Gemfibrozil in the Treatment of Dyslipidemia

An 18-Year Mortality Follow-up of the Helsinki Heart Study

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Background: The Helsinki Heart Study was a double-blind, placebo-controlled primary prevention trial among 4081 dyslipidemic middle-aged men to test the efficacy of gemfibrozil in the prevention of coronary heart disease (CHD). After the 5-year trial, the participants were notified of their treatment group and invited to continue or start gemfibrozil therapy free of charge through 1995. Approximately two thirds of participants in both groups chose gemfibrozil therapy. In this 18-year follow-up through 2000, we compared the CHD, cancer, and all-cause mortality among subjects in the original gemfibrozil (OG) group (n=2046) with those in the original placebo (OP) group (n=2035).

Methods: To provide an overview of the absolute risks in the 2 treatment groups as well as risk differences between them, we calculated crude mortality rates and presented Kaplan-Meier plots of survival with log-rank tests. We also estimated the relative risks (RRs) using Cox proportional hazards models with and without covariates.

Results: During the follow-up until 1995, subjects in the OG group had a 32% lower RR of CHD mortality (P=.03) compared with those in the OP group, and when followed up until 2000, the RR was 23% lower (P=.05). Overall, there were no differences in all-cause or cancer mortality. However, those in the OG group with both body mass index and triglyceride level in the highest tertiles had a 71% lower RR of CHD mortality (P<.001), a 33% lower RR of all-cause mortality (P=.03), and a 36% lower RR of cancer mortality (P=.22) compared with those in the OP group.

Conclusion: Long-term mortality follow-up showed that patients with dyslipidemia benefited from beginning treatment with gemfibrozil early, especially if their dyslipidemia entailed factors related to the metabolic syndrome.

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METHODS

DIFFERENT PHASES
OF THE HELSINKI HEART STUDY

Double-blind Trial

The Helsinki Heart Study was a 5-year, double-blind clinical trial to test the hypothesis that lowering serum LDL-C and triglyceride levels and elevating serum HDL-C levels with gemfibrozil reduces CHD risk in middle-aged dyslipidemic men. The design, conduct, and main results of the study have been described in detail. Briefly, the volunteers for the trial were selected in 1980 through 1982 by two successive screenings from men aged 40 to 55 years, employed by two government agencies and five industrial companies. To be eligible for the second screening or for the trial, the subjects’ non–HDL-C level had to be 200 mg/dL (5.2 mmol/L) or higher, and for the trial they also had to be without evidence of CHD or any other major illness. Of 18,936 men who participated in the trial, 2035 were randomized to receive placebo and 2046 to receive gemfibrozil, 1200 mg/d, 2 capsules twice daily. Compliance with medication was studied by several methods (eg, capsule counting).

Open-Label Phase

At the end of the 5-year trial, all subjects (including dropouts) were informed about their lipid values during the trial and invited to participate in an open 3.5-year trial extension with 2 annual visits and a choice to take gemfibrozil (Figure 1). About the same proportion of subjects in the 2 original treatment groups chose to take gemfibrozil: 66.3% in the OG group and 68.5% in the OP group. Compliance monitoring showed that in both groups the participants in the 2 original treatment groups chose to take gemfibrozil.

Register-Based Follow-up Phase

At the end of the open-label phase in June 1990, subjects taking gemfibrozil were offered a free drug supply through a central pharmacy through 1995, but no regular follow-up visits. The trial cohort was then followed up for all-cause, CHD, and cancer mortality by linkage to population-based registers, especially the Cause-of-Death Register kept by Statistics Finland, Helsinki. In Finland, there is a centralized nationwide population registration system based on personal identification numbers, kept since 1966. This system ensures that the registration of deaths is virtually complete. The Cause-of-Death Register was found to be very reliable in terms of CHD deaths compared with the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) project data and the Helsinki Heart Study data.

Present Mortality Follow-up

This study extends the follow-up from the beginning of the double-blind trial in 1980-1982 through 2000 (18-year follow-up) and is fully register based. The following CHD codes were monitored: International Classification of Diseases, Eighth Revision codes 410 to 414 through 1986; International Classification of Diseases, Ninth Revision codes 410 to 419 from 1987 through 1995; and International Statistical Classification of Diseases, 10th Revision codes 120 to 125 from 1996 through 2000. These codes imply the presence of 1 or several of the following conditions: angina, myocardial infarction, myocardial infarction with complications, other ischemic heart diseases, and chronic ischemic heart disease.
The analyses were performed on an intention-to-treat principle (ie, by comparing mortality risks in the original treatment groups). We thus estimated the mortality risk in approximately 18 years of follow-up among subjects belonging to the OG group compared with those in the original OP group. To provide an overview of the absolute risks in the 2 treatment groups as well as risk differences between them, we calculated crude mortality rates and presented Kaplan-Meier plots of survival with log-rank tests. We also tested the statistical significances of the differences using Cox proportional hazards models with and without covariates. The P values were based on the likelihood ratio test. To study whether age, baseline levels of lipids, or body mass index (BMI) would modify the treatment effect, we formed a new variable representing combinations of treatment group and levels of the other factor (eg, tertiles of TG: [OP, TGI], [OP, TGII], [OP, TGIII], [OG, TGI], [OG, TGII], [OG, TGIII]). In this way, all data were included in the model, and spurious results originating in analyses of separate subgroups were avoided. The analyses were performed using the statistical package Egret for Windows (Cytel Software Corp, Cambridge, Mass).

