison with statin drug therapy. It should be considered as part of the treatment armamentarium for patients who have failed various drug regimens or for those patients for whom statins, or combination drug protocols, may have toxic effects. In a limited number of patients, we have been eminently successful in tailoring a desired level of the LDL cholesterol by the combination of a partial ileal bypass with dose titration of a statin drug.

In conclusion, at 5 years after the trial, all POSCH mortality and atherosclerosis end points yielded statistically significant differences between the control group and the intervention group, confirming and extending the in-trial results. The POSCH trial provides long-term evidence supporting effective lipid modification in the management of atherosclerosis.

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