### RESULTS

#### LIPID LEVELS DURING THE DOUBLE-BLIND AND OPEN-LABEL TRIALS

As background information, Figure 2 shows the development of the annual mean values of TG, HDL-C, and LDL-C by treatment group during the 8.5-year follow-up. Owing to successful randomization, the baseline values were closely similar in the 2 treatment groups. During the double-blind phase, the treatment soon led to substantial differences in the lipid levels. After the beginning of the open label phase, the lipid levels in both groups settled at a level that was between that in the OP and OG groups during the double-blind trial, mirroring the fact that approximately 2 thirds of subjects in both groups were receiving gemfibrozil.

#### MORTALITY IN THE OP AND OG GROUPS

Table 1 presents mortality data for 2 periods: the 13-year follow-up from 1980-1982 until the end of the free gemfibrozil treatment at the end of 1995 (mean, 13.7 years) and the 18-year follow-up from the beginning of the study through 2000 (mean 18.1 years). Trends for all-cause and cancer mortality favored patients in the OG group but were significant only for CHD mortality: $P=0.03$ for the 13-year follow-up and $P=0.05$ for the 18-year follow-up. In all these comparisons, the differences between the OP and the OG groups decreased when the follow-up was extended beyond 1995.

Adjustment for age slightly decreased the risk differences between the OP and the OG groups. We therefore also estimated the mortality when the study group was divided into 2 groups by median age (47 years). The younger age group benefited slightly more from an early start of treatment than did the older group, particularly during the 13-year follow-up (data not shown).

Thus, among those aged 40 to 47 years at the beginning of the study, the relative risk (RR) of CHD mortality was 42% lower in the OG group compared with the OP group ($P=0.07$), but it was only 24% lower among those who were 48 to 57 years old at that time. During the 18-year follow-up, the corresponding figures were 31% ($P=0.08$) and 17% (data not shown).

The Kaplan-Meier plots of Figure 3 give an overview of the time-dependent trends in the mortality risks of the OP and OG groups. Coronary heart disease mortality was consistently lower in the OG group than in the OP group, whereas no such trend was seen in all-cause or cancer mortality.

#### CHD MORTALITY BY BASELINE LIPID AND BMI LEVELS

To study if the observed difference in CHD risks between the OP and OG groups depended on factors related to the metabolic syndrome, we calculated CHD mortality by tertiles of baseline lipid and BMI levels in the OP and OG groups during the 18-year follow-up. The CHD mortality increased with increasing TG tertiles in the OP group but not in the OG group. Indeed, in the OG group the CHD mortality in the last tertile was 50% lower ($P=0.001$) than in the corresponding

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Abbreviations: CHD, coronary heart disease; CI, confidence interval; OG, original gemfibrozil; OP, original placebo; RR, relative risk.

*Relative risk of OG group compared with the OP group.
†Adjusted for low- and high-density lipoprotein cholesterol level, systolic blood pressure, body mass index, and smoking.
‡Gemfibrozil was supplied free of charge through 1995.
tertile in the OP group. A similar difference between the 2 groups was noted for HDL-C but not for LDL-C. For comparison, we also estimated the corresponding mortality data for BMI: there was no consistent pattern of risk across the 2 lowest tertiles, but the highest tertile yielded a risk peak in the OP group and a 52% lower mortality in the OG group ($P<.001$) (data not shown).

Table 2 gives the CHD and all-cause mortalities in combinations of tertiles of baseline levels of TG and BMI. In the OG group, the subjects with both high BMI and high TG level at baseline had a 71% lower CHD mortality ($P<.001$) and a 33% lower all-cause mortality ($P=.03$) compared with those in the OP group. They also had 36% lower risk of cancer mortality ($P=.22$) (data not shown). The baseline combinations of high BMI and low HDL-C level or high TG and low HDL-C levels yielded similar patterns of risk in terms of CHD or all-cause mortality (data not shown).

**COMMENT**

In this long-term mortality follow-up study based on the intention-to-treat principle, we compared mortalities in the 2 original treatment groups of the Helsinki Heart Study (ie, those randomized to receive placebo or gemfibrozil). The only manifest difference in treatment between the groups concerned the 5-year double-blind trial, after which the same proportion of subjects in both groups continued gemfibrozil therapy at least through 1995. The major findings were a significant reduction in CHD mortality in the OG group compared with the OP group and some statistically nonsignificant reductions in all-cause and cancer mortalities. Subgroup analyses showed that participants with high BMI, high TG level, or low HDL-C level at baseline benefited most from an early start of treatment. For instance, participants with a combination of high BMI and high TG level had a 71% lower risk of CHD mortality in the OG group compared with those in the OP group.

**PARTICIPANTS WHO BENEFITED FROM THE TREATMENT**

The finding that, at baseline, a combination of high BMI and high TG level or high BMI and low HDL-C level predicts good treatment effect with gemfibrozil is consistent with our previous report from the double-blind trial phase, in which we found that gemfibrozil use reduced the risk of coronary events mainly in overweight subjects with additional risk factors known to contribute to the metabolic syndrome. In addition, a recent article from the VA-HIT trial reports that the reduction of events with gemfibrozil use was greater in subjects with insulin resistance than in those without, despite the finding that an increase in HDL-C level and a decrease in TG level with gemfibrozil use was less in subjects with insulin resistance than in those without. Actually, the authors of this article conclude that "the benefit of fibrate therapy was much less dependent on levels of HDL-C or TG than on the presence or absence of insulin resistance." In the Helsinki Heart Study trial, insulin resistance was not measured, but BMI plays a central role in the metabolic syndrome.

Several trials have studied the putative effects of gemfibrozil on insulin resistance, insulin level, or factors...
known to be related to the metabolic syndrome. In most studies, no effect of gemfibrozil has been found on insulin resistance, serum insulin levels, or glucose metabolism,\textsuperscript{12,14} whereas both insulin action and glucose metabolism were improved by gemfibrozil use in a study by Avogaro et al.\textsuperscript{15} Gemfibrozil has been reported to improve the fibrinolytic system by decreasing plasminogen activator inhibitor type 1 activity,\textsuperscript{16,17} but contrasting findings have also been reported.\textsuperscript{11} It is interesting that in the VA-HIT secondary prevention trial in subjects with low HDL-C level, gemfibrozil was found to be most effective in subjects with diabetes and in nondiabetic subjects with high fasting plasma insulin levels.\textsuperscript{18}

The studies on the actions of fibrates at the molecular level may provide a broader understanding for the observed multiple beneficial effects of gemfibrozil on CHD risk factors. The fibrates have been found to activate transcription factors, the peroxisome proliferator-activated receptors (PPARs) (particularly the PPAR-\(\alpha\) that controls lipoprotein metabolism),\textsuperscript{19} and atherosclerotic plaque thrombogenicity.\textsuperscript{20}

LESSONS FROM THE LONG-TERM FOLLOW-UP

Because compliance was monitored in several ways during the double-blind trial phase, we know that most subjects in the OG and OP groups were compliant.\textsuperscript{8} During the open-label phase, a similar proportion (approximately two thirds) of subjects in both groups chose to take gemfibrozil, which was offered free of charge through 1995. We do not know whether they continued using gemfibrozil after that date, but there is no reason to assume that the 2 groups differed substantially in their choice of therapy for dyslipidemia. Two differences thus remain between the 2 groups: first, the subjects in the OG group had a longer period of active treatment, and second, they started active treatment at a younger age. The finding that in the follow-up until 1995 the younger subjects (age, 40-47 years) in the OG group had a 42% lower CHD incidence compared with the corresponding subjects in the OP group, while the difference was only 24% for the older subjects (age, 48-57 years), lends some support to the hypothesis that not only an early start of the treatment but also the age when treatment is started may be of importance. How could we explain the benefit of an early start of gemfibrozil treatment on CHD mortality? One reasonable mechanism is drug-related prevention of the conversion of early, clinically innocent coronary lesions (fatty streaks) into clinically significant more complex lesions. This conversion already starts in coronary arteries during the second decade of life, and by the end of the fourth decade, most male subjects have intermediate or advanced lesions in their coronary tree.\textsuperscript{21}

SAFETY OF TREATMENT

The earlier start of the treatment with gemfibrozil in the OG group was not associated with increased risk of cancer or all-cause mortality. Rather, the earlier start of gemfibrozil treatment significantly reduced all-cause mortality among subjects with high BMI and high TG level at baseline. In this subgroup, cancer mortality was also reduced, albeit not significantly. It is noteworthy that high BMI is a risk factor for several types of cancer, and there is much ongoing research on the association of insulin resistance and some cancers.\textsuperscript{22,23}

LIMITATIONS OF THE STUDY

The design of the follow-up study inherently restricts the interpretation. Because there was no placebo group after the double-blind phase, there was no opportunity to evaluate the effect of gemfibrozil therapy after the initial trial phase. We could only compare the effect of a 5-year earlier start of gemfibrozil treatment in 2 randomized groups of dyslipidemic men (no women), and we could only speculate on the possible reasons for a difference in effect of this 5-year earlier start of treatment with gemfibrozil.

We had no clinical data on the participants after the 8.5-year trial, and especially after 1995 we have no information on their choice of medication. However, it
seems plausible that whether they continued using any medication or chose another drug, the study groups did not differ essentially in their choice of treatment.

In conclusion, the long-term follow-up of mortality in Helsinki Heart Study treatment groups revealed significantly reduced CHD mortality among subjects who started gemfibrozil therapy at age 40 to 47 years than those who started the treatment 5 years later at age 48 to 57 years. Subgroup analyses showed that those with dyslipidemia related to the metabolic syndrome especially benefited from an earlier start of treatment, with significantly reduced CHD and all-cause mortality.

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